UNIVERSITY of MARYLAND BALTIMORE

Calculating Conversations in Opioid Conversions

Mary Lynn McPherson, PharmD, MA, MDE, BCPS

Professor, and Executive Director

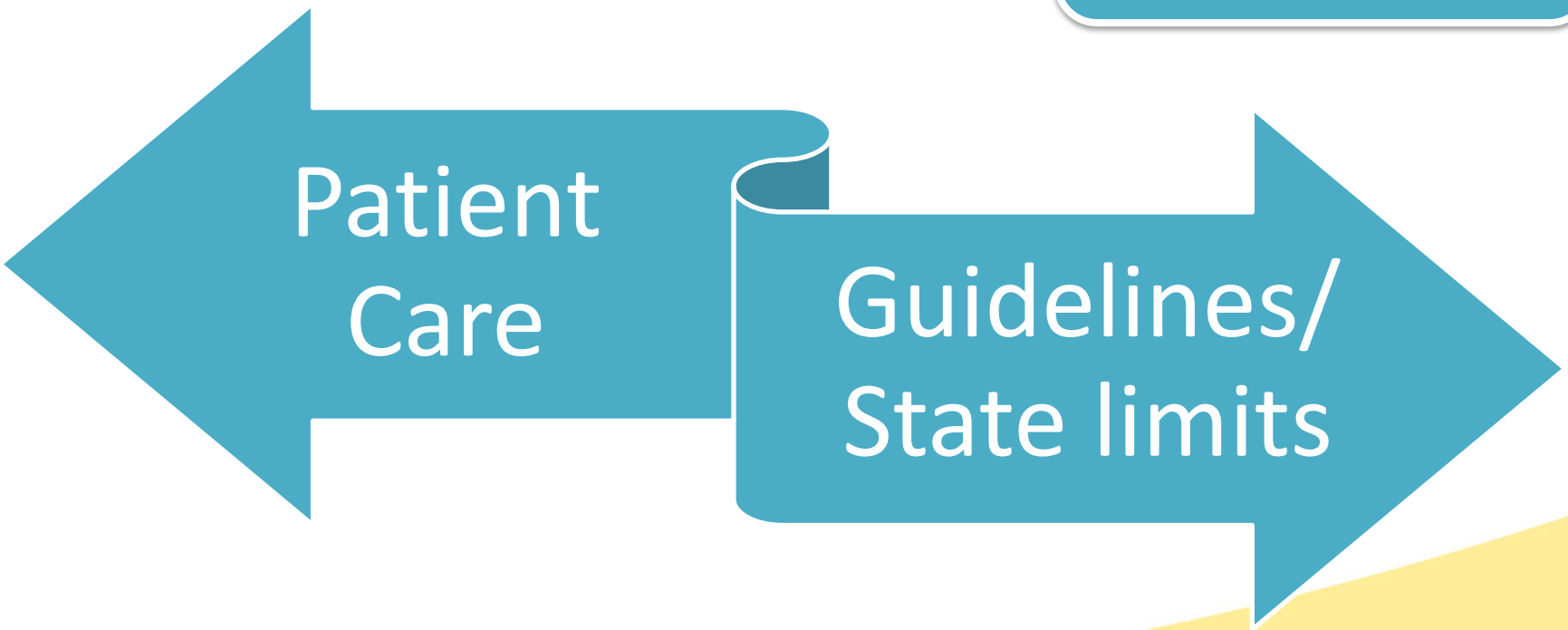
Advanced Post-Graduate Education in Palliative Care

mmcphers@rx.umaryland.edu | @mlmcpherson

Table of Contents

What is an MME?
Why do we need to calculate MME?

Morphine milligram equivalents



Guidelines and State Limits

MME limits are intended to help clinicians make safe, appropriate decisions concerning changes to opioid regimens.

MME/day metric can be used as a gauge of the overdose potential

MME/day can help predict likelihood of addiction

Does a higher MME/day result in better function?

Clinical Reasons for Changing Opioids

- Opioid rotation
- Opioid substitution
- Opioid switching
- Opioid Conversion Calculation!

Lack of therapeutic response

Development of adverse effects

Change in patient status

Other considerations

- Opioid/formulation availability
- Formulary issues
- Patient/family health care beliefs

So here are the questions…

- “If I am starting with opioid “A” at dose “B,” what dose of opioid “C” do I need to prescribe to have the same analgesic effect?”

- “If my patient is taking an opioid other than morphine, what would be the equivalent milligrams as morphine per day? And does this exceed recommended guidelines?”

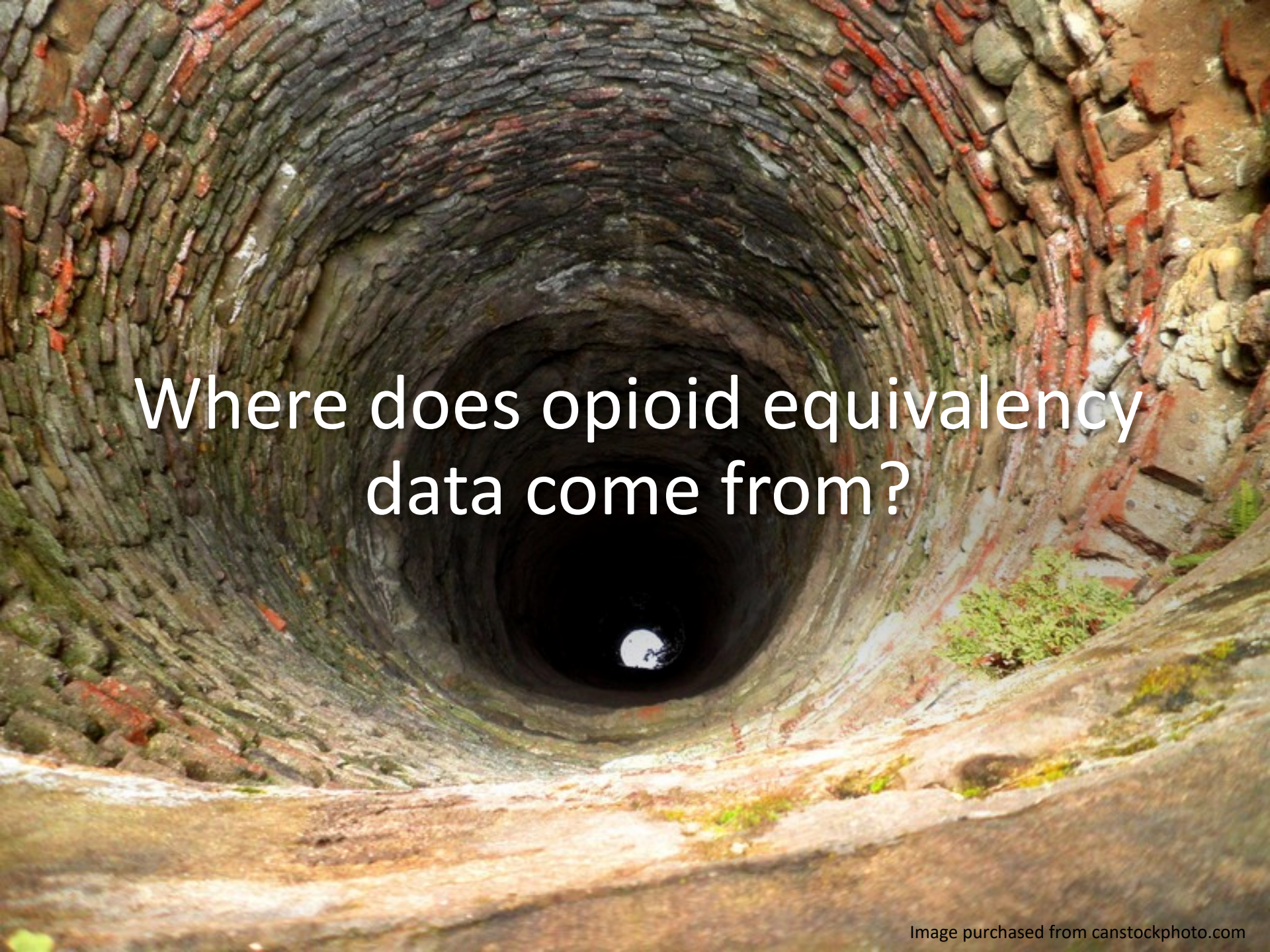
Equianalgesic Dosing Terminology

- Opioid responsiveness
  - The degree of analgesia achieved as the dose is titrated to an endpoint defined either by intolerable side effects or the 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
  - NOTE: This does NOT imply equivalent harm (or potential)
- 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%



MME for Commonly Prescribed Opioids

Opioid	Conversion Factor
Codeine	0.15
Fentanyl transdermal (in mcg/hr)	2.4
Hydrocodone	1
Hydromorphone	4
Methadone: 1-20 mg/day	4
Methadone: 21-40 mg/day	8
Methadone: 41-60 mg/day	10
Methadone: ≥61-80 mg/day	12
Morphine	1
Oxycodone	1.5
Oxymorphone	3
Tapentadol†	0.4

†Tapentadol is a mu receptor agonist and norepinephrine reuptake inhibitor. MMEs are based on degree of mu-receptor agonist activity, but it is unknown if this drug is associated with overdose in the same dose-dependent manner as observed with medications that are solely mu receptor agonists.

Calculating the total daily dose of opioids helps identify patients who may benefit from closer monitoring, reduction or tapering of opioids, prescribing of naloxone, or other measures to reduce risk of overdose.

To determine dose in MMEs, multiply the dose for each opioid by the conversion factor. For example, tablets containing hydrocodone 5 mg and acetaminophen 300 mg taken four times a day would contain a total of 20 mg of hydrocodone daily, equivalent to 20 MME daily; extended-release tablets containing oxycodone 10mg and taken twice a day would contain a total of 20mg of oxycodone daily, equivalent to 30 MME daily.

1. All doses should be in mg/day, except for fentanyl which should be in mcg/hr, before multiplying by the conversion factor.
2. Equianalgesic dose conversions are only estimates and cannot account for individual variability in genetics and pharmacokinetics.
3. Do not use the calculated dose in MMEs to determine the doses to use when converting opioid to another; when converting opioids the new opioid is typically dosed at substantially lower than the calculated MME dose to avoid accidental overdose due to incomplete cross-tolerance and individual variability in opioid pharmacokinetics.
4. Use particular caution with methadone dose conversions because the conversion factor increases at higher doses.
5. Use particular caution with fentanyl since it is dosed in mcg/hr instead of mg/day, and its absorption is affected by heat and other factors.

SOURCE: Adapted from Von Korff M, Saunders K, Thomas Ray G, et al. De facto long-term opioid therapy for noncancer pain. Clin J Pain. 2008 Jul–Aug; 24(6):521–527 and Washington State interagency guideline on prescribing opioids for pain; 2015.

https://www.cdc.gov/drugoverdose/prescribing/guideline.html

Von Korff Reference

Opioid (oral, transdermal or transmucosal)	Morphine equivalent conversion factor per mg of opioid
Morphine	1.0
Hydrocodone (+ co-analgesic)	1.0
Oxycodone (+/- co-analgesic)	1.5
Hydromorphone	4.0
Oxymorphone	3.0
Methadone	3.0
Fentanyl (transmucosal)	0.125

"References 16-20"

"The conversion factors were based on information from multiple sources (Ref 16-20). After reviewing published conversion factors, consensus was reached among two physicians with clinical experience in pain management and a pharmacist pharmacoepidemiologist."

Von Korff M, Saunders K, Ray GT et al. Defacto long-term opioid therapy for non-cancer pain. *Clin J Pain* 2008;24(6):521-527.

16. [Accessed July 5, 2007] Oregon Health Sciences University Chronic Pain Management Manual. Available at: http://www.ohsu.edu/ahec/pain/painmanual.html

17. Vieweg WV, Lipps WF, Fernandez A. Opioids and methadone equivalents for clinicians. Prim Care Companion J Clin Psychiatry. 2005; 7:86–8. [PubMed: 16027761]

18. Fine, PG.; Portenoy, RK. Palliative Medicine Handbook. Minneapolis: McGraw-Hill Healthcare Information; 2004. A clinical guide to opioid analgesia; p. 19Available at: http://book.pallcare.info/index.php?tid=125

20. American Pain Society. Principles of analgesic use in the treatment of acute pain and cancer pain. 5. Glenview: American Pain Society; 2003.

Ok, show me Ref 16-20

Von Korff M, Saunders K, Ray GT et al. Defacto long-term opioid therapy for non-cancer pain. *Clin J Pain* 2008;24(6):521-527.

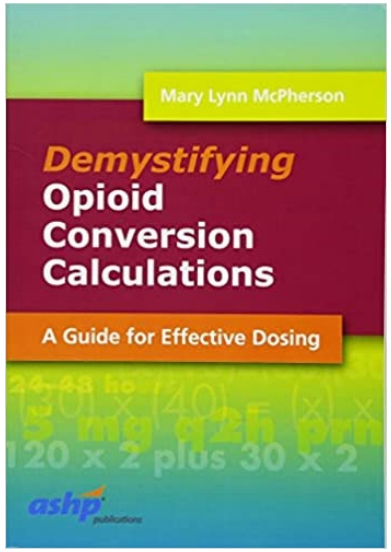
Opioid Conversion Calculations

Set in concrete?

Opioid Conversion Calculations

…or are we on shaky ground?

Image purchased from canstockphoto.com



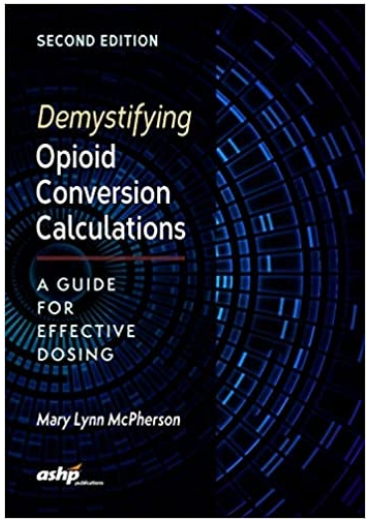
Equianalgesic Opioid Dosing

2010	Equianalgesic Doses (mg)	
Drug	Parenteral	Oral
Morphine	10	30
Fentanyl	0.1	NA
Hydrocodone	NA	30
Hydromorphone	1.5	7.5
Oxycodone	10*	20

- Heterogeneity of opioid receptors
- Variability of p'kin and p'dyn of opioids
- Differences in opioid responsiveness in different types of pain
- Source of equianalgesic data
- Patient-specific variables
  - Comorbidities
  - Other medical factors
- Unidirectional vs. bidirectional equivalencies

NOTE: Learner is STRONGLY encouraged to access original work to review all caveats and explanations pertaining to this chart.

*Not available in the US



Equianalgesic Opioid Dosing

2010	Equianalgesic Doses (mg)	
Drug	Parenteral	Oral
Morphine	10	30
Fentanyl	0.1	NA
Hydrocodone	NA	30
Hydromorphone	1.5	7.5
Oxycodone	10*	20

2018	Equianalgesic Doses (mg)	
Drug	Parenteral	Oral
Morphine	10	25
Fentanyl	0.15	NA
Hydrocodone	NA	25
Hydromorphone	2	5
Oxycodone	10*	20

NOTE: Learner is STRONGLY encouraged to access original work to review all caveats and explanations pertaining to this chart.

*Not available in the US

IV to Oral Morphine – What's the dealio?

- Equianalgesic tables range from 1:2 to 1:3
- Supported by Kalso (1990)
  - 20-30 mg of morphine by mouth ~ 10 mg IV or SQ morphine
- Starlander (2011)
  - Conversion factor of 1:2 (calls for individual adjustments)
  - 11 patients, pilot study, not definitive
- Takahashi (2003)
  - Conversion factors between 1:2 and 1:3 (based on morphine and M6G in advanced cancer patients receiving chronic morphine treatment)
- MD Anderson
  - 10 mg IV morphine ~ 25 mg oral morphine

2018	Equianalgesic Doses (mg)	
Drug	Parenteral	Oral
Morphine	10	25

But wait a minute – morphine ⟷ oxycodone?

- Because of variations between morphine (range 15-75%) and oxycodone (60% or more) the equianalgesic ratio:
  - oral morphine : oral oxycodone ranges from 1:1 to 2:1
  - Dependent on the patient's ability to absorb the opioid.

2018	Equianalgesic Doses (mg)	
Drug	Parenteral	Oral
Morphine	10	25
Oxycodone	10*	20

Anderson et al. JPSM 2001;21:397-406.
Poyhia et al. Br J Clin Pharmacol 1992;33:617-621.

Parenteral to Oral Hydromorphone

- Largely determined by oral bioavailability (of oral hydromorphone)
  - Parab - 50.7 +/- 29.8%; Ritschel – 51.35 +/- 29.3%
- Do we need to evaluate conversion from oral to parenteral?
  - No, because conversion is determined primarily by BAB
  - Secondarily by pharmacogenetics
- Clinical experience in large patient populations provide average guidance
- Best data is 1:2.5 (IV:oral)

McPherson Table	Equianalgesic Doses (mg)	
Drug	Parenteral	Oral
Hydromorphone	2	5

Biopharm & Drug Dispo, 1988;9(2):187-199.
J Clin Pharm 1987;27(9):647-653.

Conversion Ratio from IV Hydromorphone to Oral Opioids in Cancer Patients

IV Hydromorphone	→	Oral Opioid
1 mg IV hydromorphone (< 30 mg/day)	→	Oral hydromorphone 2.5 mg
1 mg IV hydromorphone (≥ 30 mg/day)	→	Oral hydromorphone 2.1 mg
1 mg IV hydromorphone (< 30 mg/day)	→	Oral morphine 11.54 mg
1 mg IV hydromorphone (≥ 30 mg/day)	→	Oral morphine 9.86 mg
1 mg IV hydromorphone	→	Oral oxycodone 8.06

Reddy's bottom line:
I:2.5 (IV hydromorphone to oral hydromorphone)
1:10 (IV hydromorphone to oral morphine)
1:8 (IV hydromorphone to oral oxycodone)

McPherson Table	Equianalgesic Doses (mg)	
Drug	Parenteral	Oral
Morphine	10	25
Hydromorphone	2	5
Oxycodone	10*	20

Reddy, et al. J Pain Sx Manage 2017;54:280-288.

*Not available in the US

Morphine ⇌ Hydromorphone

- Is it bidirectional? (IV HM to PO MS equal to PO MS to IV HM?)
- Study by Lawlor – SQ to SQ HM/MS and PO to PO HM/MS
  - Going from morphine to hydromorphone (same route) was 5:1 (M:HM)
  - Going from hydromorphone to morphine (same route) was 3.7:1 (M:HM)
- Limitations of Lawlor study:
  - Data highly skewed and variable, not normally distributed
  - Authors stated differences in direction were clinically insignificant and called for further research...in the meantime differences in M→HM and HM→M remain speculative

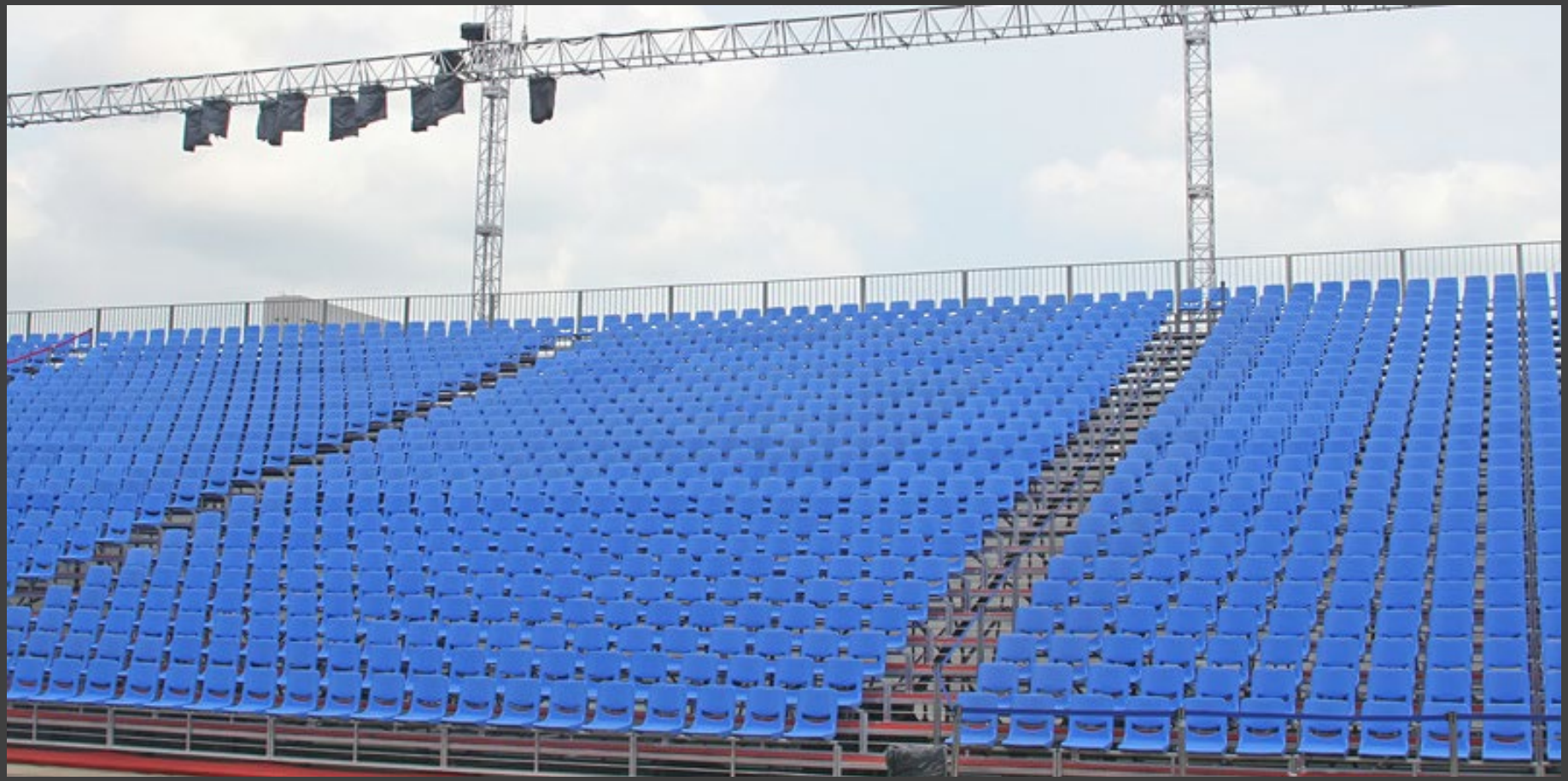
Pain 1997;72(1-2):79-85.

How about oral MS to parenteral hydromorphone?

	IV HM:PO MS - 1.5:30	IV HM:PO MS – 2:25	Comments
Switching from 10 mg IV HM per day to PO MS	A. Calculate 200 mg PO MS	B. Calculate 125 mg PO MS	New conversion more conservative, and it's consistent with Reddy findings.
Switching from 200 mg PO MS per day to IV HM	C. Calculate 10 mg IV HM	D. Calculate 16 mg IV HM	New conversion seems more aggressive than older conversion ratio.

But wait! There's more than one way to pluck a chicken!
200 mg oral morphine → 40 mg oral hydromorphone → 16 mg IV hydromorphone

2018	Equianalgesic Doses (mg)	
Drug	Parenteral	Oral
Morphine	10	25
Hydromorphone	2	5



So……

- Which is my seat?
- Don’t know – I just got you in the ball park!

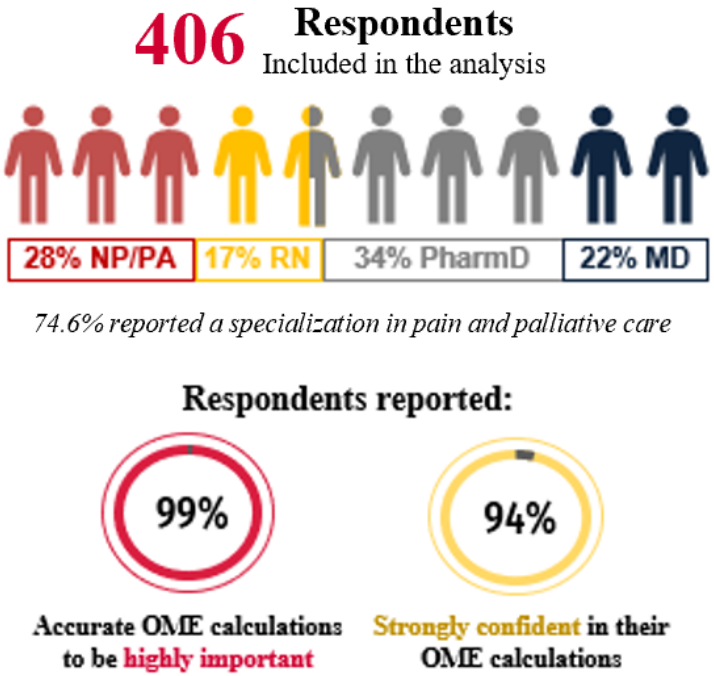
So have practitioners got their arms around this?

MedStar Health | UNIVERSITY of MARYLAND

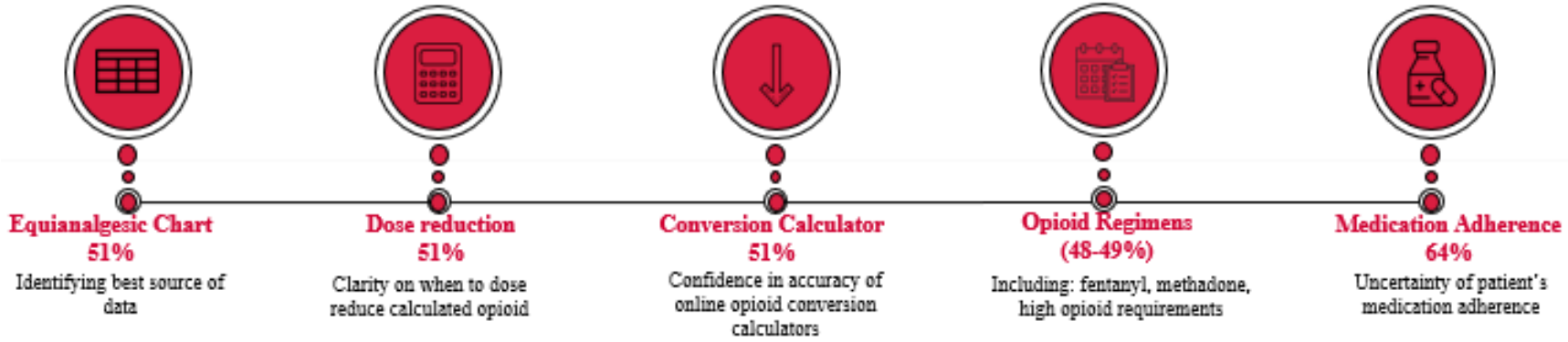
Not So Surprising -
Inconstancy of Oral Morphine Equivalents Calculations

Cindy Nguyen, PharmD, MPH[1,2], Mary Lynn McPherson, PharmD, MA, MDE, BCPS[1], Kathryn Walker, PharmD, BCPS, CPE[1,2]
1. University of Maryland School of Pharmacy; 2. MedStar Health (Baltimore, Maryland)

- Online survey to self-reported health care clinicians who dispense, administer or prescribe opioids.
- Aim – to explore the practices, perceptions and potential barriers to perform safe and effective opioid conversion calculations to calculate a patient's total daily oral morphine equivalent (OME).



Barriers to Performing Opioid Conversion Calculations



Nguyen, McPherson, Walker. Poster presentation. SPPCP 2021.

Frequency of Calculations

Frequency of Calculating OME	Number (%)
Daily	164 (40.5)
Weekly	113 (27.9)
Monthly	63 (15.6)
Rarely	65 (16.1)

Reported method of calculating total daily OME were widely divergent

Case Question: Calculate the total daily OME for a patient receiving

- **Morphine ER 30 mg by mouth every 12 hrs**
- **Morphine IR 15 mg 1 tablet by mouth every 4 hrs as needed (use of "PRN" is variable)**

Respondent Answer Choices	Concept Illustrated	n=376	Percent
(A) 150 total daily OME; Based on total daily dose of Morphine ER 30 mg Q12 hrs & all allowable Morphine IR 15 mg "PRN" doses	Incorporate all possible PRN doses in OME	123	36%
(B) 60 total daily OME; Based only on total daily dose of Morphine ER 30 mg Q12 hrs	Do not incorporate PRN doses in OME	118	31%
(C) OME based on practitioner's best guess of patient's use of Morphine IR 15mg with Morphine ER 60mg	Incorporate estimate of actual PRN use in OME	135	33%

Variability in Opioid Equivalence Calculations

Survey launched on social media and advertising to professional organizations

319 participants took survey

Asked to state estimated morphine equivalents (MEQs, aka MMEs) for:

- Hydrocodone 80 mg
- Transdermal fentanyl 75 mcg/h
- Methadone 40 mg
- Oxycodone 120 mg
- Hydromorphone 48 mg

Rennick et al. Pain Medicine 2016;17:892-898.

Opioid Regimen	Estimated MEQs (MMEs)
Transdermal fentanyl 75 mcg/h	176 +/- 118 mg
Hydrocodone 80 mg	88 +/- 42 mg
Hydromorphone 48 mg	192 +/- 55 mg
Methadone 40 mg	193 +/- 201 mg
Oxycodone 120 mg	173 +/- 39 mg

Large variability exists among clinicians (especially methadone and TDF).

Rennick et al. Pain Medicine 2016;17:892-898.

International Survey of Opioid Rotation and Conversion Ratios in Pall Care

- OR – substituting one opioid with another
- OC – changing the administration route
- Various scenarios posed by survey
- 370 responses received from 53 countries

Data courtesy of Dr. Akhila Reddy; to be presented at MASCC Conference, 2021.

Table 1. Opioid Conversion and Rotation Ratios			
Conversion or Rotation Type	n	Median (IQR)	Mode
CR from IV to PO Morphine	349	3 (2, 3)	3
CR from IV to PO Hydromorphone	228	3 (2, 5)	5
CR from IV to PO Oxycodone	141	2 (1.5, 2)	2
ORR from IV Hydromorphone to PO Morphine	225	15 (10, 20)	15
ORR from IV Oxycodone to PO Morphine	138	3 (2.5, 4)	3
ORR from PO Hydromorphone to PO Morphine	251	5 (4, 5)	5
ORR from PO Oxycodone to PO Morphine	313	1.5 (1.5, 2)	1.5
ORR from PO Hydrocodone to PO Morphine	136	1 (1, 1.5)	1
ORR from PO Oxymorphone to PO Oxycodone	82	2 (2, 2)	2
ORR from PO Oxymorphone to PO Morphine	85	3 (2.5, 3)	3
ORR from Transdermal Fentanyl mcg/hour to MEDD (mg)	331	2.4 (2, 2.5)	2
ORR from MEDD (mg) to Transdermal Fentanyl mcg/hour	329	2.4 (2, 2.7)	2
ORR from IV Morphine (mg) to IV Fentanyl (mcg)	249	10 (10, 15)	10
ORR from IV Fentanyl (mcg) to IV Morphine (mg)	247	10 (10, 15)	10
Abbreviations - CR: Conversion ratio; ORR: Opioid Rotation Ratio; IV: Intravenous; PO: Oral; MEDD: Morphine Equivalent Daily Dose; SD: Standard Deviation; IQR: Interquartile Range; mcg: micrograms; mg: milligrams			

Data courtesy of Dr. Akhila Reddy; to be presented at MASCC Conference, 2021.

International Survey

Opioid Ratio	United States		Canada		United Kingdom	
	Median (IQR)	Mode	Median (IQR)	Mode	Median (IQR)	Mode
IV to PO morphine	3 (2.5, 3)	3	2 (2, 2)	2	2 (2, 2)	2
IV to PO hydromorphone	4 (2.5, 5)	5	2 (2, 2)	2	2 (2, 3)	2
IV hydromorphone to PO morphine	15 (11, 20)	20	10 (10, 10)	10	15 (15, 15)	15
PO hydromorphone to PO morphine	5 (4, 5)	5	5 (5, 5)	5	7.5 (5, 7.5)	7.5
TDF mcg/h to MEDD	2 (2, 2.4)	2	3.5 (2, 4)	2	2.8 (2.4 3)	2.4
MEDD to TDF mcg/h	2 (2, 2.5)	2	2.44(1.33, 4)	4	2. (2.67, 3.33)	2.7
IV fentanyl (mcg) to IV morphine (mg)	10 (10, 15)	10	10 (10, 12.5)	10	6.67 (1.2, 20)	20

Data courtesy of Dr. Akhila Reddy; to be presented at MASCC Conference, 2021.

But wait…there's an APP for that!

Table 1. Available Online Opioid Dose Conversion Calculators

	WA State Agency	MedCalc	Pain Research	Pain Physician	Hopkins	Palliative Care	Global RPh	*PPM*
Opioid dosage calculator		X	X	X	X	X	X	X
Equianalgesic table displayed			X	X	X	X	X	X
Can convert multiple opioids to a single alternative			X	X	X	X	X	X
Acute vs chronic dosing for morphine and methadone							X	X
Transdermal fentanyl	X			X	X	X	X	X
Transdermal buprenorphine						X		X
Methadone	X	X	X	X	X		X	X
Tapentadol							X	X
Dose reduction for incomplete cross-tolerance				X			X	X
Availability for smartphone					X	X	X	X

Based on references 18-25.
PPM, Practical Pain Management; WA, Washington

Evaluation and Comparison on Online Equianalgesic Opioid Dose Conversion

Aims of this study:

- To compare and contrast the various online opioid conversion calculators.
- Identify the mathematical disparities in conversion.
- Compare automated conversions against manual calculations.
- Reveal potential risks to the end user.
- Make recommendations to health care providers for practical and safe approaches when predicting opioid conversions.

Variation ranged from -55% to 242%

Shaw et al. 13(7). Available at: https://www.practicalpainmanagement.com

UNIVERSITY of MARYLAND BALTIMORE

Variability among online opioid conversion calculators performing common palliative care conversions

Costantino RC, Barlow A, Gressler LE, Zarzabal LA, Tao D, McPherson ML. Variability among online opioid conversion calculators performing common palliative care conversions. Journal of Palliative Medicine. Under Review.

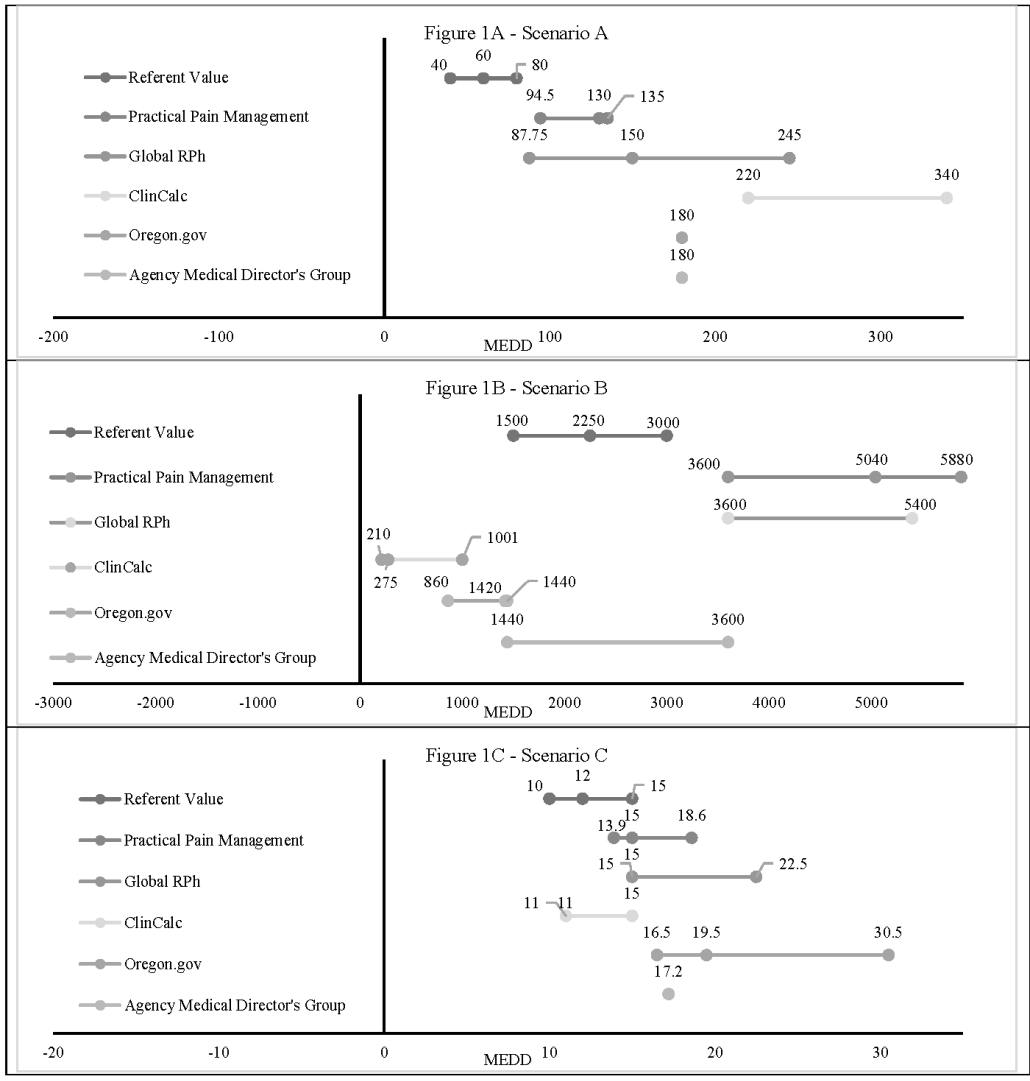
Methods

- This study was conducted among a cohort of students enrolled during the summers of 2018 and 2019 in an advanced pain management and opioid dosing course .
- Participants were asked to identify three online opioid conversion calculators and complete conversions for three scenarios described in Table.

78-year-old woman receiving transdermal fentanyl 75 mcg/h. Patient doesn't seem to be responding despite dose increases. She is 5'4" and weighs 82 pounds. Convert to long-acting oral morphine and determine a dose of short-acting oral morphine for breakthrough pain.

58-year-old man with end-stage lung cancer receiving IV hydromorphone, 6 mg/hour with 3 mg bolus every 10 minutes (uses about 3 doses/hour). The pharmacy just called and you just got the last of the IV hydromorphone they have in stock. The patient can swallow tablets and capsules. Calculate an equivalent oral morphine regimen (oral long-acting and short-acting for breakthrough pain).

42-year-old man with low back pain, receiving MS Contin 45 mg po q12h, with MSIR 15 mg po q4h as needed (takes 2 doses per day on average). His pain seems to have a neuropathic component. Convert to oral methadone.



Dosing and Reduced Tolerance Indicator for all Scenarios

	Scenario A		Scenario B		Scenario C	
	N	**Frequency**	**N**	**Frequency**	**N**	**Frequency**
Break						
<10%	18	31.03	13	22.41	-	-
10-15%	17	29.31	17	29.31	-	-
>15%	10	17.24	8	13.79	-	-
Did Not Provide	13	22.41	20	34.48	-	-
Dosing						
Q1h	4	6.90	2	3.45	-	-
Q2h	4	6.90	10	17.24	-	-
Q3h	2	3.45	1	1.72	-	-
Q4h	29	50.00	21	36.21	-	-
>Q4h	3	5.17	1	1.72	-	-
Not Stated	16	27.59	23	39.66	-	-
Reduce Cross Tolerance						
Yes	35	60.34	40	68.97	34	58.62
No	23	39.66	18	31.03	24	41.38

Five-Step Approach to Opioid Conversion

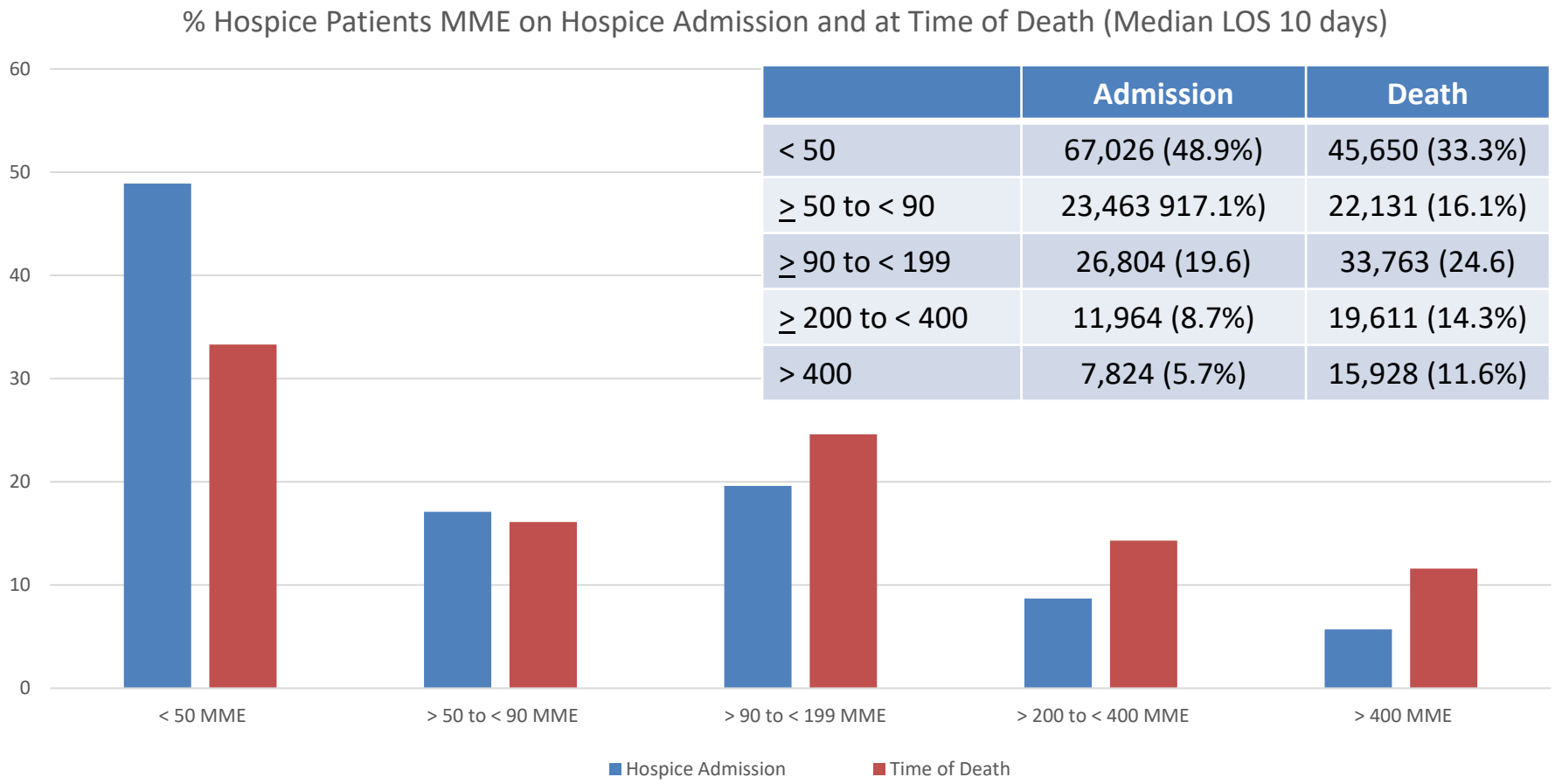
1. Globally assess the patient (i.e., PQRSTU, or another method) to determine if the uncontrolled pain is secondary to worsening of existing pain or development of a new type of pain.
2. Determine the total daily usage of the current opioid. This should include all long-acting and breakthrough opioid doses.
3. Decide which opioid analgesic will be used for the new agent and consult the established conversion tables to arrive at the proper dose of the new opioid, recognizing the limitations of the data.
4. Individualize the dosage based on assessment information gathered in Step 1 and ensure adequate access to breakthrough medication.
5. Patient follow-up and continual reassessment, especially during the first 7–14 days, to fine-tune the total daily dose (long-acting + short-acting) and increase or decrease the around the clock long-acting dosage accordingly.

Gammaitoni AR, Fine P, Alvarez N, et al. Clinical application of opioid equianalgesic data. *Clin J Pain.* 2003;19:286–297.

Opioids and Conversions Aren't Going Anywhere!

- Large hospice database
- Every medication prescribed for a hospice patient discharged by death in 2010-2019
- 137,087 patients who received an opioid
  - Length of stay: mean 51.6 days; median 10 days

Hospice Patients MME



	Admission	Death
< 50	67,026 (48.9%)	45,650 (33.3%)
≥ 50 to < 90	23,463 917.1%)	22,131 (16.1%)
≥ 90 to < 199	26,804 (19.6)	33,763 (24.6)
≥ 200 to < 400	11,964 (8.7%)	19,611 (14.3%)
> 400	7,824 (5.7%)	15,928 (11.6%)

What's the plan, Stan?

- Careful assessment to determine if opioid therapy is the best plan
- Use the best equivalency data possible based on science
- Be conservative with the scheduled dose
  - Depending on the clinical situation be generous with rescue dosing
- Let's treat patients, not numbers
  - Monitor patient response vigorously

Image purchased from canstockphoto.com