Four Competing Definitions of Morphine Equivalence **Insidiously Inhibit Evidence Synthesis**

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14 US states impose limits on opioid dose, ranging from 30 mg to 120 mg daily maximum. So do many third-party payers. Despite being enshrined in law, there is no standard way to calculate daily MME. Therefore, we reviewed the clinical guidelines, mobile apps, and literature to identify and quantify the impact of denominator dependency due to definitional variants.

Introduction

Across 4 previously unidentified definitional variants, the following simple 2 prescription scenario returns daily MME inconsistently: 75.8 or 93.5 or 31.2 or 105 mg/d. We examined how this fundamental metric impacts population-level inference.

A patient receives 30mg extended-release oxycodone twice a day for around-the-clock pain for 30 days (60 tablets), and one 5 mg oxycodone twice a day as needed for breakthrough pain for 7 days (14 tablets). Both prescriptions are dispensed on the first day of a 30-day month, with no subsequent dispensing. Assume 1.5 as the conversion factor oxycodone-to-morphine.

Total MME for the first prescription: $(60 \text{ tablets}) \times (30 \text{ mg per tablet}) \times$ (1.5 conversion factor from oxycodone-to-morphine), resulting in 2700 mg.

For the second prescription: $(14 \text{ tablets}) \times (5 \text{ mg per tablet}) \times (1.5 \text{ conversion factor}),$ resulting in 105mg.

Total MME across both prescriptions is 2805 mg, appearing as the numerator in the first 3 definitions.

Papers cited in the CDC Guideline use 4 different definitions, calling into question the consistency of the evidence base on dose-related opioid harms. Drug Overdose in a Retrospective Cohort with Non-Cancer Pain Treated with Opioids, Antidepressants, and/or Sedative-Hypnolics: Interactions with Mental Health Disorders **D1: Total Days Supply** D2: On-therapy Days $x_{i} = \frac{\sum_{j=1}^{n} a_{ij}}{\sum_{k=1}^{l} u_{ik}} = \frac{\sum_{j=1}^{n} (qmcf)_{ij}}{\sum_{k=1}^{l} u_{ik}} = \frac{\sum_{j=1}^{n} (qmc)_{ij} \left(\frac{o}{d}\right)_{ij}}{\sum_{k=1}^{l} u_{ik}}$ De Facto Long-term Opioid Therapy for Noncancer Pain Barbara J. Tumer, M.D., M.S.Ed.^{1,2,3} and Yuar an Liana. Ph.D.^{2.3.4} $\frac{\sum_{j=1}^{n} a_{ij}}{\sum_{j=1}^{n} o_{ij}} = \frac{\sum_{j=1}^{n} (qmcf)_{ij}}{\sum_{j=1}^{n} o_{ij}} = \frac{\sum_{j=1}^{n} (qmc)_{ij} \left(\frac{a}{d}\right)_{ij}}{\sum_{j=1}^{n} o_{ij}}$ Michael Von Korff, ScD.* Kathleen Saunders, JD.* Gary Thomas Ray, MBA,† Denise Boudreau, PhD.* Cynthia Campbell, PhD.† Joseph Mertill, MD, MPH.§ Mark D. Sultiman, MD, PhD,† Carolyn M. Rutter, PhD.* Michael J. Silverberge, PhD MPH,† Caleb Banta-Green, MSW, MPH,) and Constance Weisner, Dr PH, MSW1[†], The total MED was computed by summing the MEDs for all opioid prescriptions within a given 6-month interval. $\frac{1}{30 \text{ days supply}} = 93.5 \text{ daily MME}$ Cath hand-treen, MAN, MITA and Commance Weater, br II, MOWTY Total days supply is the sum of days supply for each opioid dispensed during an episode. Days supply may not represent the intended days supply of a particular prescription as it is usually calculated by pharmacists using the maximum dose and frequency permitted within the range specified by the prescription provider. Therefore, total days supply tends to underestimate the actual days supply dispensed. PMID: 18574961 The mean daily MED in a 6-month interval was calculated by dividing the total MED by days' supply for all prescrip-tions in that interval, excluding overlapping days. We examined five categories for the mean daily MED (i.e., 0, 1– 19, 20–49, 50–99, and \geq 100 mg), similar to other stud-ies.^{9,10} For the first overdose, the mean daily MED was $\frac{1}{37 \text{ days supply}} = 75.8 \text{ daily MME}$ Office of Inspector General based on data from exactly 6 months before that event (Fig. 2). PMID: 25 R Recognition and Icolkit (R - 26 KB) Number of days can be longer than calendar time. SQL programming code and Toolkit (TXT - 16 KB) Accounts for overlapping prescriptions. Method provided by HHS OIG. Underestimates daily MME when IR and ER opioids are used in Related Information combination. Ann 2011 GU 42-17-06140 A History of Being Prescribed Controlled Substances and Risk of Drug Overdose Death D3: Defined Observation Window D4: Maximum Daily Dose ozzi, MD, MPH,* urne, MD,* Nina G. Shah, MS,* ID,* Hema A. Desal, MMS,* Jen, MD, MPH,* William Harvey, y D. Loring, RPH** Critical revision of the manuscript for important intellectual content: Paulozzi, Kilbourne, Shah, Landen, Notle, Hanwa, Lasina Disclaimer: The findings and conclu are those of the authors and do not represent the views of the Centers to and Prevention. $z_{ik} = \sum_{i=1}^{n} p_{ijk}$ $x_i = \max_i (z_{i,k=1}, \dots, z_{i,k=l})$ Opioid Prescriptions for Chronic Pain and Overdose Presented: National Harold Rogers Prescription Drug Monitoring Program Meeting, Washington, DC, June 29, 2010. $x_i = \frac{\sum_{j=1}^n a_{ij}}{l_i} = \frac{\sum_{j=1}^n (qmc)_{ij} \left(\frac{o}{d}\right)_{ij}}{l_i}$ Kate M. Dann, PHD; Kathleen W. Saanders, JD; Carolyn M. Rutter, PHD; Caleb J. Banto-Green, MSW, MPH, PHD; Joseph O. Meell, MD, MPH; Mark D. Sallwan, MD; PhD; Constance M. Weisner, DPH, MSW; Michael J. Silverber Cyrkha L. Caregolel, PhD; Breck M. Pataly, MD, PhD; and Michael Von Korth; ScD dosage of opioid prescribed in MME per day [27] in three Classification of Opioids different ways. The single peak dosage was the highest amount per day in any single opioid prescription. The total We obtained medication data from GHC automated We obtained medication data from GHC automated pharmacy files. These data cover more than 90% of the prescription medications used by GHC enrollees (23). We calculated total morphine equivalents dispensed for each opioid prescription filled during follow-up, defined by the quantity of pills dispensed multiplied by their strength (in milligrams), multiplied by a conversion factor (22). We then calculated the average daily morphine equivalent dose dispensed for 90-day exposure windows (see Statistical Analysis) by adding the morphine equivalents for the pre-scriptions dispensed during the 90 days and then dividing by 90. For each 90-day exposure window and each person, we calculated the average daily opioid dose dispensed and divided these into 5 categories: none, 1 to 19 mg, 20 to 49 90 MME/day Guideline 0 ge was the highest dosage per day at any time during the exposure period after summing dosages from all overlapping opioid prescriptions. The average dosage was the average daily opioid dosage during the entire study period from all opioid prescriptions combined. For regression analysis, we categorized each measure of daily dosage into 0–40, >40–120, and >120 MME/day. CDC $\frac{2700 + 105}{90} = \frac{2,805 \text{ MME}}{90 \text{ days window}} = 31.2 \text{ daily MME}$ æ Ignores date, days supply, and previous opioid use. Other studies used 120, 180, 365 days. divided these into 5 categories: none, 1 to 19 mg, 20 to 49 mg, 50 to 99 mg, and 100 mg or more. PMID: 20083827 Full details at go.unc.edu/mme To complete all calculations and relate competing definitions of daily MME, notation is as follows: q_{ij}, quantity (units) dispensed for prescription j for person istrength per unit in milligrams for a given prescription j for person i m_{ii} , equianalgesic potency conversion factor for medication in prescription j for person i c_{ij} , days supply on a given prescription *j* for person *i*

d_{ij}, start (dispensing) date of prescription j for person i S_{ii}, start date of observation window for person i w_i, l_i, length (in days) of observation window for person *i* g_{ik} , date of follow-up day k during observation window for person i**Alan Kinlaw Yanning Wang** "Lack of consistency in calculating patient-level daily MME has always "Something that matters a lot to me is that equations can help a researcher identify the concept they want to measure, been a headache for me as an analyst and epidemiologist. To ease the computational complexity, software vendors prefer 'straightforward' calculations and then measure it And since each concept or formula has a very different relationship to the common 90 MME/day threshold, these equations clarify how we should be more nuanced with whether or how we set thresholds." but may not provide enough detail behind the measure for the clinicians." Methods

In surveillance or policy evaluation, we may want to compare how many "high dose" patients are in one state versus another. We conducted a meta analysis to determine if 4 studies using the same data would return statistically consistent results. The only source of variation comes from the 4 definitions of daily MME.

Setting

All-payer dispensing (PDMP) data from California and Florida All adult residents July through September 2018

Drugs Included

- + Outpatient prescriptions for solid oral opioid analgesics
- + Excludes buprenorphine
- + "High dose" defined as greater than 90 daily MME
- + Uniform conversion factors (CDC)

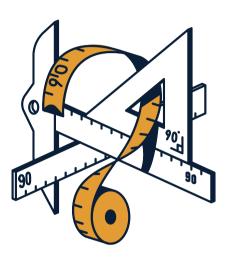
Statistical Analyses

- 1: Number of "high dose" patients compared between CA and FL
- 2: mg difference by patient between CA and FL
- 3: Meta-analysis with fixed-effects inverse variance model using
- Higgins and Thompson's I2 and X2 to assess heterogeneity 4: Sensitivity analysis at the 90.0-90.9 thereshold boundary

Sample Size

9,436,640 opioid analgesic prescriptions California n=5,677,277 Florida n=3,759,363

3,916,461 unique adult residents California n=2,430,870 Florida n=1,485,591

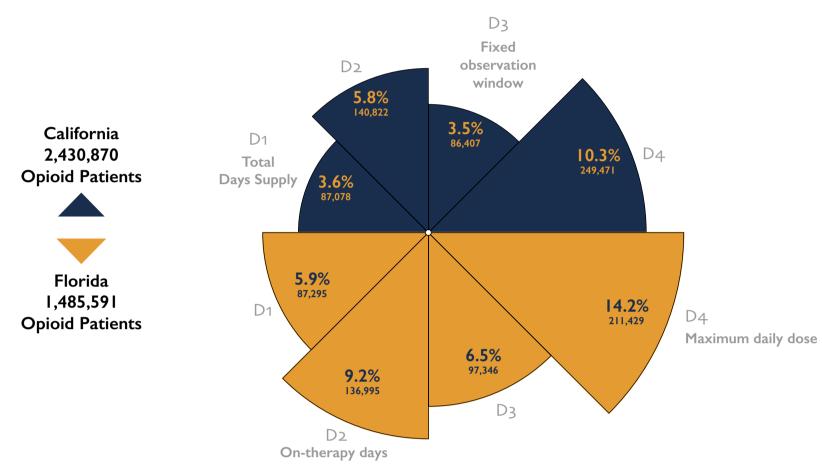


Baseline 3-month Opioid Dispensing Rate Difference 7.9 per 100 adult residents California: 8.7 per 100 adult residents Florida:

Results

The 4 definitions yielded a 3-fold range of average daily MME: 17 to 52 mg/d in CA and 23 to 65 mg/d in FL, on the same sample.

Proportion of "High Dose" Patients by Definition and State



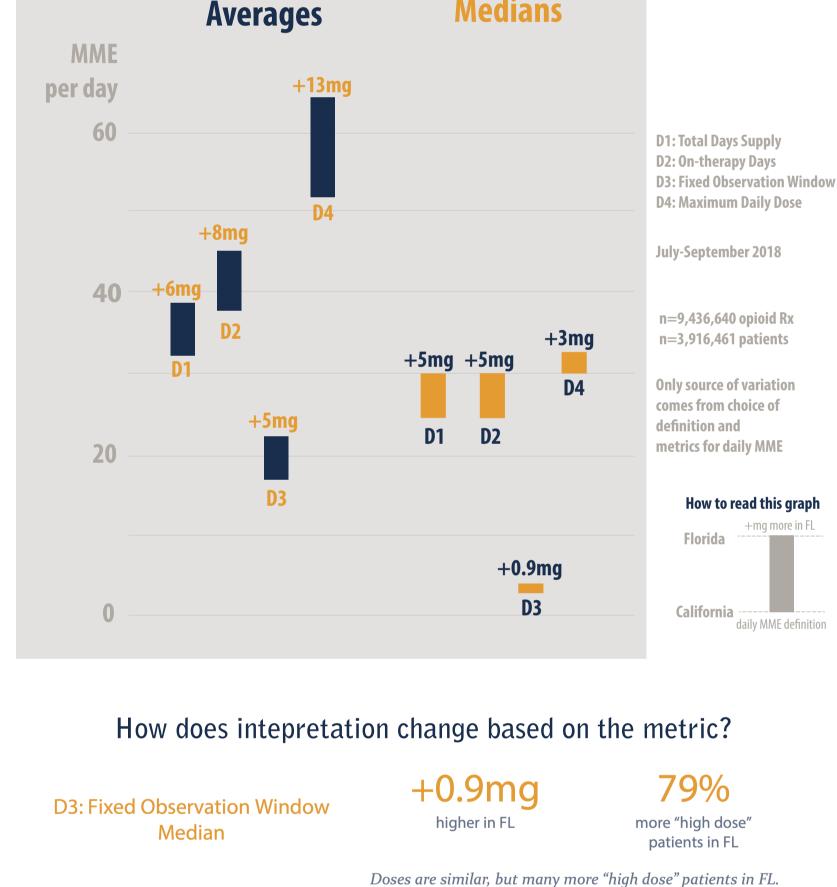
The 4 definitions could not agree how many more "high dose" patients there were in Florida compared to California, or average dose.

	% more "high dose" patients in FL vs. CA	95% CI
1. Total days supply	64.0%	62.5%, 65.5%
2. On-therapy days	59.2%	58.0%, 60.3%
3. Fixed observation window	84.3%	82.7%, 86.0%
4. Maximum daily dose	38.7%	37.9%, 39.4%
Tests for heterogeneity $I^2 = 99.9\%$ $H^2 = 1086$ $X^2 = 3257, 3 \text{ df, } p < 0.0001$		

Average daily MME ER-only	California n=40,038	Florida N=26,039
1. Total days supply	90 mg	87 mg
2. On-therapy days	104 mg	97 mg
3. Fixed observation window	73 mg	67 mg
4. Maximum daily dose	154 mg	143 mg

Analysts could legitimately claim that FL had from 0.9mg to 13mg more daily MME. Strong mean-median divergence was observed.

MME per day



Medians

D4: Maximum Daily Dose Mean

+13mg higher in FL

34% more "high dose" patients in FL

Doses much higher in FL, and somewhat more "high dose" patients.

Patient Pespective: So we wait. And we suffer.

"It is disheartening, but unfortunately not surprising. Far too often, we are victims of the good intentions of those wanting to 'do something' about the opioid overdose epidemic, but the something that is done oversimplifies the problem and pushes cookbook medicine upon those of us with complicated medical situations.

And while everyone debates whether the MME limit was the right thing to do, we are forced to live by it, because medical personnel and others treat quidelines as mandates.

So we wait. And we suffer.

And we hope it will all get sorted so we can get the care we need."

16.7 (15.0-17.3)

10.4 (9.2-11.5)

17.2 (15.1-19.3)

Meta Analysis

Liz Joniak-Grant

Relative Proportion More "High Dose" Patients in Florida	-	Difference in MME (95% CI)	-
(vs. California) More "High Dose" Patients, % (95% CI)	Immediate-release only (n = 3,611,8) Total days supply On-therapy days Fixed observation window	56) (mg) 3.7 (3.3-4.1) 3.5 (3.1-3.9) 2.2 (2.2-2.3)	
aily MME definition variant (n = 3,916,461) Total days supply 64.0 (62.5-65.5) On-therapy days 59.2 (58.0-60.3) Fixed observation window 84.3 (82.7-86.0) Maximum daily dose 38.7 (37.9-39.4) $I^2 = 99.91\%$ Test of heterogeneity: $\chi^2 = 3257$, 3 df, $P < 0.0001$ Mean difference in daily MME in Florida (vs. California)	Maximum daily dose $f^2 = 98.6$ Test of heterogeneity: $\chi^2 =$ Extended-release only (n = 66,077) (Total days supply On-therapy days Fixed observation window Maximum daily dose $f^2 = 86.3$ Test of heterogeneity: $\chi^2 =$	= 219, 3 df, P < 0.0001 mg) -3.3 (-1.8 to -4.8) -6.8 (-4.9 to -8.7) -5.9 (-4.4 to -7.4) -10.6 (-7.7 to -13.6) 18%	

On-therapy days Fixed observation window

Maximum daily dose

Sensitivity Analysis

	Definition	Patients >90 Daily MME, n (%)	Patients ≥90 Daily MME, n (%)	Rate Difference Per 1000 (95% CI)	Number Needed to Harm*
	California Total days supply On-therapy days Fixed observation window Maximum daily dose	87,078 (3.6) 140,822 (5.8) 86,407 (3.6) 249,471 (10.3)	106,240 (4.4) 155,254 (6.4) 87,407 (3.6) 285,807 (11.8)	7.9 (7.5, 8.2) 5.9 (5.5, 6.4) 0.41 (0.07, 0.75) 15.0 (14.3, 15.5)	1 in 127 1 in 169 1 in 2430 1 in 67
June Bae	Total adult opioid patients	2,430	,870		
	Florida	97 205 (5 0)	112 009 (7.7)	18.0 (17.4, 18.6)	1 :- 50
"The difference between including 90 MME and excluding the category boundary (≥90 vs. >90 mg) was unexpectedly huge.	Total days supply On-therapy days Fixed observation window	87,295 (5.9) 136,995 (9.2) 97,346 (6.6)	113,998 (7.7) 157,794 (10.6) 98,541 (6.6)	18.0 (17.4, 18.6) 14.0 (13.3, 14.7) 0.80 (0.22, 1.4)	1 in 56 1 in 72 1 in 1244
The inclusion of the 90 daily MME cut point could potentially introduce misclassification especially when studies use the two different thresholds interchangeably."	Maximum daily dose Total adult opioid patients	211,429 (14.2)	261,335 (17.6)	33.6 (32.7, 34.5)	1 in 30
		e one would be misclassified as "lo val; MME, milligrams of morpl		nsidered "high dose" by using 90 mg inst	ead of 91 mg as a threshold.

 $I^2 = 98.34\%$ Test of heterogeneity: $\chi^2 = 181$, 3 df, P < 0.0001

Misclassification based on 90.0-90.9 mg threshold boundary (number needed to harm)

D1: Total Days Supply	1 in 56	••••••
D2: On-therapy Days	1 in 72	•••••••••••••••••••••••••••••••••••••••
D3: Fixed Observation Window	1 in 1,244	
D4: Maximum Daily Dose	e 1 in 30	••••••

Clinical Pespective: The Art of Medicine

Brooke Chidgey, Pain Management Physician

"Payers and lawmakers have grasped on to MME to guide policy decisions. While payers insist they are not dictating care because the patient can still pay out-of-pocket for the medication (I have many who do), for most patients this is not financially feasible.

As scientists, we often feel uncomfortable without objective data. While pain scores and MME give us numbers by which judgments are being made, they do not begin to tell the full story of the patient's pain condition. Because of this, the management of pain truly typifies the art of medicine."

Limitations

- Assumed all medications taken as described
- Did not consider other sources, pharmaceutical or unregulated
- Did not differentiate cancer from non-cancer pain
- Did not consider atypical mu-opioid receptor agonism for respiratory depression (e.g., tapentadol, buprenorphine)
- Did not consider pharmacist-based days supply variation
- Did not consider social determinants of opioid prescribing

Conclusions

D1. Total Days Supply

+ Computationally simple - Underestimates MME

 \rightarrow Single Rx scenarios



D3. Fixed Observation Window

+ Most robust to misclassification bias

- + Most commonly used in evidence base
- Less clinical relevance
- \rightarrow Long-term studies
- \rightarrow Gaps between episodes



"There's no one size fits all approach

here. It's not practical to have a universal MME formula when many factors go into patient care.

But what we can do is make all the calculations and code visible. Regardless of the audience, from clinical practice to legislation, it all should be seen."

D2. On-therapy Days

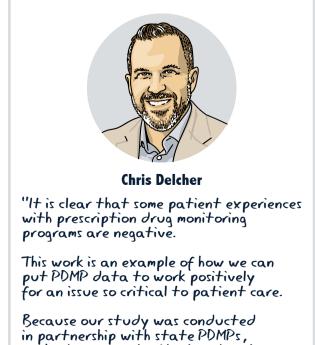
+ Strongest scientific and clinical precedent + Can be modified to account for gaps and unused medication

- Computationally complex
- \rightarrow Most research studies
- \rightarrow Clearest clinical interpretation

D4. Maximum Daily Dose

+ Used in CDC mobile app +/- Ignores days supply - Inaccuracy grows with long-term use \rightarrow Opioid naïve patients where toxicology is a concern





we had an opportunity to educate them on the impact of these important measures."

Full Paper Now Published in Clinical Journal of Pain!

ORIGINAL	ARTICLE	
OPEN		
Inches, Centim	eters, and Yards	
	oices Inhibit Interpretation Equivalence	
Nabaras Daugapta PhD,* Yannin Alan C. Kinises, PhD,17 B Tonka Cooper, MPR,* a		
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description Supported by FDA and BER, US Find and Drug Administration, Short Spring, MD (HEBF22001010000) funded the efforts of N.D., B. A.C., and T.L. The USE Disactional of Justice, Barray of J.L.	 Key Work: opicids, milligness of morphise opairsizes (HME), definitions, epidemicity; Proceedings, Drug Manihering Programs (PDMP) 	
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Dasgupta N, Wang Y, Bae J, Kinlaw AC, Chidgey BA, Cooper T, Delcher C. Inches, Centimeters, and Yards: Overlooked Definition Choices Inhibit Interpretation of Morphine Equivalence. Clinical Journal of Pain. 2021 Aug 1;37(8):565-574. doj: 10.1097/AJP.000000000000948 PMID: 34116543 PMCID: PMC8270512

OpioidData.org for code and further details



"The computational ease and the evocative lure of molecular fundamentals collide in an optimal level of cognitive complexity to engender MME's with an unsubstantiated aura of immutability.

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Our analysis revealed definitional inconsistencies that have been overlooked. There are implications for clinical care, policy, and epidemiology, and the potential to capriciously impact many thousands of patients."

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