Decoding Opioids: Indications for Best Practice

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Opioid Myths & Misconceptions…

- Opioids always lead to addiction
- Opioids always cause heavy sedation
- Morphine hastens death in a terminally ill pt.
- Effective pain management can be achieved with the PRN use of opioids

Addiction

- When sufficient doses are used for pain management, there are no indications that opioids lead to addiction
  (Hospice Foundation of America 2007)
- Under-treatment of pain leads to more chronic pain w/ patients requesting more or stronger drugs (pseudo-addiction)

Excessive Sedation w/ Opioids ?

- Severe pain results in exhaustion & insomnia
- Once pain is controlled w/ opioids the patient can finally rest and sleep
  - may be misinterpreted as excessive sedation due to the drug
- Once caught up on rest: - often may resume a more normal level of mental alertness & orientation while continuing opioids
- Excessive sedation may often be the result of *other drugs* in the regimen (anxiolytics, sedative-hypnotics)

Do Opioids Hasten Death in Terminally ill ?

Opioids are often temporally related to death but not causative in hospice patients
- Used at end of life for both pain and dyspnea
- Often used in the final hours for severe discomfort

- Allowing for death with minimal suffering is the objective with hospice

Effective Pain Management Can be Achieved w/ PRN Opioids

- "Around-the-clock" analgesic therapy better than PRN for chronic pain
  - improved overall pain management
  - better to blunt or prevent pain episodes
  - do not want to be "chasing" pain with PRNs
  - fewer side effects
- Objective is to titrate opioid to individual's need and continue with fixed routine dosage "around the clock" …
- Long-acting opioids help achieve this objective

Opioid Selection: Classification by potency (1)

Moderate strength opioids

(for moderate to severe pain)

- Codeine (codeine only, Tylenol w/ Codeine) C-III
- Hydrocodone (*only in combo* w/ acetaminophen or ibuprofen) (Lortab, Norco, Vicodin, Vicoprofen) C-III
- Tramadol (Ultram, Ultram ER, Ultracet) Not controlled
- Tapentadol (Nucynta, Nucynta ER) *C-II*
- Buprenorphine (Butrans patch) C-III

*Long-acting opioid

Opioid Selection: Classification by potency (2)

Strong opioids

(for severe pain only)

- Morphine (MSIR, Roxanol, MS-Contin, Avinza, Kadian)
- Oxycodone (OxyIR, Oxyfast, Oxycontin)
- Methadone (Dolophine)
- Hydromorphone (Dilaudid, Exalgo)
- Oxymorphone (Opana, Opana ER, Numorphan)
- Fentanyl (Duragesic patch, Fentora, Actiq, Onsolis, others)
- Meperidine (Demerol)

***** Long - acting opioid

Initiating Opioid Therapy in Opioid Naive Patient

- Start with *short-acting* opioids in the opioid naïve
  - titrate to effective dose
- Avoid Extended Release/Long acting drugs initially because…
  - difficult to rapidly titrate dose for adequate pain control
  - may easily over-shoot the therapeutic window
  - impact of excessive dosage may be profound and long-lasting …difficult to reverse
  - may start L-A opioids after pt. is no longer opioid naïve (*Conservative R.O.T.* - OME of 60mg/day or more for 5 days)

Examples of starting doses: Opioid Naive

- **Moderate strength opioids:**
  - Hydrocodone 5-10mg Q4h prn (Vicodin, Norco, Lortab)
  - Codeine 30 – 60mg Q4h prn (Tylenol w/ Codeine)
  - Tramadol 50 -100mg Q6h prn (Ultram, Ultracet)
- **Strong opioids:**
  - Morphine 5 -10mg (MSIR, Roxanol) PO Q 2 - 4h prn
  - Oxycodone 5mg (OxyIR, Oxyfast) PO Q 2 - 4h prn
  - Hydromorphone 2mg (Dilaudid) PO Q 2 - 4h prn
- Titrate dose to control pain / minimize side effects

Is there a maximum ceiling dose for opioids ??

For most opioids in general : No.

-Titrate dose gradually based upon pain control & emergence of side effects.

- LD-50 increases as therapeutic dose requirement increases

Specific Drug Limitations:

Combination drugs with *Acetaminophen*: max of 4,000mg/day)
- liver toxicity

Tramadol (Ultram) max: 400mg/day (300mg/day for patients 75 yr and up)
- increased seizure risk

Tapentadol (Nucynta) max: 500mg/day
- increased seizure risk

Buprenorphine (Butrans patch) max: 20mcg/hr patch
- cardiac toxicity (prolonged QTc interval)

Methadone oral max: 200mg/day , 300mg/day ??
- cardiac toxicity (prolonged QTc interval)

When, how, & why start a Long-Acting opioid ?

When: After pt is opioid tolerant (no longer opioid naïve)

How: - Determine average total daily S-A opioid dose
- Initiate the equivalent daily dose of L-A opioid
- Continue w/ S-A opioid for PRN needs only

Why: - *prevention* of persistent pain (instead of *"chasing"* pain with "prn" doses)
- provide steady baseline level of analgesic drug
- reduced side-effects associated w/ "peak" levels
- reduce total number of doses per day
- enhance patient compliance and convenience

Long – acting strong opioids

Drug	Usual Dosage interval
Morphine ER oral (Avinza, Kadian, MS-Contin)	12-24h
Oxycodone ER oral (OxyContin)	12h
Oxymorphone ER oral (Opana ER)	12h
Methadone oral (Dolophine)	12h
Hydromorphone (Exalgo)	24h
Fentanyl transdermal (Duragesic patch)	72h

How soon can the LA opioid dose be increased ?

Minimum interval to reach steady-state level :

Fentanyl patch	initial increase in 3 days, then every 6 days
Methadone	every 5 days
Morphine ER	every 2 days
Oxycodone ER	every 2 days

Dose should not be increased more frequently than above time frames

Cost Comparison: Long-acting Opioids

Cost of a 15 day supply of equivalent doses (based on AWP) :

Dosage:	Cost:
Oxycontin 80mg Q12h	$420.00
Opana ER 40mg Q12h	$400.00
Fentanyl Patch 100mcg Q72h	$185.00
Morphine ER tablet 100mg Q12h	$110.00
- Avinza *capsule* 240mg Q24h	$210.00
- Kadian *capsule* 200mg Q24h	$190.00
Methadone 10mg Q12h	$12.00

When to increase the L-A opioid dose and by how much ?

- When 3 or more PRN doses are required in 24hr for BTP ?
- Goal is prevention of pain vs "chasing" pain with PRNs
- Increase by equivalent amount of prn opioid used in prior 24hr
- Always have a short-acting opioid order for BTP

- Think in *percentages* not just mg:
  - Dose increases < 25% are often NOT noticed by the patient
  - ***Example:***
    Patient on Morphine ER 100mg Q12h is still c/o significant pain
    - an increase of 30 to 40mg/day may not have a significant impact
    - appropriate minimum increase would be 60mg (130mg Q12h)

- Don't forget to increase the PRN opioid dose accordingly

How do we determine the appropriate PRN dose ?

- PRN dose = 10% - 15% of total daily routine opioid dose

  Ex: MSER (MS-Contin) 100mg Q12h (total daily dose: 200mg)
  PRN dose: MSIR or Roxanol 20mg

- PRN Morphine oral interval ? :
  - for initial titration (*orally*) in severe pain *or* in pain crisis:
    Q1-2hr prn
  - for other breakthrough pain (BTP) in stable patient: Q4h prn
  - above interval appropriate for:
    morphine, oxycodone, hydromorphone
    (not applicable to fentanyl transmucosal products)

Fentanyl Transmucosal products for BTP

Rapid onset short-acting opioids (onset w/in minutes; peak at 20 min; duration 4h)
Only for opioid tolerant patients also taking regular routine opioid therapy
Absorbed through oral or nasal mucosa – ability to swallow not required.

Cost prohibitive for most hospices

- Fentanyl buccal lozenge: Fentora
- Fentanyl lollipop: Actiq
- Fentanyl buccal soluable film: Onsolis
- Fentanyl sublingual tablets: Abstral
- Fentanyl sublingual oral spray: Subsys
- Fentanyl nasal spray: Lazanda

Each product has strict guidelines for initiating therapy per manufacturer
Effective dose must be determined by titration (not predictable from usage of other opioids)
Products are *NOT* interchangable on a mcg per mcg equivalancy

Transmucosal Immediate Release Fentanyl REMS

REMS: Risk Evaluation and Mitigation Strategy (FDA mandate)

TIRF REMS Access Program (www.TIRFREMSaccess.com)

Goal of program: Reduce risks for misuse, abuse, over-dosage. Ensure safe use & access to these drugs for patients who need them

Physicians & Pharmacies/Pharmacists: Must enroll in the TIRF access program, review an education program, and complete a test.

Patients: Must sign a Patient-Prescriber Agreement

Avoid Meperidine in Chronic Pain Management

Meperidine (Demerol)

- Not recommended for chronic pain management in palliative care
- Weak analgesic by the oral route:
  (Meperidine oral 300mg = Morphine oral 30mg)
- IV/IM meperidine is 4X more potent than meperidine po
- Only appropriate for short-term use (i.e. immediate post-op)
- Toxic metabolite (nor-meperidine)
  - accumulates in renal impairment or repetative high doses
  - associated with seizures

Morphine – notes

- Gold standard: all opioids are measured against morphine
- Wide range of dosage forms (suppository, oral IR, oral ER, oral soln, injection)
- Renal excretion (active metabolites) - use caution in renal failure patients
- Kadian, Avinza: - once-a-day oral dosage forms
  - *expensive (brand only)*
  - capsules can be opened for patients who cannot swallow pills (sprinkle over applesauce, or place in 10ml water for G-tube)
- Morphine ER tabs (MS Contin) can be effectively administered rectally*
  * J. Pain & Symptom Manag. 1992; 7:400
- Has active metabolites that contribute to both potency and adverse effects

Morphine Active Metabolites:

Morphine-6-glucuronide & Morphine-3-glucuronide

- Two active metabolites of Morphine
- Both accumulate with renal impairment or with relatively high doses
- Morphine-6-glucuronide: Twice the analgesic potency of Morphine
- Morphine -3-glucuronide: Cause of neurotoxicity
  - myoclonus
  - mental status changes
  - allodynia
  - hyperalgesia

Reference: Anderson, et al. (2003) J. Pain & Symptom Management

Alternative: Methadone

Hydromorphone - notes

- Oral dosage form 4X more potent than oral morphine;
  IV dosage-form 20X more potent than oral morphine
- Variety of dosage forms (oral IR, oral ER, suppository, injection)
- Generics available for Dilaudid PO short acting - inexpensive
- Long acting form: Exalgo sustained release (Q24h) –very expensive
- Renal excretion & drug metabolites –use caution in renal patients
  (same issues as w/ morphine)
- Use for continuous IV infusion when high potency opioid is required

Oxycodone - notes

- Oral dosage form 1.5 x more potent than oral morphine
- Only oral dosage forms available
  - oral solution - Oxyfast
  - immediate release tablets (short acting) - OxyIR, Percocet (w/ APAP)
  - extended release tablets (long acting) - OxyContin
- Possible advantages over morphine ?
  - Less itching than morphine – less histamine release
  - Less nausea ?
- Single source brand: Oxycontin
  (generics are phased out -***very expensive***)

Oxymorphone - notes

- Available as:
  - oral tablets: Opana (immediate release) or Opana-ER
  - suppositories or injection: Numorphan
- Oral form is 3X more potent than oral morphine
- No clear advantage over morphine ?
- Expensive - brand only

Fentanyl Patch – notes

- Fentanyl patch 50mcg/hr approx. equivalent to oral morphine 100mg/day
- May be over-used in patients who can take oral medication
- Usually dosed Q 72 hr (some may need Q48h)
- Drug reservoir is in the skin, not just the patch
  - drug continues to be absorbed 12 hr after patch removed
- Conversely: if converting ***to*** the patch, continue previous opioid dose for 12hr after application of initial patch (slow onset)
- Drug absorption & release into systemic circulation will vary with:
  - amount of subcutaneous fat (problematic in cachexia)
  - skin condition (i.e. aging changes, atrophy)
  - body temperature (problematic in febrile pts)
  - non-intact skin (cuts, abrasions, dermatitis)

Tramadol (Ultram, Ultracet) - notes

- Moderate potency: Tramadol 100mg = Morphine oral 10mg
- Dual action: - Mild inhibitor of serotonin, & norepinephrine reuptake (CNS)
  - mu opioid agonist
- Beneficial for moderate neuropathic pain (due to SSRI/SNRI activity)
- Seizure risk when exceeding maximum dosage (400mg/day adults; 300mg/day geriatrics)
- Often tolerated better than Tylenol w/ Codeine and Vicodin
- Inexpensive
- Interaction with SSRI/SNRI antidepressants - Serotonin Syndrome (Prozac, Paxil, Celexa, Lexapro, Zoloft, Effexor, Cybalta)

Tapentadol (Nucynta) - notes

- Moderate potency: Tapentadol 50mg = 10mg oral morphine
- Dual mechanism of action (similar to Tramadol , but more potent)
  - *mu* opioid agonist similar to other opioids
  - significant norepinephrine re-uptake inhibition (SNRI)
- May have a role in moderate to severe neuropathic pain
- Dose range:
  IR: 50-100mg Q4-6h prn ER: 100mg - 250mg Q12h
- Expensive
- Interaction potential: Same as listed for Tramadol

Butrans Patch – notes

- Buprenorphine patch 20mcg/hr = 50mg oral morphine/day
- Indicated for moderate to severe pain
- Patch is changed *every 7 days*
- Available as 5mcg/hr, 10mcg/hr, & 20mcg/hr strengths
- Max dose: 20mcg/hr patch (risk for cardiac toxicity w/ higher dose)
- Expensive

Methadone - notes

- Oral methadone is 5 – 20X more potent than oral morphine depending upon dosage
- Dosage forms:
  -oral solution, oral tablets, injection
- Onset of action orally = 30min
- Duration of action (bi-phasic nature)
  - with initial therapy 4 hours
  - upon continuous chronic therapy 8 – 12hr
- Very cheap !

Methadone Advantages

- Long-acting opioid w/ unique characteristics:
  - a naturally long acting opioid, not sustained release tab – tabs can be crushed
  - oral solution is long-acting as well
  - good L-A opioid for patients that can't swallow
- Effectively absorbed via sublingual route
- NMDA receptor antagonist (effective for neuropathic pain)
  - only opioid with this activity
- No active metabolites & no renal excretion
  - good alternative to morphine or hydromorphone for opioid neurotoxicity
- Very inexpensive

Methadone dosage forms

- Tablets: 5mg or 10mg
  (40mg tablets are restricted to hospitals or detox clinics)
- Oral solutions:
  5mg/5ml, 10mg/5ml, 10mg/ml (oral concentrate)
- Solution for injection
- May be compounded into suppository form

Opioid Conversion / Rotation ?

- Why do it:
  - lack of adequate pain control on current opioid
  - intolerable adverse effects or allergy
  - loss of swallowing ability
  - renal impairment
  - acetaminophen limitation
  - formulary or cost control issues
- Use equi-analgesic conversion chart as a guide *(next slide)*
- Temper results from the guide based upon pt. variables
  - current level of pain control
  - how aggressive the pain-control intervention should be
  - patient history of susceptibility of to side effects

Equi-analgesic Opioid Conversion Chart

Drug	Oral Dose	Parenteral Dose
Morphine	30mg	10mg
Hydromorphone	7.5mg	1.5mg
Oxycodone	20mg	n/a
Methadone	See methadone guidelines	
Hydrocodone	30mg	n/a
Codeine	200mg	n/a
Tramadol	150mg	n/a
Meperidine	300mg	75mg
Fentanyl Patch	25mcg *topical patch* = 50mg Oral Morphine/day	

Adjustments to Opioid Conversion Chart Results ?

- Opioid tolerance develops with chronic therapy
- There are differences in the level of cross-tolerance among opioids
- Equi-analgesic charts may not account for differences in tolerance
- Should adjustments be made to results from equi-analgesic chart ??
- Numerous schools of thought & expert opinion

- Many experts follow this guidance…
  1) If pain is well controlled on current opioid: reduce new by 50%
  2) If pain somewhat controlled: reduce new by 25%
  3) If pain not controlled: no adjustment to result from the chart

EQUI-ANALGESIC ORAL MORPHINE EQUIVALENT (OME) CHART

Opioid drug	Multiply current opioid dose by this factor to equal Oral Morphine Equivalent dose (OME)
Hydromorphone oral	4
Hydromorphone IV, IM, SC	20
Oxycodone	1.5
Morphine IV, IM, SC	3
Hydrocodone	1
Codeine	0.15
Tramadol	0.1
Buprenorphine patch	10mcg/hr patch is equivalent to 25mg oral morphine/day
Fentanyl patch	25mcg/hr patch is equivalent to 50mg oral morphine /day
Methadone	See morphine to methadone guidelines (next slide)

Morphine to Methadone Conversion Chart

Converting to Methadone
Outcome Resources Conversion Guide

Total Daily Oral Morphine Dose	Morphine to Methadone Ratio
<100mg	5:1
101-750mg	10:1
751-1500mg	12:1
>1500mg	15:1

Adapted from MD Anderson Cancer Center guidelines, Ayonrinde and Bridge (Med J Aust 2000), and Ripamonti (Cancer Pain & Palliative Care 1999)

Questions

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Contact me for a copy of these slides:

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