NOT YOUR MAMA'S OPIOID CONVERSION CHART! EVIDENCE-BASED OPIOID CONVERSION CALCULATIONS

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LEARNING OBJECTIVES

- Describe reasons why patients need to switch from one opioid regimen to a different opioid regimen.
- Describe recent data that evaluates switching from IV hydromorphone to oral hydromorphone, morphine or oxycodone.
- Describe recent data that evaluates the potency of hydrocodone relative to other opioids.
- Describe recent data that evaluates switching to and from transdermal fentanyl.
- Explain the "utility" of opioids and the feasibility of using utility as an "equivalent" opioid measure.

OPIOIDS CONVERSIONS, TITRATIONS, AND BREAKTHROUGH: OH MY!

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REASONS FOR CHANGING OPIOIDS

- Lack of therapeutic response
- Development of adverse effects
- Change in patient status
- Other considerations
  - Opioid/formulation availability
  - Formulary issues
  - Patient/family health care beliefs

Opioid rotation
Opioid substitution
Opioid switching
Opioid Conversion Calculation!

EQUIANALGESIC DOSING TERMINOLOGY

- Opioid responsiveness
  - The degree of analgesia achieved as the dose is titrated to an endpoint defined either by intolerable side effects or th occurrence of acceptable analgesia
- Potency
  - Intensity of the analgesic effect of a given dose
  - Dependent on access to the opioid receptor and binding affinity
- Equipotent doses = equianalgesic
- Equianalgesic Opioid Dosing

CONVERTING AMONG ROUTES: SAME OPIOID

- Bioavailability
  - The rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action
- Oral bioavailability
  - Morphine 30-40% (range 16-68%)
  - Hydromorphone 50% (29-95%)
  - Oxycodone 80%
  - Oxymorphone 10%

EQUIANALGESIC OPIOID DOSING

	Equianalgesic Doses (mg)	
Drug	Parenteral	Oral
Morphine	10	25
Codeine	100	200
Fentanyl	0.15	NA
Hydrocodone	NA	25
Hydromorphone	2	5
Meperidine	100	300
Oxycodone	10*	20
Oxymorphone	1	10
Tapentadol	NA	100
Tramadol	100*	120

*Not available in the US

Source of equianalgesic data?
Patient-specific variables?
Unidirectional vs. bidirectional equivalencies?

Reprinted with permission from McPherson ML. Demystifying opioid conversion calculations: a guide for effective dosing, 2nd ed. Bethesda: ASHP; ©2018 in press.
NOTE: Learner is STRONGLY encouraged to access original work to review all caveats and explanations pertaining to this chart.

5-STEP OCC PROCESS

1. Globally assess pain complaint (PQRSTU)
2. Determine TDD current opioid (LA and SA)
3. Decide which opioid analgesic will be used for the new agent and consult established conversion tables to determine new dose
4. Individualize dosage based on assessment information gathered in Step 1
5. Patient follow-up and continual reassessment (7-14 days)

Gammaitoni AR, et al. Clinical J Pain 2003;19:286-297

CASE 1

- WP is a 62 year old man with multiple myeloma and diffuse bony mets admitted to hospice.
- Current analgesic regimen extended-release oral morphine 30 mg po q12h plus oral morphine solution 10 mg prn (takes six times per day), plus dexamethasone.
- Admitted to inpatient to switch to IV morphine due to continued pain.
- Pain assessed
- TDD oral morphine = 30 mg po q12h = 60
- Oral morphine solution 10 mg x 6 = 60 mg
- TDD = 120 mg oral morphine
- Consult equianalgesic dosing chart for equivalency

TDD – total daily dose

CASE 1

"x" mg new opioid = equivalent mg new opioid
mg of current opioid equivalent mg current opioid

"x" mg IV morphine = 10 mg (IV morphine)
120 mg oral morphine 25 mg (oral morphine)

(x)(25) = (10)(120)
X = 48 mg IV morphine per day
25-50% increase → morphine 10 mg IV q4h (TDD 60 mg)

CASE 1 TO GO POINTS

- You're converting from morphine to morphine, BUT you're converting between routes of administration (oral to IV)
  - Morphine IV dose = ~ 1/3 of morphine PO dose
  - So, morphine IV dose is ~ 1/3 morphine PO dose (work in total daily doses for ease of calculation)

CASE 1 TO GO POINTS

- When you do a conversion calculation if you are SWITCHING from one opioid to a DIFFERENT opioid, you usually need to reduce the dose you calculated
  - This patient was going from morphine to morphine so you don't have to do that
- BUT he is in pain, so you need to increase the dose

CASE 2

- MJ is a 68 year old man admitted for total hip replacement.
- He was started on a PCA pump, hydromorphone 0.2 mg IV q10min.
- From hours 49-60 he used a total of 7.2 mg IV hydromorphone
- Convert to shorting-acting AND long-acting oral morphine (at 50% of IV requirements).

CONVERTING FROM IV HYDROMORPHONE

- Median conversion FROM IV hydromophone to oral hydromorphone was 2.5
  - Receiving < 30 mg IV hydromorphone per day:
    - 1 mg IV hydromorphone converted to 2.5 mg oral hydromorphone
  - Receiving ≥ 30 mg IV hydromorphone per day:
    - 1 mg IV hydromorphone converted to 2.1 mg oral hydromorphone

	Equianalgesic Doses (mg)	
Drug	Parenteral	Oral
Morphine	10	25
Hydromorphone	2	5

Reddy A, Vidal M, Stephen S, et al. The conversion ratio from intravenous hydromorphone to oral opioids in cancer patients. *J Pain and Sympt Manage.* 2017;54:280-288.

CONVERTING FROM IV HYDROMORPHONE

- Median conversion FROM IV hydromophone to oral morphine was 11.54
  - Receiving < 30 mg IV hydromorphone per day:
    - 1 mg IV hydromorphone converted to 11.54 mg oral morphine
  - Receiving ≥ 30 mg IV hydromorphone per day:
    - 1 mg IV hydromorphone converted to 9.86 mg oral hydromorphone

	Equianalgesic Doses (mg)	
Drug	Parenteral	Oral
Morphine	10	25
Hydromorphone	2	5

Reddy A, Vidal M, Stephen S, et al. The conversion ratio from intravenous hydromorphone to oral opioids in cancer patients. *J Pain and Sympt Manage.* 2017;54:280-288.

CASE 2

- 7.2 mg IV hydromorphone over 12 hours = 14.4 mg IV hydromorphone over 24 hours

"x" mg PO morphine = 25 mg PO morphine
14.4 mg IV HM 2 mg IV HM

- (2)(x) = (25)(14.4)
- X = 180
- Reduce by 50% - 90 mg oral morphine a day
- 90 mg/6 = 15 mg → MSIR 15 mg po q4h
- LA MS
  - 108 mg/2 → Kadian 50 mg po q12h
  - 108 mg/3 → Oramorph SR 30 mg po q8h

CASE 2 TO GO POINTS

- Going from IV to oral opioid
- This is ACUTE pain – should be getting better every day
- Consider giving as short-acting opioid
  - Unless pain expected to last a good while, then consider long-acting opioid

CASE 3

- Mr. Johnson is a 62 year old cancer pain patient who is unable to swallow tablets or oral solution.
- He refuses rectal administration of medications, and is not interested in a parenteral infusion.
- He is currently receiving Oramorph SR 30 mg po q8h with MSIR 10 mg po q3h prn (taking about 4 doses per day).
- His pain is well controlled on this regimen.
- What do you need to consider before converting him to transdermal fentanyl (TDF)?
- How do you make this conversion?

CASE 3

- Calculate total daily dose of morphine:
  - Oramorph 30 mg po q8h = 90
  - MSIR 10 mg x 4 per day = 40
  - TDD = 130 mg oral morphine
- Generally give 50% of total daily morphine dose as transdermal fentanyl
  - TDF in mcg/hour ~ 50% of oral morphine TDD
- 65 mcg – need to round up or down
  - Transdermal fentanyl 50 mcg/hour q3days
- Considerations? Timing?

From TDF to oral morphine equivalent daily dose is 2.4
(TDF 100 mcg/h ~ 240 mg MEDD)

From MEDD to TDF equivalent daily dose is 0.01
(An MEDD of 100 is equivalent to 1 mg TDF daily, or approximately 40 mcg/h)

Reddy A, Tayjasanat S, Haider A, et al. *Cancer.* 2016;122:149-156.
Reddy A, Yennurajalingam S, Reddy S, et al. *J Pain Symptom Manage.* 2016;51(6):1040-1045.

CASE 3 TO GO POINTS

- You CANNOT start transdermal fentanyl is an opioid-naïve patient (must meet FDA definition)
- If patient not on oral morphine, convert to oral morphine total daily dose
- Take 50% of oral morphine TDD and that's ~ the mcg/h TDF patch strength

CASE 4

- Mr. Jones is a 72 year old man seen in Palliative Care clinic
- Primary diagnosis is Stage 4 lung cancer
- Receiving hydrocodone/acetaminophen 10/325, every 4 hours ATC
- Physician wants to switch to oral morphine long-acting

Median opioid rotation ratio of hydrocodone to MEDD was 1.5 with hydrocodone dose < 40 mg/day
(this suggests hydrocodone is stronger than morphine; contribution of acetaminophen?)

Median opioid rotation ratio of hydrocodone to MEDD was 1.0 with hydrocodone dose ≥ 40 mg/day

Switch Mr. Jones to 60 mg oral morphine per day.

Reddy A, et al. The Oncologist 2014;19:1186-1193.

EXTREME MEDICATION ROTATIONS: WHEN EQUIVALENCE TABLES DON'T CUT IT!

DOUGLAS GOURLAY MD, MSC, FRCP(C), DFASAM

OBJECTIVES

- How do patients get onto excessively high doses of medication
  - Physician Components
  - Patient Components
- Consider the difference between "therapeutic need" vs "ability to tolerate"
- Novel agents for rotation, substitution and taper-discontinuation

HOW DO PATIENTS GET INTO THESE MESSES?

- No one rationally pushes these medications to "infinity and beyond"
  - But it has been said in the past – "full agonists have no ceiling effect…" which has been interpreted as meaning "no (dose) limit" - NONSENSE
- In fact, CNS neuroadaptation allows a patient to 'tolerate' far higher dose than they actually 'need'
  - "it takes 30 seconds to say "yes" but 30 minutes to say "no" when writing a prescription – use your time wisely!"

PATIENT FACTORS VS PRESCRIBER FACTORS

- Patient
  - Unrealistic or undefined expectations
    - Pain relief vs pain elimination
  - Chemical Cop'ers
    - Coping skills-openia
  - Unofficial-unplanned maintenance therapy
    - Opioids are clearly μ analgesics…But also serve the role (in some patients) to stabilize endogenous opioid systems
  - Financial advantage – "it's complicated!"

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PATIENT FACTORS VS PRESCRIBER FACTORS

- Prescriber
  - "the 5 D's"
    - Dated – Disabled – Duped – Dishonest – DEFIANT
  - Clinical time constraints
  - Patient expectations
  - Institutional (ie HCAPS) patient satisfaction expectations
  - Desire to 'do good'
    - Easy to say "yes" - difficult to say "no"

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CORE PRINCIPLES IN (HIGH-DOSE) ROTATIONS

- First, your plan should be:
  - Defensible
  - Rational
  - Compassionate
- Risk CAN'T be eliminated – it can only be managed!
  - "if you've got a pulse – you've got a risk"
- Therapeutic Effect is a secondary goal!

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PRACTICAL ISSUES WITH THESE PATIENTS

- What we know:
  - We know what we've advised the patient to do
  - We know what the patient is 'saying' that they're doing
  - But… what *could* the patient be doing in the worst case scenario?
    - For the most part, we have no idea about the 3rd issue
      - Uncertain opioid tolerance?
      - Impossible to even guess at equivalent dose

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PRACTICAL ISSUES:

- The assumption that the patient is using the medications 'exactly' as directed/stated can be dangerous
  - Starting doses should reflect this
    - You can always give more – but you can't take it back!
  - There is always uncertainty in terms of cross tolerance between molecules of therapeutic effect
    - Calculated equivalence with 'substantial' dose reduction for 'cross tolerance' IS NOT SAFE at these doses

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ROTATION GOALS

- Obviously, the usual goals of a rotation apply
  - Lower dose
  - Few side effects
  - Better therapeutic effect etc
- But when rotating from excessively high agonist doses, more caution is required
  - the primary short-term goals should be different: not equivalent but "sufficient"…

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ROTATION STRATEGIES

- Try not to rotate onto medications that have been problematic in the past
  - "don't do the same thing, hoping for a different outcome"
  - A new agent typically has less 'baggage' for the patient to deal with – they're aren't beaten before they start
- MANAGE EXPECTATIONS CAREFULLY

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PRACTICAL APPROACH

- 1st, incur an "agonist debt"
  - So, if the patient is on 100mg MME of hydromorphone reduce by 50% on day 1
    - While adding in the second agent
  - The goal of the second agent is NOT to eliminate pain – it is to reduce/eliminate withdrawal symptoms
    - Pain symptoms *may* increase initially – this is NORMAL
      - After we titrate the second agent to stable state (ie No evidence withdrawal), the issue of μ-analgesia can be explored later!

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WITHDRAWAL MITIGATION ROTATION

- Many patients who are on a substantially lower MME / day at the end of the rotation actually have markedly improved pain scores!
  - Clearly, high dose opioids may have been part of the problem, not the solution

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AGONIST WITHDRAWAL

- Myths
  - "if you go slowly enough, you can eliminate withdrawal"
    - Withdrawal is a delicate tension between going slowly enough to allow optimum neuroadaptation while going fast enough to avoid tedious misery
  - "withdrawal is related to agonist levels"
    - No! Withdrawal is related to the rate of change of agonist levels

AGONIST WITHDRAWAL

- So… some people easily withdraw from their agonists – others struggle
  - Higher doses/higher potency/longer exposures will *tend* to be more difficult, but not reliably so
    - A person who reduces their opioid levels by 50% easily has not demonstrated that they were diverting some/all of there drug
      - End of a taper is usually tougher than the beginning of the taper
    - w/d is a highly personal process

BEYOND EQUIANALGESIA INTO UTILITY

UTILITY

- Opioid utility function introduced by the Leiden group in 2013
- The opioid crisis and increasing deaths(which are largely respiratory deaths) are due to poor utility opioids such as fentanyl
- Utility includes not only the "good" but the "bad" outcomes to opioid therapy and incorporates safety into equianalgesia
- Utility functions combines PK/PD studies with experimental pain and respiratory depression- depressed response to PCO2)

Boom M 2013

INDIRECT MEASURES TO CURB OPIOID DEATHS-UTILITY

- American Pain Society guidelines for methadone dosing were based on safety rather than equianalgesia
- CDC guidelines were based on analgesic choices for reasons of safety rather than equianalgesia
- UF provides a mechanism to make opioid choices based on safety and analgesia and is a step ahead of equianalgesic tables which do not involve safety

Chou R 2014
Dowell D 2016

UTILITY FUNCTION

Utility Function (UF)= profit-loss paradigm

Equianalgesia= equal profits to scale

UF= benefits – harms (-1 to+1)

Therapeutic Index (TI)= harms/benefits

UTILITY INDEX OR THERAPEUTIC INDEX

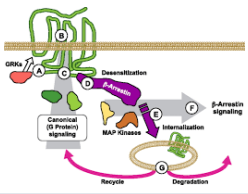
- TD50-opioid concentration in which 50% experience a given toxicity
- ED50-opioid concentration in which 50% experience pain relief
- TI= TD50/ED50
- TI assumes steady state, static
- Mechanism of toxicity can differ from analgesia (G – protein activation vs. beta arrestin-2 activation)
- TI may change with dose or pain severity or chosen outcome
- TD50 and ED50 may not change in parallel
- UF are differences in predicted probability for analgesia and respiratory depression over dose and time

UTILITY FUNCTION

Utility Function allows objective and reliable characterization of individual opioid benefits and risks over time and dose in order to determine which opioid is safer to use and what dosing strategy places the patient at the least risk during opioid therapy

Kharasch E 2013

WHY ARE THERE DIFFERENCES IN UTILITY FUNCTION



- Bias signaling differences-G-protein (analgesia) vs. beta arrestin-2 (respiratory depression)
- Mu subtype interactions- 7TM opioid vs. 6TM & 7TM mu opioids (nalbuphine, buprenorphine, levorphanol)

Raehal K 2005

Grinnell S 2016

OPIOID GTP GAMMA-S BINDING AND BETA ARRESTIN-2 ACTIVATION

	GTP (EC50)	B-Arrestin-2 (EC50)
DAMGO	33nM	229nM
Morphine	64nM	372nM
Sufentanil	1.3nM	1.5nM
Fentanyl	43nM	53nM

Schmid C 2017

FENTANYL UTILITY FUNCTION

- D- Prospective study, 2 separate study days
- P- Healthy controls (n=12)
- I- Fentanyl 3.5ug/kg over 90m seconds
- O- PK/PD
  - Analgesia to electrical cutaneous pain
  - Respiratory response to PCO2

Boom M 2013

FENTANYL UTILITY FUNCTION

- Probability of analgesia (PA) > respiratory depression (PR) at < 0.7ng/ml
- PA< PR at >0.7ng/ml
- Pain reduction (50%) occurred at 0.9ng/ml
- Reduced response to PetCO2 (50%) occurred at 1 ng/ml
- Bolus fentanyl favored PR>PA which reversed at 60 minutes post bolus (PA>PR)

Boom M 2013

ALFENTANIL

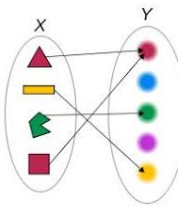
- D- Prospective study
- P- Healthy volunteers (n=48)
- I-Alfentanil targeted 50-100ng/ml, bolus 50ug/kg
- O- PK/PD
  - Pain- cutaneous electrical
  - Ventilation to controlled PetCO2
  - UT PR>0.5,PA>0.25,PA>0.5

Roozekrans M 2018

ALFENTANIL

- PA>.0.25 with PR<0.5 occurred at 26-158ng/ml UF 0.31
- PA>0.5 with PR<0.5 did not exceed zero using steady state levels
- Negative UF with bolus at 1-21 minutes UF -0.51
- PA 0.25 with < PR 0.5 UF of 0.41 at 68ng/ml over time
- PA 0.5 with PR<0.5 UF 0.21 and at 93ng/ml over time (post bolus)
- UF worsens with bolus and with increasing doses
- Mirrors mortality risk with dose and bolus strategies as well as opioid choices.

Roozekrans M 2018



BUPRENORPHINE, FENTANYL PK?PD EFFECTIVENESS AND SAFETY

- D- prospective animal study
- P- Mouse model
- I- Buprenorphine and Fentanyl
- O- PK/PD
  - Plethysmography quantitative ventilation
  - Tail flick antinociception
  - Respiratory depression- "yes/no" with 50% decline in ventilation
  - Antinociception-"yes/no" tail flick latency >10 s
  - Concentration/effect odds ratio

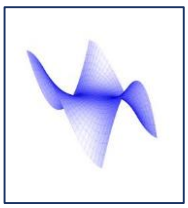
Yassen A 2007

BUPRENORPHINE, FENTANYL, PK/PD EFFECTIVENESS, SAFETY

- Buprenorphine antinociception OR 28.5 (6.9-50.1)
- Buprenorphine respiratory depression OR 2.10 (0.71-3.49)
- Fentanyl antinociception OR 3.03 (1.87-4.21)
- Fentanyl respiratory depression OR 2.54 (1.26-3.82)
- OR (PA/PR) 13 to 1 in favor of buprenorphine

Yassen A 2007

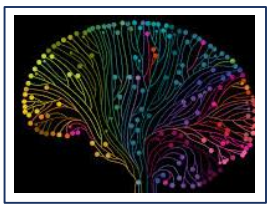
PK/PD RESPIRATORY EFFECTS FENTANYL AND BUPRENORPHINE



- D- Prospective study
- P- 74 healthy volunteers
- I- Buprenorphine 0.05 to 0.6mg, fentanyl 0.075 to 0.5mg
- O-Respiratory response to PetCO2 at 50% PK/PD modeling

Yassen A 2007

PK/PD BUPRENORPHINE , FENTANYL RESPIRATORY DEPRESSION



- Biophase equilibrium- 16 vs. 75 minutes (buprenorphine)
- Buprenorphine was a partial agonist with intrinsic activity of 0.51 and ceiling effect
- Fentanyl was a full agonist with an intrinsic activity of 0.91

Yassen A 2007

UTILITY FUNCTION DRAWBACKS

- Clinical correlates to PetCO2 studies are missing
- UF will change based on type of pain and pain intensity
- UF in the healthy and animals may not reflect a sick population with comorbidities- UF may diminish with age and disease
- Dichotomized data has limitations
- Context sensitive (measures for pain and respiratory depression

NALBUPHINE VS. MORPHINE

Pain

- 10 RCT, 618 patients, 299 received nalbuphine
- Pain relief- RR 1.01 (0.91-1.11), heterogeneity 40%, p=0.09
- Credible interval RR 1.102 (0.6697-1.627) based on 1000 simulations
- No publication bias

Zeng, 2016

NALBUPHINE VS. MORPHINE ACUTE PAIN

Nausea

- RR (nalbuphine to morphine) 0.75 (95% CI 0.6-0.997) p=0.048

Vomiting

- RR 0.65 (95% CI 0.5-0.85) p=0.001

Pruritus

- RR 0.17 (95% CI 0.09-0.34) p=0.000

Respiratory depression

- RR 0.27 (95% CI 0.27-0.57) p=0.003

Zeng 2015

SUMMARY

- UF looks at the good and bad where equianalgesia scales the good
- Studies demonstrate that fentanyl has a low UF relative to buprenorphine
- Opioid choices should include intrinsic safety with nalbuphine>morphine for acute pain and buprenorphine> fentanyl for chronic pain
- Need to classify opioids based on UF using a standardized protocol