Four Competing Definitions of Morphine Equivalence Insidiously Inhibit Evidence Synthesis

Nabarun Dasgupta, Yanning Wang, Jungjun Bae, Alan C. Kinlaw, Brooke A. Chidgey,
Toska Cooper, Elizabeth Joniak-Grant, Chris Delcher
University of North Carolina • University of Kentucky • University of Florida
Opioid Data Lab, OpioidData.org

Hand drawn by Brittain Peck

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.

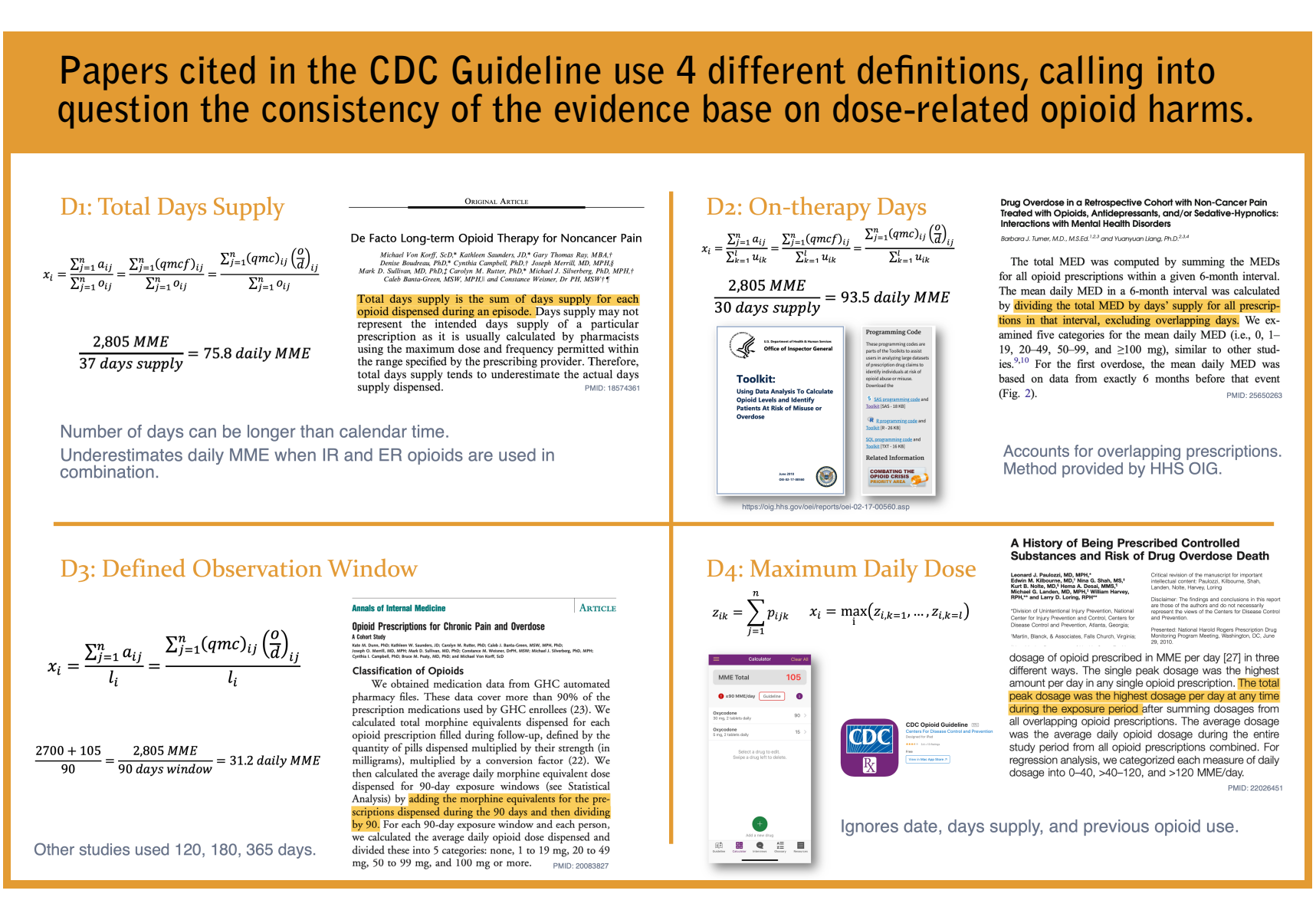
A patient receives 30mg extended-release oxycodone twice a day for around-the-clock pain for 30 days (60 tablets), and one 5 mg oxycodone twice a day as needed for breakthrough pain for 7 days (14 tablets). Both prescriptions are dispensed on the first day of a 30-day month, with no subsequent dispensing.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

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

For the second prescription:
(14 tablets) × (5 mg per tablet) × (1.5 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.



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 i
- m_{ij}, strength per unit in milligrams for a given prescription j for person i
- c_{ij}, equianalgesic potency conversion factor for medication in prescription j for person i
- d_{ij}, days supply on a given prescription j for person i
- s_{ij}, start (dispensing) date of prescription j for person i
- w_i, start date of observation window for person 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

Yanning Wang

"Lack of consistency in calculating patient-level daily MME has always been a headache for me as an analyst and epidemiologist. To ease the computational complexity, software vendors prefer 'straightforward' calculations but may not provide enough detail behind the measure for the clinicians."

Alan Kinlaw

"Something that matters a lot to me is that equations can help a researcher identify the concept they want to measure, 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."

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.

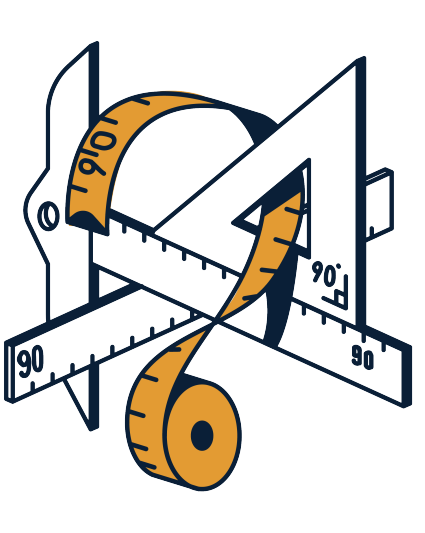
Setting
All-payer dispensing (PDMP) data from California and Florida
All adult residents
July through September 2018

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

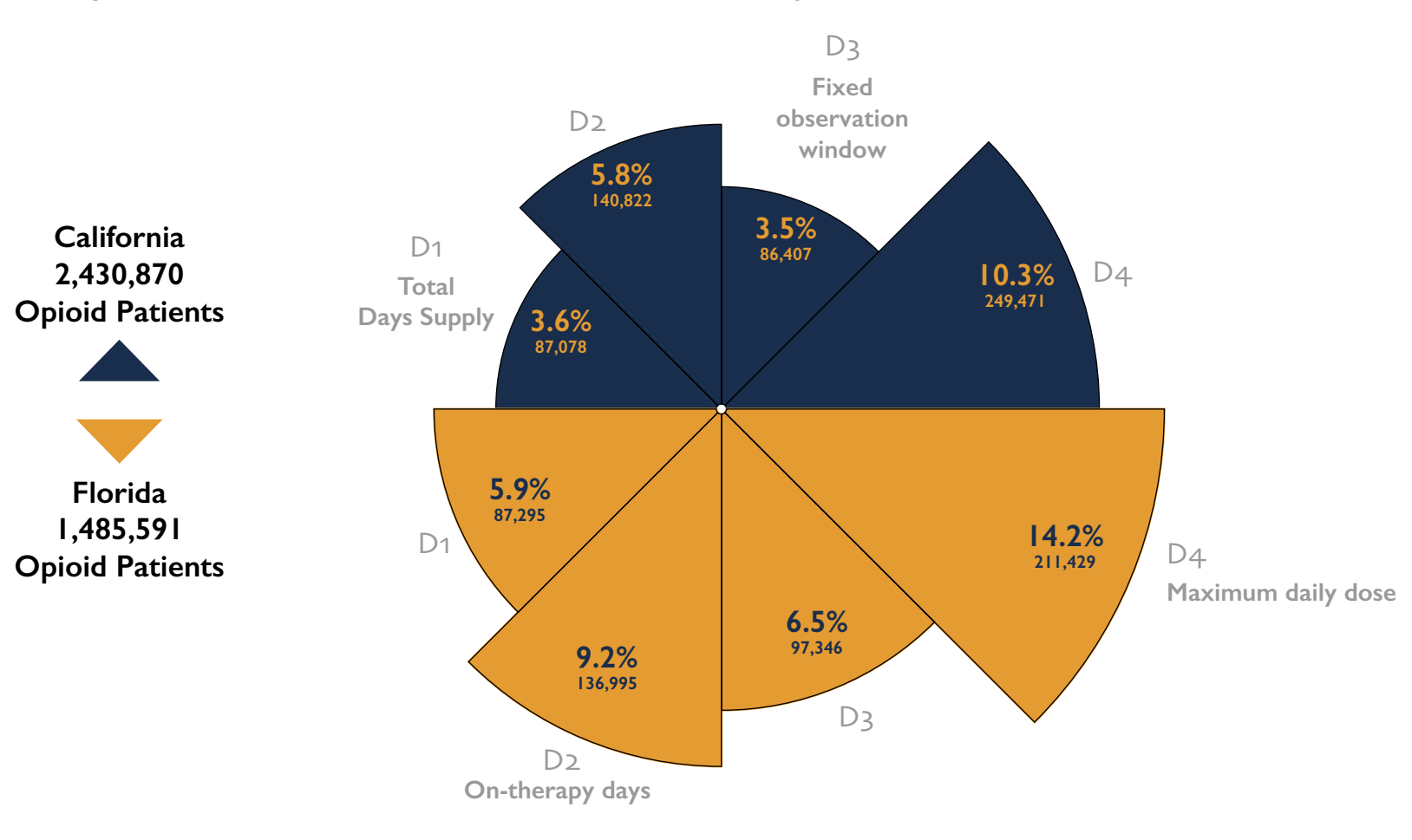


Baseline 3-month Opioid Dispensing Rate Difference
California: 7.9 per 100 adult residents
Florida: 8.7 per 100 adult residents

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

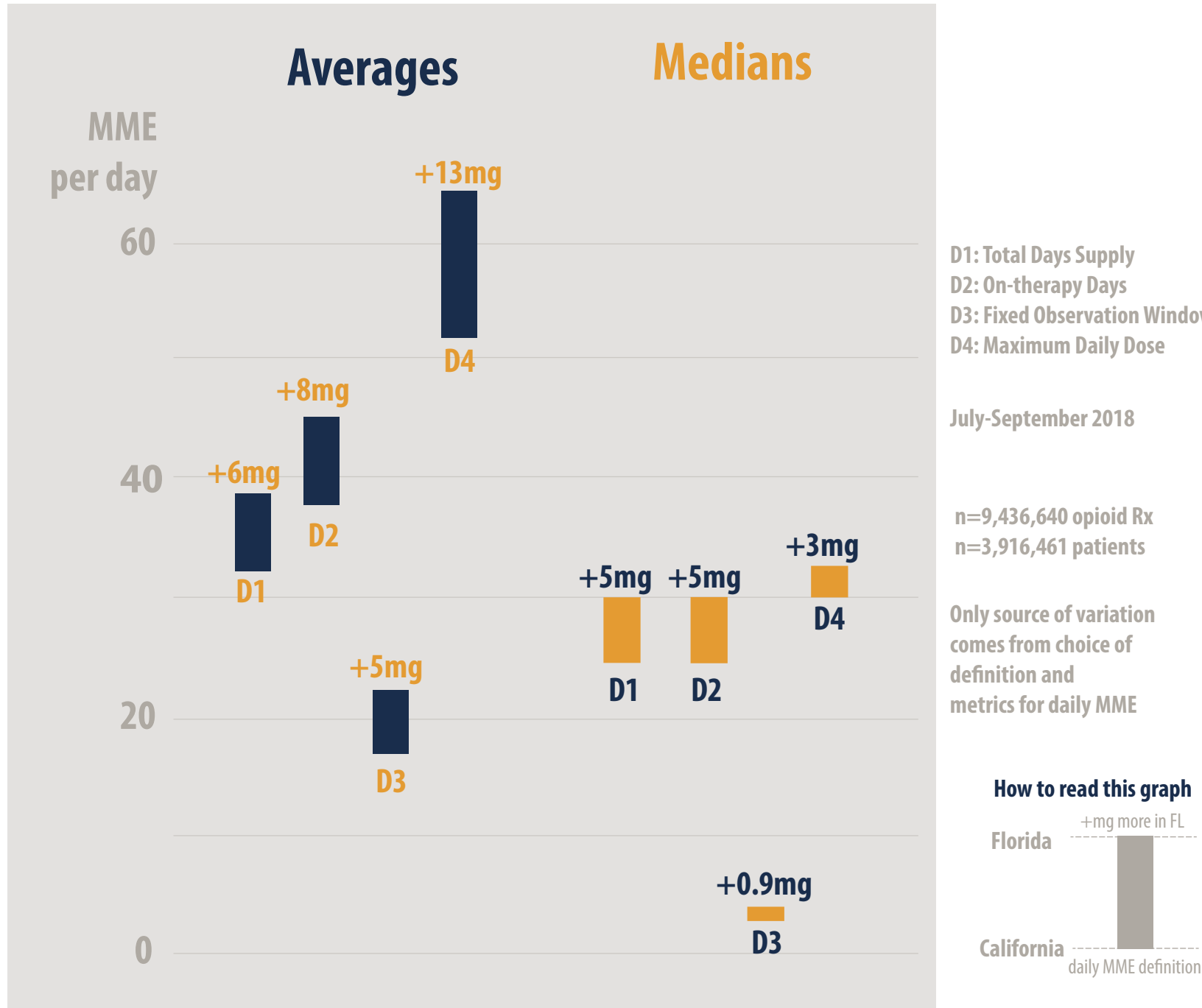


The 4 definitions could not agree how many more "high dose" patients there were in Florida compared to California, or average dose.

	% 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 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.



How does intepretation change based on the metric?

D3: Fixed Observation Window Median	+0.9mg higher in FL	79% more "high dose" patients in FL
	Doses are similar, but many more "high dose" patients in FL.	
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.

Liz Joniak-Grant

"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 guidelines as mandates.

So we wait. And we suffer.

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

Meta Analysis

Relative Proportion More "High Dose" Patients in Florida (vs. California)

	More "High Dose" Patients, % (95% CI)
Daily 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)	

	Difference in MME (95% CI)
Immediate-release only (n = 3,611,856) (mg)	
Total days supply	3.7 (3.3-4.1)
On-therapy days	3.5 (3.1-3.9)
Fixed observation window	2.2 (2.2-2.3)
Maximum daily dose	5.1 (4.6-5.6)
$I^2 = 98.63\%$	
Test of heterogeneity: $\chi^2 = 219$, 3 df, $P < 0.0001$	
Extended-release only (n = 66,077) (mg)	
Total days supply	−3.3 (−1.8 to −4.8)
On-therapy days	−6.8 (−4.9 to −8.7)
Fixed observation window	−5.9 (−4.4 to −7.4)
Maximum daily dose	−10.6 (−7.7 to −13.6)
$I^2 = 86.38\%$	
Test of heterogeneity: $\chi^2 = 22$, 3 df, $P = 0.0001$	
Both extended-release and immediate-release (n = 238,528) (mg)	
Total days supply	8.8 (8.3-9.3)
On-therapy days	16.7 (15.0-17.3)
Fixed observation window	10.4 (9.2-11.5)
Maximum daily dose	17.2 (15.1-19.3)
$I^2 = 98.34\%$	
Test of heterogeneity: $\chi^2 = 181$, 3 df, $P < 0.0001$	

Sensitivity Analysis

June Bae

"The difference between including 90 MME and excluding the category boundary (≥90 vs. >90 mg) was unexpectedly huge.

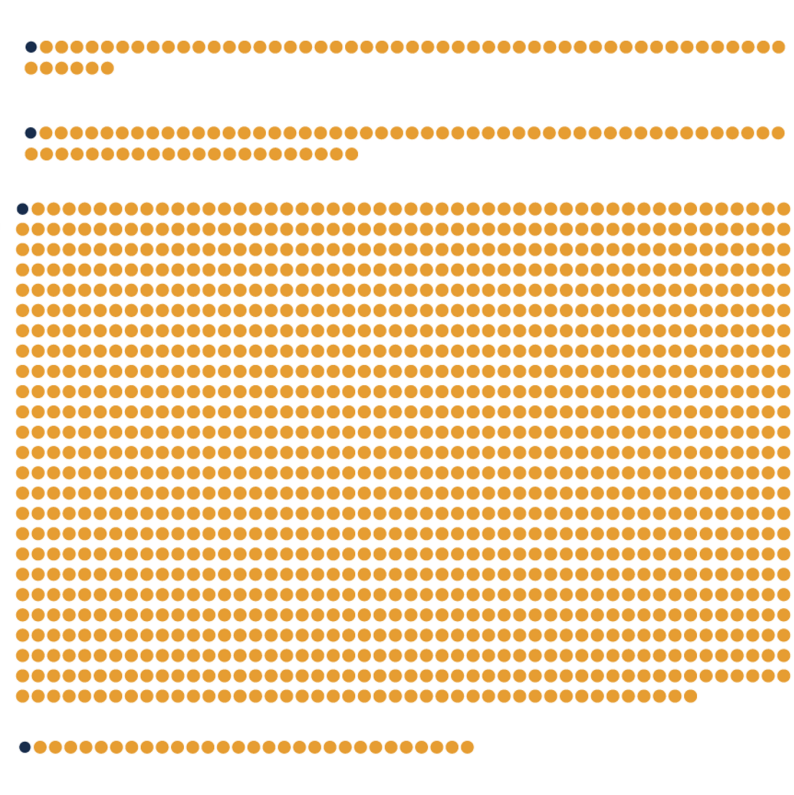
The inclusion of the 90 daily MME cut point could potentially introduce misclassification especially when studies use the two different thresholds interchangeably."

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	87,078 (3.6)	106,240 (4.4)	7.9 (7.5, 8.2)	1 in 127
On-therapy days	140,822 (5.8)	155,254 (6.4)	5.9 (5.5, 6.4)	1 in 169
Fixed observation window	86,407 (3.6)	87,407 (3.6)	0.41 (0.07, 0.75)	1 in 2430
Maximum daily dose	249,471 (10.3)	285,807 (11.8)	15.0 (14.3, 15.5)	1 in 67
Total adult opioid patients	2,430,870			
Florida				
Total days supply	87,295 (5.9)	113,998 (7.7)	18.0 (17.4, 18.6)	1 in 56
On-therapy days	136,995 (9.2)	157,794 (10.6)	14.0 (13.3, 14.7)	1 in 72
Fixed observation window	97,346 (6.6)	98,541 (6.6)	0.80 (0.22, 1.4)	1 in 1244
Maximum daily dose	211,429 (14.2)	261,335 (17.6)	33.6 (32.7, 34.5)	1 in 30
Total adult opioid patients	1,485,591			

*Number of patients seen before one would be misclassified as "low dose" who should have been considered "high dose" by using 90 mg instead of 91 mg as a threshold. CI indicates confidence interval; MME, milligrams of morphine equivalents.

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 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
→ Single Rx scenarios

D2. On-therapy Days
+ Strongest scientific and clinical precedent
+ Can be modified to account for gaps and unused medication
- Computationally complex
→ Most research studies
→ Clearest clinical interpretation

D3. Fixed Observation Window
+ Most robust to misclassification bias
+ Most commonly used in evidence base
- Less clinical relevance
→ Long-term studies
→ Gaps between episodes

D4. Maximum Daily Dose
+ Used in CDC mobile app
+/- Ignores days supply
- Inaccuracy grows with long-term use
→ Opioid naïve patients where toxicology is a concern

Toska Cooper

"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."

Chris Delcher

"It is clear that some patient experiences with prescription drug monitoring programs are negative.

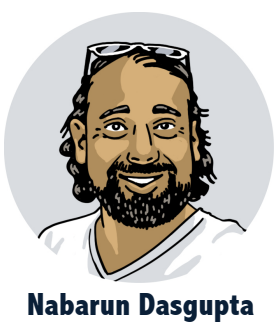
This work is an example of how we can put PDMP data to work positively for an issue so critical to patient care.

Because our study was conducted in partnership with state PDMPs, we had an opportunity to educate them on the impact of these important measures."

Full Paper Now Published in Clinical Journal of Pain!

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.
doi: 10.1097/AJP.0000000000000948
PMID: 34116543
PMCID: PMC8270512

OpioidData.org for code and further details



Nabarun Dasgupta

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

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."

nab@unc.edu
Twitter @nabarund
OpioidData.org

Presented at the 37th Annual International Conference on Pharmacoepidemiology and Therapeutic Risk Management

Acknowledgements

The authors thank Maryalice Nocera and LaMonda Sykes for project management and actuarial support. We are also grateful to the California and Florida PDMPs for providing de-identified data access. We are appreciative of the patients who's experiences are reflected in these data, and hope that our research contirbutes to their wellbeing.

Funding and Conflicts of Interest

This study was supported by funding from the US Food and Drug Administration and the US Department of Justice (Bureau of Justice Assistance). Funding agencies had no involvement in design, analysis, or interpretation. Views presented are not necessarily those of the funders.
Awards: HHSF223201810183C and 2017-PM-BX-K038

Authors declare no financial relationships with any organizations that might have an interest in this work.

ND is a methods advisor to the RADARS System of Denver Health and Hospitals Authority, a non-profit hospital. RADARS System does not use the metrics described herein.