Opioids – Basic and Clinical Pharmacology in Pain Management

- Part 1 -

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Objectives:

- Understand the basic and clinical pharmacology of the opioid analgesics
- Identify important clinical considerations related to managing acute and chronic pain with opioids.
- Discuss the rationale for opioid rotation and the newer dosing calculations.

Disclosures

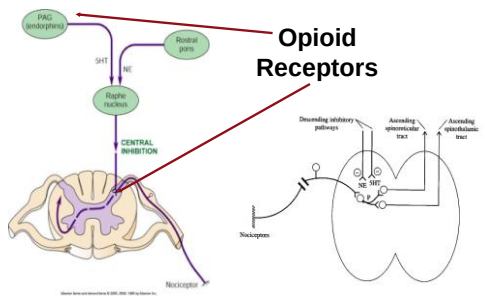
Neither of us has and financial or other conflicts of interest to disclose

Opioid Mechanisms

Act only in CNS

- Inhibit pre and post synaptic fibers in doral horn of spinal cord
- Prevent ascending transmission of pain signal
- Turn on descending inhibitory systems
- Inhibit cells that release inflammatory mediators
- Alter perception of pain at higher cortical processes

Opioid Targets



Opioid Receptors

- Mu receptors (mu-1 and mu-2)
  - Beta endorphins the natural agonist
  - Mu-1 receptors
    - supraspinal
    - responsible for central interpretation of pain
    - A number of subtypes exist (MOR_x or MOP)
  - Mu-2
    - located throughout CNS
    - respiratory depression, spinal analgesia, euphoria, physical dependence, GI motility

Opioid Receptors

– Kappa (κ_1, κ_2, κ_3)
- Dynorphins natural agonist
- Significant Spinal analgesia
- Less respiratory depression / dependence
- Miosis (pinpoint pupils), sedation, dysphoria, nausea
- Activation may antagonize mu receptors
- Basal ganglia, PAG, hypothalamus, cortex, spinal cord

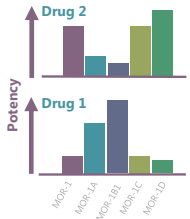
– Delta (δ_1, δ_2)
- Enkephalins natural agonist
- Mostly spinal locations
- Some analgesia (< mu-receptor)

Opioid Receptors and Effect

- Response to an opioid depends on:
  - the receptor(s) to which it binds
  - its affinity for that receptor
  - if it's an agonist, partial agonist of antagonist
- Each opioid is unique in its distinct binding affinity to the various classes of opioid receptors (e.g. the μ, κ, δ)
- Opioid receptors are activated at different magnitudes according to the specific receptor binding affinities of the opioid

Opioid Receptors and Effect

- Subtle differences in receptors may be responsible for:
  - Inter-patient variability in analgesic responses, tolerability (side effects) and subjective experience
  - Incomplete cross-tolerance among mu opioids
  - Rationale for opioid rotation



Opioids

- Most effective for somatic or visceral pain
  - Post-op, cancer, deep pain
- Less effective for neurogenic pain
- Incident pain difficult to control
- Higher potency agents may be more effective
  - Greater mu affinity?
  - Multiple actions (ie, analgesic, anesthetic)
  - Greater fat solubility – CNS entry
- No predictable relationship between opioid serum levels and analgesic responses

Opioids "Full" Agonists No Ceiling effect

***Strong Agonists* (C-II)**

Morphine
Hydromorphone
Oxymorphone
Oxycodone
Meperidine
Fentanyl
Methadone
Tapentadol
Codeine (> 90 mg)

Moderate

Hydrocodone **(C-III)**
< 15 mg/dose unit + APAP, etc
Codeine **(C-III)**
< 90 mg/dose unit + APAP
Buprenorphine **(C-III)**
Pentazocine **(C-IV)**
Butorphanol **(C-IV)**
Tramadol **(C-IV)** (AR, KY, MS)

Morphine

Most commonly used opioid for moderate to severe pain

Available in a wide variety of dosage forms

- PO, SC, IM, Rectal, Epidural, Intrathecal

Well-characterized pharmacokinetics and pharmacodynamics

Relatively low cost

When given to a pain free individual first experience is often dysphoric

Morphine

Pharmacokinetics

- Poor oral bioavailability
- Significant 1st pass effect (non-CYP450)
  - Thus: oral:parenteral effectiveness reportedly varies from 1:6 in opioid naive patients to 1:3 with chronic use
  - Renal elimination (caution in renal failure)
- Half life = 2.5 to 3 hrs (does not persist in body tissue)
- Duration of 10 mg dose is 3 to 5 hours
- SR and ER formulations (MS Contin, Avinza, Kadian)
  - Duration longer (8 – 24 hr)
  - Half-life remains the same as above

Hydromorphone

- ~ 4x more potent than morphine (7.5 = 30)
- highly water-soluble - allows for very concentrated formulations
- Good choice when opioid dose (pill burden) an issue
  - opioid tolerant patients
  - trouble with swalloing multiple pills, etc
- More rapid onset and shorter half life
- Safe in renal failure
- Does not produce miosis (mostly mu receptor binding)
- Tolerance and physical dependence is more intense than morphine because of its high potency
- Respiratory depression same as morphine

Oxymorphone

- Semi-synthetic - primarily mu receptor agonist
- 3x more potent than morphine
- Oral bioavailibity ~ 10%
  - Hepatic metabolism (non-P450)
- More lipid soluble than morphine
  - IR – faster onset than morphine or oxycodone
    - May be good for breakthrough pain
- Duration of action: IR 4–6 hours; ER 12 hours

Fentanyl

Synthetic opioid

- Parenteral (IV, IM)
- Topical (patch, nasal spray)
- Transmucosal (lozenge, buccal film/tablet, sublingual)

- 80 to 100 times more potent than morphine
- Preferred to other opioids in anesthesia due to its ability to maintain cardiac stability
- Used for breakthrough pain ➔ chronic pain
- Highly abused in recent years, known as *china white* as street name

Fentanyl

- Onset of action
  - IV: Almost immediate
  - IM: 7-8 minutes
  - Transdermal (initial placement): 6 hours
  - Transmucosal: 5-15 minutes
- Duration:
  - IV: 0.5-1 hour
  - IM: 1-2 hours
  - Transdermal (remove patch/no replacement): 12 hours
  - Transmucosal: Related to blood levels / dose

In all cases, respiratory depressant effect may last longer than analgesic effect

Meperidine

- Synthetic = produced in 1940's
  - wanted drug with less addictive liability than morphine, but it has same addictive liability as morphine
- Has atropine-like structure / action
- Also has local anesthetic / antispasmotic properties
- Potency same as morphine
- Sedation, analgesia, respiratory depression
- Tachycardia (unlike most opioids), no miosis
- **Toxic metabolite**, normeperidine may accumulate with chronic dosing or when renal function is impaired - causes CNS stimulation, which may lead to dysphoria, agitation, and seizures.

Oxycodone

- Semi-synthetic
- ~ 1.5x more potent than morphine (20 mg = 30 mg)
- Equally effective as morphine
- Available as immediate-release tablets, controlled-release tablets, or as oral solution
- No comparative trials showing that oxycodone is more effective than any other opioid
- May cause less sedation, pruritus, and nausea than morphine
- Second most commonly abused prescription opioid (after hydrocodone)

Oxycodone

Metabolized by CYP3A4 (major) and CYP2D6 (minor)

- Inhibitors / genetics can increase toxicity
- Can accumulate in renal or hepatic impairment

CYP3A4 inhibitors
- macrolides (not azith)
- azole antifubgals
- protease inhibitors
- verapamil, other CCBs
- grapefruit juice

CYP3A4 inducers:
- rifampin
- phenytoin
- carbamazepine
- pioglitazone
- St John's wort

Hydrocodone (C-III in US)

- Equianalgesic as Morphine
  - 1 mg IV hydrocodone = 0.4 mg of IV morphine.
  - Due to morphine's low oral bioavailability, a 1:1 relationship exists for PO hydrocodone and morphine
- About 6x greater analgesia than codeine (PO)
- Hydrocodone (+ acetaminophen) most widely prescribed drug in US
  - Nearly 131 million prescriptions in 2010.
- Also - the most widely abused prescription drug!!!

Hydrocodone

- Pure hydrocodone (and pure codeine) = Schedule II drugs
- To qualify as a Schedule III in US these opioids must be combined with a non-narcotic ingredient (ie., NSAID, ASA or acetaminophen) in a recognized therapeutic amount.
- The dosage forms recognized in the U.S.
  - per dosage unit (i.e., pill or capsule), must have no more than 15 mg of hydrocodone in addition to the therapeutic amount of a non-narcotic ingredient
  - per 100 ml (i.e., a liquid), must have no more than 300 mg of (dissolved) hydrocodone in addition to the therapeutic amount of a non-narcotic ingredient

Methadone

Synthetic containing two isomers (d,l)
- One isomer = Mu receptor agonist
- One isomer = NMDA (glutamate receptor) antagonist

- Equianalgesic with morphine
  - not an easy conversion
  - non-linear relationship in opioid tolerant pts
- Tolerance and dependence develop more slowly than with morphine.
- Withdrawal signs and symptoms are milder but more prolonged.

Methadone

Pharmacokinetics
- Rapid absorption and distribution
  - GI absorption nearly complete
  - onset of analgesia in 30-60 mins
- Slow elimination
  - T1/2 = 15-40 hours
  - T1/2 = 22 hours in chronic state
- steady state in 4 - 5 days
- acculumation likely – difficult to work with

Methadone

Side Effects:

Respiratory depression, QT prolongation, arrhythmia(s), bradycardia, cardiac arrest, constipation, diaphoresis

Interactions:

- CYP3A4 (inhibitors, inducers)
- Drugs prolonging QT_c interval
  - » Incl hypokalemia, hypomagnesemia, hypocalcemia
- Serotonin-enhancing drugs
- CNS depressants

Methadone

Recent CDC Vital Signs report:

- 15,500 annual deaths annually from Rx ODs
- Methadone = 2% of painkiller prescriptions in US but causes > 30% of Rx analgesic OD deaths
- Why?

  (1) available as a low-cost generic drug and often listed as a preferred drug by insurance companies.

  (2) > 4 million methadone prescriptions written for pain in 2009, despite FDA warnings about the risks associated with methadone

Methadone

CDC Recommends:

1. Only HCPs with substantial experience with methadone use it – and - follow consensus guidelines for appropriate opioid prescribing
2. Only use for conditions where benefit outweighs risk to patients and society.
3. Not for mild pain, acute pain, "breakthrough" pain, or on an as-needed basis.
4. For chronic non-cancer pain, methadone should not be considered a drug of first choice by prescribers or insurers.

Buprenorphine (C-III)

- Partial mu agonist <high affinity> / weak κ antagonist
- Less reinforcing than a full agonist (milder)
  - – Easier withdrawal (less dysphoria)
  - – Safety – overdose ceiling effect
- Acute & Chronic moderate – severe pain
- Used in treating Opioid Dependence
- Strong safety profile
  - – Little respiratory depression
  - – Little overdose potential

Buprenorphine

- Poor oral absorption
  - – IM, IV, subligual, buccal
- 25 to 50 times more potent than morphine
- Maximal effects peak slower than morphine
- Analgesia lasts longer (6 hours)
- Cleared by CYP3A4
  - – see oxycodone and methadone interactions

Opioid Side Effects

Common

- Constipation
- Nausea & vomiting
- Sedation & mental clouding
- Pruritis / Flushing
- Respiratory depression
  - – (subacute OD)

Less Common

- Hallucinations / Delirium
- Hypothermia
- Bradycardia / tachycardia
- Orthostatic hypotension
- Urinary retention
- Biliary spasm

Less Common – Side Effects

- **Decreased DHEA - Hypogonadism**
  - Associated with Chronic ER oral opioid use
  - Test patients who report symptoms for hormonal deficiencies
    - eg, decreased libido, sexual dysfunction or fatigue

Other Important Side Effects

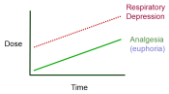
- **Opioid Induced Hyperalgesia (OIH)**
  - Pain intensity increased above level of preexisting pain in absence of apparent disease progression
  - Diffuse, less defined in quality, and beyond the distribution of the preexisting pain state
  - Mechanism(s) not fully elucidated
  - May require opioid rotation or discontinuation (wean)

Opioid Tolerance

- Complex phenomenon
  - Uncoupling/desensitization of opioid receptors
  - Internalization of surface receptors
  - NMDA receptors correlate with tolerance
  - Blockade of NMDA receptors may slow process
    - Methadone less likely
- Rate of tolerance varies greatly
  - Intermittent use doesn't generally lead to tolerance
  - Repeated administration does
- Cross tolerance occurs – usually incomplete

Opioid Tolerance

- **High degree of tolerance develops to**
  - ✓ analgesia
  - ✓ euphoria
  - ✓ respiratory depression



- **Minimal tolerance develops to**
  - ✓ constipation
  - ✓ seizures
  - ✓ miosis

Physical Dependence:

The appearance of the abstinence syndrome defines physical dependence on opioids, which may occur after just 2 weeks of opioid therapy

Physical dependence occurs with the development of tolerance.

Is not the same as addiction!

Physical Dependence

- Withdrawal
- A set of symptoms that occur due to specific physiological changes - rebound phenomena
  - Reduced release of dopamine in nucleus accumbens
  - Three-fold increase in norepinephrine release
- Abstinence vs Precipitated

Withdrawal - Abstinence

– Onset related to time-effect curve and t½ of narcotic.
- **6-8hr** =>drug seeking behavior, restless, anxious.
- **8-12hr** => Pupils dilated, reactive to light; increased pulse rate, ↑blood pressure, yawning; chills; rhinorrhea; lacrimation; gooseflesh; sweating; restless sleep.
- **48-72** hrs (peak) => All of the above plus muscular weakness, aches (cramps) and twitches; nausea, vomiting and diarrhea; ↑ temperature and respiration rate elevated; heart rate and blood pressure elevated; dehydration.

Withdrawal - Abstinence

Can be life-threatening

Depends on degree of physical dependence and health status of patient

No seizures, no delirium, no disorientation

Treatment of withdrawal: symptoms => clonidine

Used to block autonomic symptoms of withdrawal

✓tachycardia
✓ sweating
✓ hypertension
✓ cramping
✓ nausea
✓ vomiting

Withdrawal - Precipitated

- Produced by administration of:
  - Opioid antagonists
    - naloxone, naltrexone, including Vivitrol
  - Mixed partial agonist / antagonists
    - Talwin, Nubain
- Peaks sooner than abstinence withdrawal
- More severe - more difficult to reverse

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- Part 2 -

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Clinical Interview: Pain & Treatment History

- Description of pain
  - Location
  - Intensity
  - Quality
  - Onset/duration
  - Variations/patterns/rhythms
- What relieves the pain?
- What causes or increases pain?
- Effects of pain
- Patient's pain & function goal

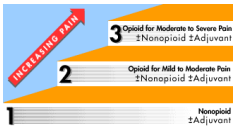
Clinical Interview: Pain & Treatment History

- Pain medications
  - Past use
  - Current use
    - Query state **Prescription Drug Monitoring Program** where available to confirm patient report
    - Contact past providers & obtain prior medical records
    - Conduct **Urine Drug Test**
  - Dosage
    - For opioids currently prescribed: opioid, dose, regimen, & duration
      - Important to determine if patient is **opioid tolerant**
  - General effectiveness
- Nonpharmacologic pain relief & effectiveness

Physical Examination & Assessment of Presenting Pain Condition

- Objective data to confirm History & Diagnosis
- Components of physical exam (appropriate to pain location)
  - General physical exam
    - Vital signs: overall health & comorbidities
    - General appearance, posture, gait, & pain behaviors
  - Neurologic exam
  - Musculoskeletal exam
    - Inspection
    - Palpation
    - Percussion
    - Auscultation
    - Provocative maneuvers
  - Cutaneous or trophic findings
- Order diagnostic tests (appropriate to complaint)

WHO 3-step ladder



		3 - SEVERE
	2 - MODERATE	Morphine
	A/Codeine	Hydromorphone
1 - MILD	A/Hydrocodone	Methadone
ASA	A/Oxycodone	Levorphanol
Acetaminophen	A/Dihydrocodeine	Fentanyl
NSAID's	Tramadol	Oxycodone
+/- Adjuvants	+/- Adjuvants	+/- Adjuvants

Pain Medication Arsenal

Primary Analgesics

Non-opioid

- Acetaminophen, ASA, NSAIDs

Opioid

- PRN administration of IM/IV/oral short-acting
- Regularly scheduled administration of long-acting agents
- Topical / PCA

Adjuvant analgesics

- Antidepressants
- Anticonvulsants
- Local anesthetics
- Sympatholytics
- NMDA antagonists
- Topical products
- Muscle relaxants
- Benzodiazepines

When to Consider a Trial of Opioids

- **Pain is moderate to severe**
  - Failed to adequately respond to nonopioid & nondrug interventions
- **Potential benefits are likely to outweigh risks**
  - Consider referral to pain or addiction specialist for patients where risks outweigh benefits
- No alternative therapy is likely to pose as favorable a balance of benefits to harms
- Continuous, around-the-clock opioid analgesic is needed for an extended period of time

Assess for Risk of Abuse: Including Substance Use & Psychiatric History

- **Current & past substance misuse**
  - Prescription drugs
  - Illegal substances
  - Alcohol & tobacco
    - Substance abuse History does not prohibit treatment with opioids and will require additional monitoring & expert consultation/referral
  - Family history of substance abuse & psychiatric disorders
  - History of sexual abuse
- Social history also relevant
  - Employment, cultural background, social network, marital history, legal history, & other behavioral patterns

Relevent Medical History

- Potential problems with opioids
  - Pulmonary disease, constipation, nausea, cognitive impairmen
  - Cardiac disease
- Diseases associated with prior use
  - Hepatic, renal disease
    - Hepatitis
  - HIV, Tuberculosis, STDs, Staph infections
  - Cellulitis,Trauma, Burns

Adequately DOCUMENT all patient interactions, assessments, test results, & treatment plans

Case Study – New Patient (5 PM on a Friday)

John

31 year old male with chronic pain

Choosing an opioid

- **Type of Pain being treated**
  - Acute vs chronic
  - Severe vs moderate
  - Strong vs weak opioid (ceiling effect)
- **Duration and onset of action**
  - "Rate hypothesis"
    - fast on, fast off – most addicting
  - PRN vs Scheduled
  - Frequency of dosing
  - Potential pill burden

Choosing an opioid

- **Patient's prior experience**
  - differences in opioid responsiveness
  - Pharmacokinetic variability
- **Route of administration**
- **Side effects**
- **Cost**
- **Potential for abuse by patient**
  - Past history
  - Others who may have access
- There are **NO** abuse-resistant opioids or opioid formulations – only "tamper-resistant"!!

Initiating Treatment

- **Consider initial treatment as a "therapeutic trial"**
  - May last from several wks to several months
  - Decision to proceed w/ long-term treatment should be intentional & based on careful consideration of outcomes during the trial
    - Progress toward meeting therapeutic goals
    - Presence of opioid-related AEs
    - Changes in underlying pain condition
    - Changes in psychiatric or medical comorbidities
    - Identification of aberrant drug-related behavior, addiction, or diversion

Patient-Prescriber Agreement (PPA)

- Document signed by both patient & prescriber at time an opioid is prescribed
- Clarify treatment plan & goals of treatment w/ patient, patient's family, & other clinicians involved in patient's care
- Assist in patient education
- Inform patients about the risks & benefits
- Document patient & prescriber responsibilities

Patient-Prescriber Agreement (PPA)

- Obtain opioids from a single prescriber
- Fill opioid prescriptions at a designated pharmacy
- Safeguard opioids
  - Proper storage – no sharing / selling
- Instructions for disposal when no longer needed
- Commitments to return for follow-up visits
- Comply w/ appropriate monitoring
  - E.g., random UDT & pill counts
- Frequency of prescriptions
- Discuss behaviors that may lead to opioid d/c
- Exit strategy

Opioids: Important Clinical Points

- **Titration**
  - Increase dose 25 – 50% for mild to moderate
  - Increase dose 50 – 100% for moderate to severe
- **Tolerance**
  - Patients actively abusing heroin or prescription opioids generally have pharmacologic tolerance
    - May need to start at higher doses with shorter intervals
  - Have a plan for long-term patients for rotation

Monitor Patients During Opioid Therapy

- Therapeutic risks & benefits do not remain static
- Identify patients:
  - Who are benefiting from opioid therapy
  - Who might benefit more w/ restructuring of treatment or receiving additional services (e.g., addiction treatment)
  - Whose benefits from treatment are outweighed by risks
  - Periodically assess continued need for opioid analgesic
  - Re-evaluate underlying medical condition if clinical presentation changes

Monitor Patients During Opioid Therapy

- **Periodically evaluate:**
  - **Pain control**
    - Document pain intensity, pattern, & effects
  - **Functional outcomes**
    - Document level of functioning
    - Assess progress toward achieving therapeutic goals
  - Health-related QOL
  - SE frequency & intensity
  - Adherence to prescribed therapies

Monitor Patients During Opioid Therapy

- Patients requiring more frequent monitoring:
  - Patients taking high opioid doses
  - **High-risk patients**
    - **Patients at risk for abuse**
      - Consider Urine Drug Testing (UDT)
      - Point-of-Care - quick but not as sensitive or encompassing
      - Can send to labs for more confirmatory
    - **Patients with comorbid conditions, etc**

Side Effects & Management

- **Constipation**: Scheduled, stepped program
  - *Docusate 100mg* + **Senna** then Lactulose, etc
  - Relistor (methylnaltrexone)
    - Blocks gut opioid receptors - doesn't cross BBB
    - Expensive / SC admin
- **Nausea & vomiting**
  - Compazine, reglan, promethazine, atarax, etc
- **Sedation & mental clouding**
  - Dose reduction or increase CNS stimulants
    - Caffeine, methylphenidate, dextroamphetamine, provigil

Side Effect Management

- **Pruritis**
  - Opioids can cause release of histamine from mast cells
  - Histamine related – antihistamine
  - Centrally mediated μ effect – small doses of antagonists
- **Subacute overdose: Most common**
  - Slow progression (hrs-days) somnolence & respiratory depression
  - Withhold 1-2 doses, until symptoms resolve, then reduce standing dose by 25%

Drug Interactions

- MAOIs may increase respiratory depression
- Certain opioids (methadone, tapentadol, meperidine, tramadol) are serotonin-enhancing – serotonin syndrome
- Opioids may reduce efficacy of diuretics
  - Inducing release of antidiuretic hormone
- Methadone & buprenorphine can prolong QTc interval
- Drugs that inhibit or induce CYP enzymes can increase or lower blood levels of some opioids
  - Methadone, oxycodone CYP3A4

Drug Interactions

- Concurrent use w/ other CNS depressants can increase risk of respiratory depression, hypotension, profound sedation, or coma
  - Reduce initial dose of one or both agents
- Partial agonists & mixed agonist/antagonist analgesics† may reduce analgesic effect or precipitate withdrawal
  - Avoid concurrent use
- May enhance neuromuscular blocking action of skeletal muscle relaxants & increase respiratory depression
- Concurrent use w/ anticholinergic medication increases risk of urinary retention & severe constipation
  - May lead to paralytic ileus

Worsening Pain or Opioid-induced?

- **Undertreatment** of preexisting pain or development of pharmacologic **tolerance** may be overcome by a trial of opioid dose escalation.
- In contrast, opioid-induced pain could be worsened by an increase in opioid dose.
- Opioid-induced hyperalgesia will improve after supervised opioid tapering or by switching to other opioid

Treating OIH

- Hyperalgesia may likely worsen early in the discontinuation process.
- Switching from one structural class of opioids to another has been an effective option for mitigating OIH in some studies.
- OIH is more strongly associated with opioids from the phenanthrene class
  - Natural and semisynthetic opioids
  - Exceptiom - not been demonstrated in trials involving oxymorphone

Extended-Release / Long-Acting ER/LA Opioids: Benefits and Concerns

Benefits	Concerns
• Lower pill burden • Less frequent administration • More continuous analgesia	• Greater likelihood of abuse • Improper use significantly increases risk of morbidity and/or mortality

July 2012, FDA approved a Risk Evaluation and Mitigation Strategy (REMS) for extended-release (ER) and long-acting (LA) opioid medications.

CO*RE: Collaborative for REMS Education

CO*RE: Collaborative for REMS Education

- **Education regarding appropriate prescribing practices & patient education when using ER/LA opioids**
  - Patients assessment for treatment w/ ER/LA opioids
  - Initiation of therapy, dose modification & discontinuation
  - Managing ongoing therapy w/ ER/LA opioids
  - Patient and caregiver counseling regarding safe use of ER/LA opioids, including proper storage & disposal
  - Increase awarness of product-specific drug information concerning ER/LA opioids

Initiating & Titrating (ER/LA drugs): Opioid-Naive Patients

- **Drug & dose selection is critical**
  - Some ER/LA opioids or dosage forms only for **opioid-tolerant** patients
    - Check individual drug Packaged Insert
- **Monitor patients closely for respiratory depression**
  - Especially within 24-72 h of initiating therapy & after dose increase
- **Individualize dosage by titration based on efficacy, tolerability, & presence of AEs**
  - Check ER/LA opioid product PI for minimum titration intervals
  - Supplement w/ IR analgesics (opioids & nonopioid) if pain is not controlled during titration

Initiating (ER/LA): Opioid-Tolerant Patients

- If opioid tolerant—no restrictions on which products can be used
  - Patients considered opioid tolerant are taking at least
    - 60 mg oral morphine/day
    - 25 mcg transdermal fentanyl/hr
    - 30 mg oral oxycodone/day
    - 8 mg oral hydromorphone/day
    - 25 mg oral oxymorphone/day

    } For 1 wk or longer
    - An equianalgesic dose of another opioid
  - Still requires caution when rotating a patient on a IR opioid to a different ER/LA opioid

ER/LA opioids

Counsel Patients About Proper Use

- Product-specific information about the prescribed ER/LA
- How to take the ER/LA opioid as prescribed
- Importance of adherence to dosing regimen, handling missed doses, & contacting their prescriber if pain cannot be controlled

Instruct patients / caregivers to:

- Read ER/LA opioid **Medication Guide** received from pharmacy every time an ER/LA opioid is dispensed
- At every medical visit explain all medications they take

ER/LA Opioid-Induced Respiratory Depression

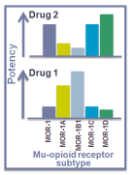
- **More likely to occur**
  - In elderly, cachectic, or debilitated patients
  - **Contraindicated** in patients w/ respiratory depression or with other drugs that depress respiration
- **Reduce risk**
  - Proper dosing & titration are essential
  - **Do not overestimate** dose when converting from another opioid product - Can result in fatal overdose w/ first dose
  - Instruct patients to swallow tablets/capsules whole
    - Dose from cut, crushed, dissolved, or chewed tablets/capsules may be fatal, particularly in opioid-naïve individuals

Opioid Rotation

- **Poor opioid responsiveness**
  - Dose titration yields intolerable/unmanageable AEs
  - Poor analgesic efficacy despite dose titration
- **Other potential reasons**
  - Patient desire or need to try a new formulation
  - Cost or insurance issues
  - Adherence issues
  - Concern about abuse or diversion
  - Change in clinical status requires an opioid w/ different PK
  - Problematic drug-drug interactions

Opioid Rotation

- **Rationale**
  Differences in pharmacologic or other effects make it likely that a switch will improve outcomes
  Effectiveness & AEs of different opioids vary among pts



- Patients show incomplete cross-tolerance to new opioid
- Patient tolerant to 1st opioid can have improved analgesia from 2nd opioid at a dose lower than calculated from an EDT

Equianalgesic Dose Tables (EDT)

- **Many different versions**:
  - Published, Online (± interactive), cell-phone apps
- **Vary in terms of -**
  - **Equianalgesic values**
    - Fixed dose vs ranges
  - **Which opioids included**
    - May or may not include transdermal opioids, rapid-onset fentanyl, ER/LA opioids, or opioid agonist-antagonists

Limitations of EDTs

- Single-dose potency studies using a specific route, conducted in patients w/ limited opioid exposure
- Does not consider
  - Chronic dosing / high doses / different routes
  - Different pain types
  - Comorbidities or organ dysfunction
  - Gender, ethnicity, advanced age, or other medications
  - Direction of switch from 1 opioid to another
  - Interpatient variability in response to opioids
  - Incomplete cross-tolerance among mu opioids

Example of an EDT

Drug	Oral	Parenteral
Morphine	30 mg	10 mg
Oxycodone	20 mg	NA
Hydrocodone	20 mg	NA
Hydromorphone	7.5 mg	1.5 mg
Oxymorphone	10 mg	1 mg

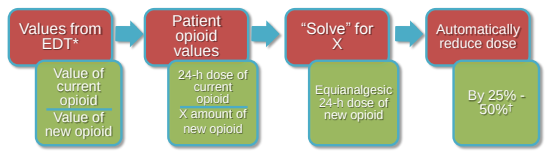
Guidelines for Opioid Rotation

Calculate equianalgesic dose of new opioid from EDT

- Reduce calculated equianalgesic dose by 25%-50%*
  - **Select % reduction based on clinical judgment**
    - Closer to 50% reduction if patient is
      - Receiving relatively high dose of current opioid regimen
      - Elderly or medically frail
    - Closer to 25% reduction if patient
      - Does not have these characteristics
      - Switching to different route (administration) of same drug

***75%-90% reduction for methadone**

Guideline for Opioid Rotation:



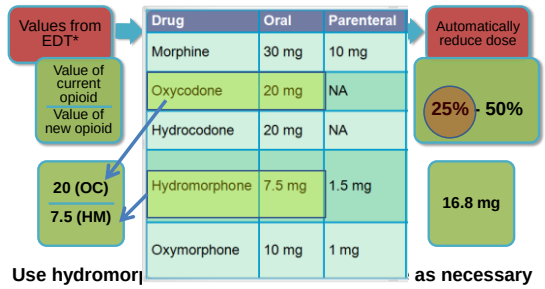
- Frequently assess initial response
- Titrate dose of new opioid to optimize outcomes

Case Study – Opioid Rotation Dose Calculations

Shirley

65 year old female with ovarian cancer and chronic pain

Oxycodone ➡ Hydromorphone



Use hydromor… as necessary

If supplemental rescue dose require calculate at 5%-15% of total daily dose

Guidelines for Opioid Rotation

- **If switching to methadone**
  - Reduce calculated equianalgesic dose by **75%-90%**
  - Patients on very high opioid doses (eg, ≥1,000 mg morphine equivalents/d), be cautious converting to methadone ≥100 mg/d
    - Consider inpatient monitoring, including serial EKG monitoring
- **If switching to transdermal**
  - **fentanyl**, calculate dose conversion based on equianalgesic dose ratios included in the Packaged Insert
  - **buprenorphine**, follow instructions in the PI

Opioid Discontinuation

- Taper dose to avoid withdrawal symptoms in opioid dependent patient
- Recommend outpatient setting for patients without severe medical or psychiatric comorbidities
- Recommend rehabilitation setting for patients unable to reduce opioid dose in less structured settings
- May use a range of approaches from slow 10% dose reduction per week to more rapid 25%-50% reduction every few days

Case Study – Opioid Discontinuation

Albert

Post Spinal Surgery
Stable on 60 mg/day oxycodone ER
Back to work

Questions?

Thanks for listening

Alan & Jody

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