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# Equianalgesic Dosing

## It's not just about the math

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# Objectives

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- ❖ Discuss the difference of route conversion and opioid rotation
- ❖ Discuss when it is appropriate to rotate and/or convert an opioid
- ❖ List 3 considerations when determining an opioid dose

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# Equianalgesic Dose Definitions

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- ❖ Equianalgesic dose - Defined “as that dose at which two opioids (at steady state) provide approximately the same pain relief.” (Shaheen, Walsh, Lasheen, Davis, & Lagman, 2009)
  - ❖ Usually standardized to 10mg of parenteral morphine
- ❖ Route conversion - same opioid but different route
  - ❖ Oral morphine to IV morphine
- ❖ Opioid rotation - different opioid but same route
  - ❖ Oral oxycodone to PO hydromorphone
- ❖ Potency “refers to the power of a medicinal agent to generate its desired outcome, the dose required to produce a given effect.” (Anderson, Saiers, Abram, & Schlicht, 2000)

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# Equianalgesic Dose Definitions

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- ❖ Incomplete cross-tolerance - refers to the development of tolerance to the effects of other structurally similar drugs in the same pharmacologic class after long term exposure. This effect is rarely complete in opioids. Complete cross tolerance can develop as evidenced by the lack of analgesic effect.
- ❖ Bidirectional conversions -- the conversion ratio will change depending on the direction of the conversion. (eg. morphine to methadone versus methadone to morphine)
- ❖ Opiate--narcotic analgesic derived from a opium poppy, not synthetic, eg. heroin
- ❖ Opioid--narcotic analgesic derived at least in part synthetically, eg. Oxycontin

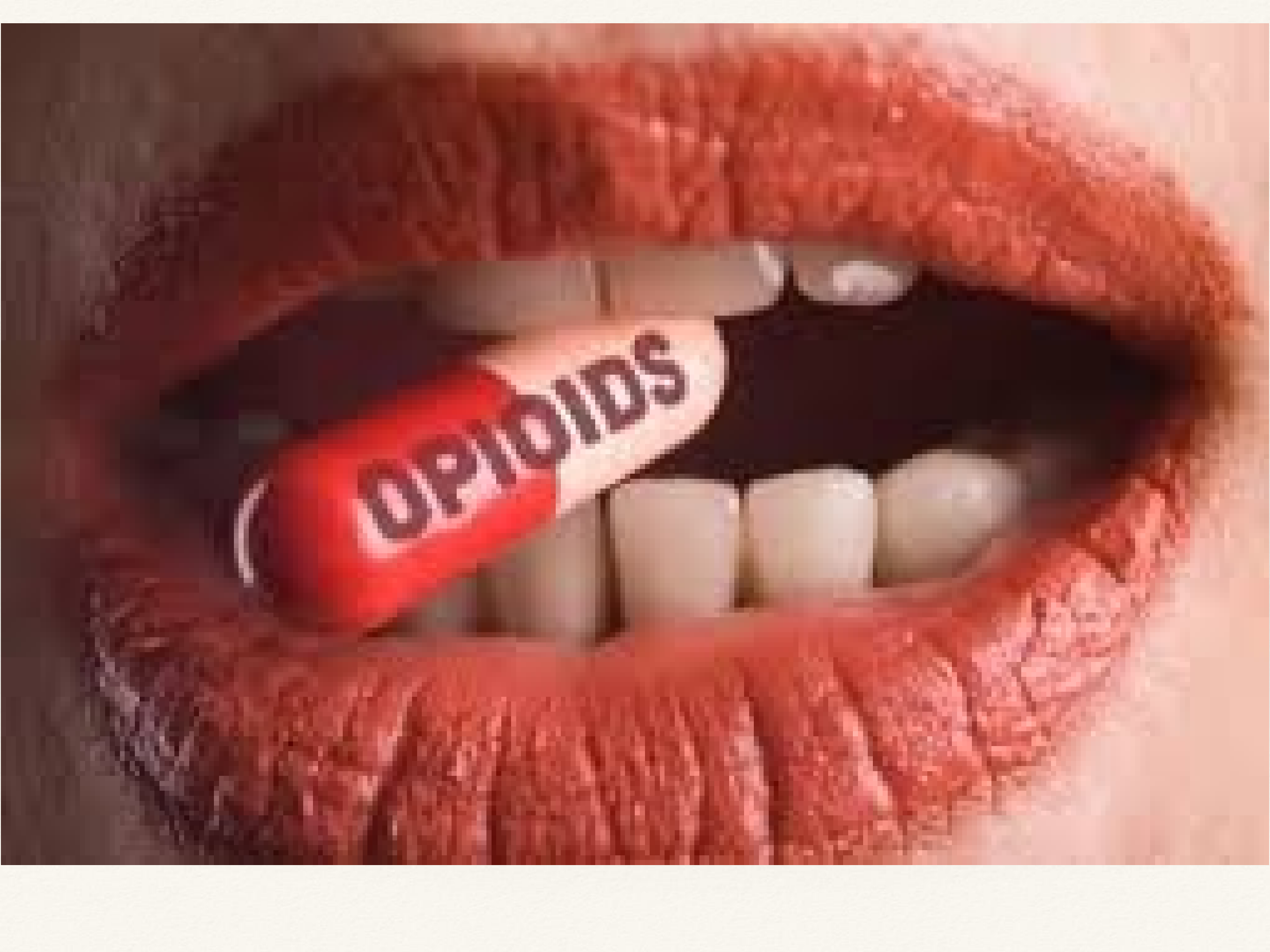


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# Opioids are Tricky

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- ❖ Opioids do not have a ceiling effect nor uniform therapeutic plasma levels
- ❖ Acceptable practice is to titrate to effect
- ❖ Titration is often limited by opioid induced side effects, constipation, respiratory depression or neurological problems
- ❖ Furthermore, inappropriate application of a conversion table can result in poor pain control, excessive side effects and death from respiratory depression



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# Equianalgesic Tables

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- ❖ Shaheen, et al., 2009 searched the available equianalgesic tables from the PDR (online reference), available teaching material provided by pharmaceutical companies and online resources designed to assist in opioid rotation and conversion.
- ❖ What they found - widely variable route conversion ratios
- ❖ For example the conversion ratios of oral to parenteral morphine ranged from 3:1 to 2:1 to 6:1.
- ❖ Oral to parenteral hydromorphone varied from 2:1 to 5:1



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# Study

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- ❖ Most tables use 3:1 (a factor of 3) when converting IV morphine to oral oxycontin
- ❖ Ginsberg, B. MB, Bch, et al.; conducted a study of 139 patients with abdominal, orthopedic and gynecologic surgeries.
- ❖ Pts were converted from IV PCA to ER Oxycodone with IR Oxycodone, adjuvants as needed
- ❖ They used 1:2 conversion factor

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# Study

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- ❖ The reduction in pain scores from baseline was statistically significant for the abdominal surgery subgroup and for all surgeries combined.
- ❖ The factor of 3 previously reported was consistent with a previous thoracic/abdominal post-operative pain study. Where it might be expected that patients require large doses of oxycodone as they may experience longer periods of rest and effort-dependent pain.
- ❖ They concluded that the 3:1 ratio was more generally acceptable for chronic pain patients and is probably too high for acute post-surgical patient when pain was expected to decrease daily.



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# Equianalgesic Tables

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- ❖ No equianalgesic table can fully address all clinical factors that influence opioid pharmacology
- ❖ Most of the tables are derived from single-dose studies, expert opinion and studies in noncancer patients
- ❖ Designing a study to adequately address all variables that influence equianalgesia would be extremely difficult if not impossible

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# Equianalgesic Tables

## The Pitfalls

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- ❖ Failure to standardize a reference opioid (usually morphine)
- ❖ Failure to address bidirectional differences
- ❖ Inclusion of a wide range of doses in equianalgesic comparison
  - ❖ results in confusion and inaccuracy
- ❖ Use of equianalgesic tables as references for other tables
- ❖ Equianalgesic dosing between short and long-acting opioids not at steady state



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# Equianalgesic Dosing Pitfalls

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- ❖ Studies used single dose short acting
  - ❖ this may limit the applicability of repetitive administration
- ❖ Use of computations instead of clinical trial to determine equianalgesic ratios
- ❖ Equianalgesia between opioid formulations and opioid/adjuvant combinations (adjuvant contributes to pain relief)

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# Equianalgesic Tables

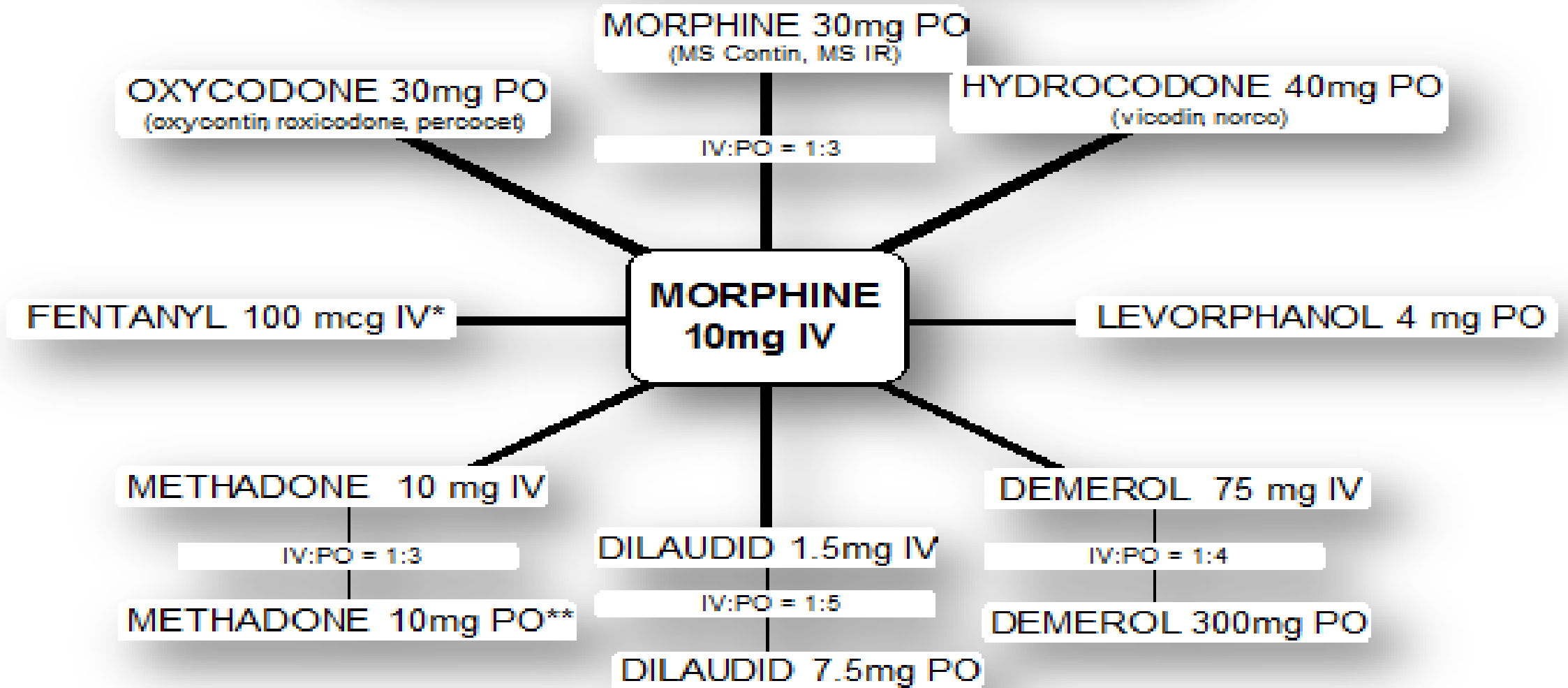
## What's not addressed

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- ❖ Gender difference
- ❖ Organ dysfunction
- ❖ Bidirectional differences with certain opioids
- ❖ Drug interactions
- ❖ Individual differences in pharmacokinetics and pharmacodynamics
- ❖ Incomplete cross-tolerance



**Narcotics Conversion Tool –**  
For opiates frequently used on the Acute Pain service\*



\*This chart does not replace clinical decision-making. Use caution when dosing for elderly patients or patients with severe hepatic or renal disease.

\*\*Methadone IV:PO ratio of 1:1 does not hold at higher doses (>100mg IV).

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## Opioid Conversion Table Instructions

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- ❖ Convert all IV medications to IV morphine
- ❖ Convert IV morphine to PO morphine
  - ❖ 1:3 respectively
- ❖ There is limited conversion data
- ❖ 60mg of po morphine = 25mcg transdermal fentanyl patch
- ❖ When converting short acting to long acting, take 50% of totally daily dose of short acting and add into long acting



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# Equianalgesic Dosing

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- ❖ While there are no evidence based recommendations for appropriate reduction when converting from one opioid to another...
- ❖ The American Pain Society guidelines and most pain experts recommend dose reduction between 25-50% when converting between different opioids
- ❖ For poorly controlled pain, give consideration for little or no cross tolerance reduction



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# Practice

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- ❖ convert 45mg of IV PCA dilaudid to PO oxycodone
  - ❖ 1.5mg IV dilaudid = 10mg IV morphine = 20mg PO oxycodone
  - ❖  $45/1.5 = 30$  doses of 1.5mg IV dilaudid
  - ❖  $30 \times 20 = 600$ mg of po oxycodone
- ❖ What are the next steps?
- ❖  $1/2$  this total = 300mg does this make sense for your patient?



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# Practice

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- ❖ Convert 60mg oxycontin BID + 20mg of oxycodone TID to a starting dose for IV dilaudid PCA.
  - ❖ 20mg PO oxycodone = 1.5mg of IV dilaudid
  - ❖  $120 + 60 = 180/20 = 9$  20mg doses of oxycodone  $\times 1.5 = 13.5\text{mg}$
  - ❖  $13.5\text{mg} / 24 \text{ hours} = 0.5\text{mg}/\text{hour}$



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# Methadone

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- ❖ Immediate release product with a 4-6 hour duration of analgesia following a single dose administration
- ❖ With chronic dosing, there can be a substantial increase in duration of action, due to accumulation in tissue
- ❖ Elimination phase half-life 15-60 hours with outliers up to 120 hours
- ❖ The long half life allows for convenient 2-3x day dosing
- ❖ Available in a liquid so can provide long-acting analgesia for patients with a feeding tube
- ❖ Also available in IV form, so can provide a long acting analgesic for patient who are NPO



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# Methadone

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- ❖ Relatively inexpensive
- ❖ Disadvantages include: unpredictable half-life and tissue accumulation can cause serious, life-threatening toxicity.
- ❖ Limited knowledge concerning titration, dose schedule and equianalgesic conversion
- ❖ As total daily dosing of morphine increases, the conversion factor decreases

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# Methadone

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- ❖ < 60mg morphine/day converts to 15mg methadone
- ❖ 60-90 mg morphine/day converts to 25% of the morphine dose
  - ❖ 16-22mg methadone
- ❖ > 100mg morphine/day converts to 16% of the morphine dose
  - ❖ 16mg methadone
  - ❖ (Anderson, Saiers, Abram, & Schlicht, 2001)
- ❖ Expert consultation is recommended when converting to methadone
  - ❖ A good starting rule is no more than 30mg/day

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# Math Practice

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- ❖ Convert MS Contin 30mg tid to IV morphine
- ❖ Convert 46mg IV dilaudid to PO dilaudid
- ❖ Convert 120mg of Oxycodone to IV dilaudid
- ❖ Some of us use the table in the previous slide, someone use an online converter, some use the table you are most familiar with



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# Answers

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- ❖ 10mg IV morphine
- ❖ 230mg PO dilaudid
- ❖ 9mg IV dilaudid
- ❖ Did we get some different answers?
- ❖ No consensus on which table is most accurate

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# The Math is Done

## Other Considerations

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- ❖ What are the indications for rotation/conversion?
- ❖ Was the current opioid given enough time to judge its efficacy?
- ❖ What are the alternatives to opioid rotation?
- ❖ Can the goals of opioid rotation be best achieved by using a different route of administration rather than a different opioid?
- ❖ Are there any factors that would interfere or change the equianalgesic dose
- ❖ Is the rotation taking place between opioids with different half-lives?

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# Other Considerations

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- ❖ Is the equianalgesic dose safe? Does it make sense for your patient?
- ❖ In the pain syndrome responsive to the new opioids or opioids at all?
- ❖ Is the patient opioid tolerant or naive?
- ❖ Rotation secondary to toxicity requires a dose 30-50% lower because of incomplete cross-tolerance
- ❖ Rotation secondary to uncontrolled pain requires equianalgesic doses



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# Opioid Tolerance

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- ❖ Tolerance is defined as a decrease in pharmacologic response following repeated or prolonged drug administration.

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# Opioid Tolerant Warning

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- ❖ Patients who are deemed opioid tolerant can still be at risk for respiratory depression
  - ❖ Benzodiazepines
  - ❖ Sleep medications
  - ❖ Undiagnosed sleep apnea
  - ❖ Antihistamines

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# Opioid Naive

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- ❖ Patients who do not take opioids regularly



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# Other Considerations

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- ❖ Is the pain expected to improve over time?
- ❖ Is the pain expected to worsen over time?
- ❖ Acute on chronic pain?
- ❖ Organ function?
- ❖ Functionality?
- ❖ Who is going to manage the medications?
- ❖ Is the pain opioid responsive?

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# Reasons to convert or rotate

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- ❖ Pt is now NPO
- ❖ Poor analgesic efficacy
- ❖ Unacceptable side effects
- ❖ Requirement for more potent opioid
  - ❖ this becomes an issue when a limited volume is required or the number of units per dose is excessive or inconvenient

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# Dosing in Renal or Hepatic Dysfunction - Morphine

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- ❖ Renal dysfunction - use cautiously, metabolites can accumulate
  - ❖ respiratory depression, somnolence, dizziness and hallucinations which can persist even after discontinuation
- ❖ adjust dose as appropriate
- ❖ Dialysis patients - use cautiously
  - ❖ likely to be removed during dialysis
  - ❖ Pt can have rebound effect - unpredictable analgesia and sedation



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# Dosing in Renal and Hepatic Dysfunction - Morphine

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- ❖ Liver dysfunction
  - ❖ in severe hepatic impairment, the parent drug may not be readily converted to metabolites
  - ❖ increase dosing interval by twice the usual time period
- ❖ In general, patients with severe liver disease should be prescribed lower doses of opioids with extended dosing intervals
- ❖ (Johnson, S.J., 2007)

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# Dosing in Renal and Hepatic Dysfunction - Oxycodone

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- ❖ Renal dysfunction - use cautiously, metabolites can accumulate causing toxic and CNS depressant effects
  - ❖ Adjust dosing as necessary
- ❖ Dialysis patient - do not use or use with caution
  - ❖ No data on oxycodone and its metabolites in dialysis
- ❖ Liver dysfunction - use cautiously, decrease initial dose by 50%
- ❖ (Johnson, S.J., 2007)

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# Hydromorphone/Hydrocodone

- ❖ Renal dysfunction - use cautiously, metabolite can accumulate causing neuro-excitatory effects
- ❖ Dialysis - use cautiously
- ❖ Severe liver impairment - use cautiously, decrease dosing by 50%



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# Dosing in Renal and Hepatic Dysfunction

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- ❖ Fentanyl appears safe for renal dysfunction and in dialysis with dose adjustments as necessary
  - ❖ dosing not generally affected in liver failure
- ❖ Methadone appears safe for renal dysfunction and in dialysis
  - ❖ not advised in severe liver failure
- ❖ Codeine, meperidine, propoxyphene are not advised for renal dysfunction, dialysis or severe liver failure

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# Dosing in Renal and Hepatic Dysfunction - Dialysis

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- ❖ the degree of clearance varies with different dialysis equipment. The filter pore size, flow rate, the efficiency of the technique used and the dialysis method. (intermittent vs continuous)
- ❖ opioid withdrawal or failure of pain control can occur

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# Putting it all together

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- ❖ Is the pain opioid responsive?
- ❖ Is the patient opioid naïve or tolerant?
- ❖ Status of renal and hepatic function
- ❖ Functionality of the patient
- ❖ Treating pain that is acute, chronic or both
  - ❖ Pain expected to improve, worsen or stay the same
- ❖ Does the dosing make sense for your patient
  - ❖ Adjust dose for incomplete cross tolerance



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# Case Studies

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- ❖ Mr. W 43 y M, takes 70mg of Oxycontin tid and 30mg q 6 hours of Oxycodone at home. Clonazepam 4mg BID. Now he is NPO s/p ex-lap, LOA and gastrostomy tube. Convert/rotate to IV.
- ❖ PMH: includes multiple abdominal surgeries, gastric outlet syndrome, generalized abdominal pain, chronic pancreatitis, depression, anxiety
- ❖ Low functioning at baseline. Spends his time in bed and watching TV. Lives with his mom.
- ❖ Patient is now tolerating PO, convert back to PO pain medications

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# Clinical decision making

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- ❖ What medication will you use?
- ❖ What will the dose be? Why?
- ❖ What adjuvants can you use while patient is NPO?
- ❖ Would you want a pain service consult?

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# Here's what we did

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- ❖ While NPO
  - ❖ IV lidocaine 1mg/kg/hour. Lidocaine levels q 8 hours. Would like to see level between 3.5-4.5 but not greater than 5. What are some s/s of anesthetic toxicity?
- ❖ IV methadone 5mg q 8
- ❖ Dilaudid PCA 1mg q 10 minutes, then 1.2mg q 10 minutes
  - ❖ Utilized between 36 -42mg IV/day
- ❖ Now convert back to PO pain meds



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# Clinical decision making

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- ❖ What medication do you want to use and why?
- ❖ What dosing?
- ❖ What are some of your concerns, considerations for making decisions about

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# Here's what we did

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- ❖ Stopped lidocaine infusion, IV methadone and PCA
- ❖ Restarted home medications, 70mg tid Oxycontin and 30mg oxycodone q 6 hours
  - ❖ (staff who had been seeing the pt was off this day)
- ❖ Do you think this was successful? Why or Why not?

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# Mr. W case study continued

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- ❖ Failed, pt was restarted on dilaudid PCA overnight
- ❖ The pt's primary pain provider is back and has a discussion with the pt. Most of the conversation is a pep talk and encouragement on how good the pt looks. The pt responds to this very well and is agreeable to having the PCA weaned while his short acting oxycodone is increased
- ❖ Oxycodone increased to 30-50mg q 3 hours prn
  - ❖ PCA lockout changed to q 20 minutes. Pt instructed to use only for emergency pain



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# Mr. W case study continued

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- ❖ Pt used the Oxycodone but also used about 40mg of IV PCA dilaudid
- ❖ PCA was stopped, oxycodone dosing was increased to 30-60mg q 3 hours prn
- ❖ Pain Service called one time overnight was a request for IV dilaudid, an extra dose of PO oxycodone was given
- ❖ Pt was discharged from our service and presumably discharged to home

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# Case Study

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- ❖ Mrs. R 72 y F, takes 60mg of MS Contin tid and 30mg of morphine immediate release 3x/day. She is no longer able to swallow and is now s/p a gastrostomy tube. Convert/rotate to long term pain medications
- ❖ What medication do you want to rotate to?
- ❖ What dose?

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# The Math

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- ❖ Using 60mg morphine = 25mcg fentanyl patch
- ❖  $180\text{mg morphine}/60 = 3$  25mcg fentanyl patches



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# Case Study

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- ❖ Pt was rotated to a 50mcg Fentanyl patch in the morning
  - ❖ Immediate release morphine was changed to elixir with same dosing (30mg morphine tid prn)
- ❖ Later that evening, pt with respiratory rate of 6-8 with 15 seconds of apnea. Observed by Pain Service staff. RNs felt that she was doing well because her oxygen saturation was 98% on oxygen
- ❖ Patch was taken off and the next morning a 25mcg patch started
- ❖ What went wrong? What would you have done differently?



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# Questions?

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