

Inches, Centimeters, and Yards Overlooked Definition Choices Inhibit Interpretation of Morphine Equivalence

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Objective: Morphine-standardized doses are used in clinical practice and research to account for molecular potency. Ninety milligrams of morphine equivalents (MME) per day are considered a “high dose” risk threshold in guidelines, laws, and by payers. Although ubiquitously cited, the “CDC definition” of daily MME lacks a clearly defined

denominator. Our objective was to assess denominator-dependency on “high dose” classification across competing definitions.

Methods: To identify definitional variants, we reviewed literature and electronic prescribing tools, yielding 4 unique definitions. Using Prescription Drug Monitoring Programs data (July to September 2018), we conducted a population-based cohort study of 3,916,461 patients receiving outpatient opioid analgesics in California (CA) and Florida (FL). The binary outcome was whether patients were deemed “high dose” (>90 MME/d) compared across 4 definitions. We calculated I^2 for heterogeneity attributable to the definition.

Results: Among 9,436,640 prescriptions, 42% overlapped, which led denominator definitions to impact daily MME values. Across definitions, average daily MME varied 3-fold (range: 17 to 52 [CA] and 23 to 65 mg [FL]). Across definitions, prevalence of “high dose” individuals ranged 5.9% to 14.2% (FL) and 3.5% to 10.3% (CA). Definitional variation alone would impact a hypothetical surveillance study trying to establish how much more “high dose” prescribing was present in FL than CA: from 39% to 84% more. Meta-analyses revealed strong heterogeneity (I^2 range: 86% to 99%). In sensitivity analysis, including unit interval 90.0 to 90.9 increased “high dose” population fraction by 15%.

Discussion: While 90 MME may have cautionary mnemonic benefits, without harmonization of calculation, its utility is limited. Comparison between studies using daily MME requires explicit attention to definitional variation.

Key Words: opioids, milligrams of morphine equivalents (MME), definitions, epidemiology, Prescription Drug Monitoring Programs (PDMP)

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Morphine-standardized analgesic doses are calculated in clinical practice and research routinely. And, in support of safer opioid prescribing, clinical guidelines suggest limits or cautions above 90 mg of morphine equivalents (MME) to prevent respiratory depression. Yet, subtle variations in MME per day calculations have been overlooked.¹ Therefore, we sought to quantify the practical impact of definitional variants to provide clarity.

Equianalgesic conversion factors between opioids were intended to guide dosing when switching patients by accounting for potency.^{2,3} Conceptually, an equianalgesic dose is that at which 2 opioids provide the same pain relief. Contrary to conventional wisdom, conversion values are not based on pharmacologic properties. Instead, they arose 60 years ago from small single-dose clinical studies in postoperative or cancer populations with pain score outcomes; toxicologic effects (eg, respiratory depression) were not evaluated.⁴

Amid concerns about opioid overdose, the concept of equianalgesic potency resurfaced.⁵ In 2016, the US Centers

for Disease Control and Prevention (CDC) issued a guideline for chronic noncancer pain management including strong cautions above 90 daily MME based on population-level mortality studies.⁶ The CDC Guideline formalized a shift in the MME concept from antinociception to toxicology. The 90 daily MME recommendation was not absolute; however, some state laws, policies, and insurance requirements now invoke the threshold explicitly. For example, the State of Maine prohibits “any combination of opioid medication in an aggregate amount in excess of 100 MME of opioid medication per day.”⁷ CDC recognized this misapplication with a statement softening the “hard limits” inferred.⁸ The American Medical Association has expressed similar concerns.⁹

Definitional issues in opioid management^{10,11} and MME criticism are longstanding.^{1,12–19} Studies used by CDC to establish the 90 mg threshold employed approaches to calculating daily MME that differed silently. Total MME can be divided by days supply to calculate the average daily MME *per prescription*. However, the CDC Guideline does not address measurement *per patient*. Therefore, we quantified how daily MME definitions impact clinical practice, as well as interpretation of the evidence base.

METHODS

Sources of Definitions

Because of their considerable impact on opioid prescribing and frequent citation in the literature, we examined the 27 studies cited in the CDC Guideline to identify definitions of daily MME, based on our previous review.²⁰ Despite documentation challenges, we identified 4 distinct approaches among 18 studies^{1,21–37} and applied them to dispensing data from California and Florida. Supplemental Digital Content 1 (<http://links.lww.com/CJP/A783>) contains verbatim extracts from the original studies. Other approaches were identified,^{38–40} but described inadequately or infrequently.

In demonstrating how to calculate MME, the online continuing medical education module associated with the CDC Guideline⁴¹ presents the following clinical scenario, to which we added an additional prescription for illustrative purposes.

A patient receives 30 mg 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 for oxycodone-to-morphine.⁴²

Alarming, for this simple scenario, 4 definitional variants return daily MME inconsistently: 75.8 or 93.5 or 31.2 or 105 mg/d.

Definitions

Total MME for the first prescription equals (60 tablets) × (30 mg per tablet) × (1.5 conversion factor from oxycodone-to-morphine),⁴² resulting in 2700 mg. For the second prescription (14 tablets) × (5 mg per tablet) × (1.5 conversion factor) results in 105 mg. Total MME across both prescriptions is 2805 mg, appearing as the numerator in the first 3 definitions. Formulas are provided in Supplemental Digital Content 2 (<http://links.lww.com/CJP/A783>).

Definition 1—Total Days Supply

This common definition appears in studies^{1,26,43} cited in the CDC Guideline and elsewhere.^{44,45} The numerator is

the sum of MMEs across all prescriptions (2805 mg), and the denominator is the sum of days supply across all prescriptions (37 d), for 75.8 mg/d. The same day may contribute multiple times to the denominator (ie, prescriptions overlap), allowing the denominator to potentially exceed the number of unique calendar days.

Definition 2—On-therapy Days

Consistent with standard practice in pharmacoepidemiology, this definition identifies on-therapy days to account for overlapping prescriptions. This method is used in studies^{33,37} cited in the CDC Guideline and elsewhere.⁴⁶ The numerator is the sum of MMEs across all prescriptions, and the denominator is the total unique person-days explicitly exposed according to days supply, counting overlap days once. No gap allowances are made for early refills. Applying this definition, 2805 is divided by 30 days, resulting in 93.5 mg/d.

Definition 3—Fixed Observation Window

This common definition from early studies^{23,25,30} cited in the CDC Guideline often reference an even earlier study,⁴⁷ and is still used.^{48,49} The US Department of Health and Human Services Office of the Inspector General recommends this method, which is one of the only definition sources with adequate documentation to allow replication.⁵⁰ The numerator is again the sum of MMEs across all prescriptions, and the denominator is days elapsed during follow-up, hospital stay,⁵¹ or beneficiary enrollment.⁵² Although 90-day observation windows are most common,^{23,25} 180 days⁴³ and 365 days³⁰ were also used in studies supporting the CDC Guideline. Applying this definition 2805 divided by 90 days results in 31.2 mg/d.

Definition 4—Maximum Daily Dose

Toxicologic framing identifies the highest single-day MME exposure, irrespective of days supply or opioid tolerance. This definition appears to underlie the calculator in the CDC Opioid Guideline mobile app.⁵³ Prescriptions dispensed *pro re nata* are assumed to be consumed immediately, regardless of how long the prescription is written for. Yet, paradoxically, the “maximum” does not conceptually include consumption for intentional self-harm. This method was used by studies^{24,28,32,35} cited in the CDC Guideline and may be most relevant for prescriptions to patients who are opioid naive. The first prescription is 30 mg × 2 (twice per day) × 1.5 (the conversion factor) for 90 MME, plus the second prescription with 5 mg × 2 × 1.5 for 15 MME, resulting in 105 mg/d.

Medication Dispensing Data

Our study used deidentified data from Prescription Drug Monitoring Programs (PDMPs) in California and Florida, which we had analyzed previously.^{54,55} Inclusion criteria were any complete opioid analgesic dispensing record for state residents aged 18 years and older in California (adult population: 30,571,507) and Florida (adult population: 17,071,450) from July 1, 2018, to September 30, 2018.⁵⁶ To minimize left-censoring, we included fractional prescriptions dispensed before the observation period which continued past July 1. A short time period was chosen to limit seasonal variation, secular trends, and to allow stabilization of dispensing after earlier changes in Florida law to limit days supply and require checking of the PDMP.^{57,58} Solid oral and transdermal formulations of opioid analgesics were included (detailed in Supplemental Digital Content 2, <http://links.lww.com/CJP/A783>).

Primary Analysis

Descriptive statistics were calculated under the standard assumption of consumption exactly and completely as directed. We applied the 4 definitions separately to identify the prevalence of patients who would be considered “high dose” (>90 daily MME), such as would be conceptualized in a hypothetical policy evaluation. We stratified into 3 mutually exclusive subgroups: (1) patients receiving only immediate-release or short-acting opioids, generally used for acute pain, initial management, or titration of persistent pain (hereafter *immediate-release*); (2) patients receiving only extended-release or long-acting opioids labeled for chronic pain (hereafter *extended-release*); and (3) patients receiving both immediate-release and extended-release opioids contemporaneously within the 3-month observation period (eg, including, but not limited to, patients with chronic pain receiving opioids for breakthrough pain or during taper). From continuous models of daily MME, we report arithmetic means and medians by subgroup. Data management was conducted in SAS 9.4 (SAS Institute Inc., Cary, NC); code available at www.opioiddata.org.

Meta-analyses

Applying a Food and Drug Administration (FDA) method for opioid measurement dilemmas,⁵⁹ we used meta-analytic techniques to quantify how much heterogeneity would have been observed across hypothetical state-comparison studies, each applying one of the 4 variants on the same sample (fixed effects). In preliminary analyses, Florida generally had higher opioid use than California, presumably due to an older population,⁵⁶ scope of practice legislation,^{58,60} and other factors.⁶¹ Conceptualized as a comparative surveillance study, we evaluated differences between the 2 states: (1) daily MME as categorical comparing the proportion of “high dose” patients, and (2) calculating mean differences in milligrams as a continuous variable, stratified by the 3 opioid categories from subgroup analyses. To quantify heterogeneity between definitions, we computed Higgins and Thompson I^2 metric⁶² and χ^2 statistics in Stata/MP 16.0 (Stata Corp., College Station, TX). Code and annotated output are provided in Supplemental Digital Content 3 (<http://links.lww.com/CJP/A783>).

Sensitivity Analysis

We explored the impact of inconsistency at the threshold borderline: Some studies use >90 daily MME (eg, 91 and higher), while others use \geq 90 daily MME. Like the primary analysis, the outcome was the proportion of patients considered “high dose” with prevalence differences. The corresponding number needed to harm (NNH) represents the number of patients seen before one would be misclassified as “low dose” who should have been considered “high dose.”

Ethics Statement

The study was approved by the University of Kentucky Institutional Review Board.

Patient Involvement

The Opioid Data Lab (www.opioiddata.org) is a collaboration between the authors' 3 institutions; professional representation by patients with chronic pain and people who use drugs is a core organizational tenet. Representatives review the portfolio of research projects, providing guidance from study conceptualization to findings dissemination. The definitional and clinical nature of this particular analysis

elicited limited input from representatives, mostly on clinical plausibility and impact.

RESULTS

Descriptive Findings

The analytic sample contained 9,436,640 opioid analgesic prescriptions (California, $n=5,677,277$ and Florida, $n=3,759,363$) dispensed for use between July and September 2018, encompassing 3,916,461 unique adult residents (California, $n=2,430,870$ and Florida, $n=1,485,591$). The 3-month rate of opioid dispensing was lower in California at 7.9 per 100 adult residents than in Florida with 8.7. The prevalence of prescriptions with overlapping days supply was 39.0% in California and 44.9% in Florida, corresponding to 23.0% and 27.4% of patients, respectively. Total MME per prescription was heavily right-skewed, with divergent arithmetic means and medians. In California, average MME per prescription was 1547 mg (95% confidence interval [CI]: 1540-1554), but median was 300 (25th and 75th percentile: 100 to 1275). In Florida, total MME per prescription was higher at 2146 mg (95% CI: 2138-2154), and median 382 mg (25th and 75th percentile: 113 to 1818). Arithmetic means and medians convey dramatically different perspectives on population-level prevalence of “high dose” patients.

Primary Analysis of Definitional Variants

The 4 definitions yielded a 3-fold range of MME: 17 to 52 mg/d in California and 23 to 65 mg/d in Florida (Table 1), on the same sample. The 2 states had 2.4 and 2.9-fold differences in the number of “high dose” patients >90 daily MME (Fig. 1), respectively. In California, the 4 definitions resulted in a range of 3.6% ($n=86,407$) to 10.3% ($n=249,471$) of opioid recipients identified as “high dose.” In Florida, the range was 5.9% ($n=87,295$) to 14.2% ($n=211,429$) having >90 daily MME. In both states, Definition 4 (maximum daily dose) identified the highest number of “high dose” patients. However, in California, Definition 3 (fixed observation window) returned the fewest patients with >90 daily MME, whereas in Florida Definition 1 (total days supply) provided the least.

Subgroup Analysis

We found that 92.2% of adult opioid patients were treated only with immediate-release opioids, nearly identical to national estimates.⁵⁹ In addition, 78.3% of patients with extended-release opioids also received concurrent immediate-release opioids.

We next analyzed the impact of definition choice among mutually exclusive opioid patient subgroups: immediate-release only ($n=3,611,856$), extended-release only ($n=66,077$), and any combination of extended-release and immediate-release ($n=238,528$). Patients receiving only extended-release opioids showed the least variation, with about 2-fold relative differences between the highest and lowest definitions (Table 1).

At a clinical level, the definitional variants led to different conclusions. If assessing whether a single patient was receiving a “high dose” of opioids, on average some definitions would say yes, others no. For patients receiving only extended-release, 2-out-of-4 definitions returned an average dose >90 daily MME. For patients receiving both extended-release and immediate-release opioids, 3-out-of-4 variants returned average dose >90 mg/d.

TABLE 1. Definitional Variation in MME by Type of Pain Medication

Definition	Average Daily MME		Daily MME, Median (IQR)	
	California	Florida	California	Florida
All patients on opioid analgesics (mg)				
Total days supply	33	39	25 (18, 40)	30 (20, 45)
On-therapy days	38	46	25 (18, 40)	30 (20, 46)
Fixed observation window	17	23	3.3 (1.1, 13.9)	4.2 (1.2, 19.8)
Maximum daily dose	52	65	30 (20, 50)	33 (20, 60)
No. patients	2,430,870	1,485,591	2,430,870	1,485,591
Average on-therapy days (d)	30	34	13 (5, 56)	17 (3, 69)
Immediate-release only (mg)				
Total days supply	30	34	24 (17, 38)	30 (19, 40)
On-therapy days	31	35	25 (18, 38)	30 (19, 43)
Fixed observation window	10	13	2.7 (1.1, 10.2)	3.3 (1.1, 13.0)
Maximum daily dose	40	45	30 (20, 45)	30 (20, 50)
No. patients	2,273,028	1,338,828	2,273,028	1,338,828
Average on-therapy days (d)	27	30	10 (5, 46)	12 (3, 58)
Extended-release only (mg)				
Total days supply	90	87	60 (30, 120)	60 (30, 120)
On-therapy days	104	97	62 (31, 121)	63 (32, 120)
Fixed observation window	73	67	42 (15, 90)	41 (14, 90)
Maximum daily dose	154	143	90 (45, 180)	90 (55, 180)
No. patients	40,038	26,039	40,038	26,039
Average on-therapy days (d)	61	60	75 (30, 89)	73 (29, 89)
Extended-release and immediate-release (mg)				
Total days supply	74	83	55 (38, 90)	66 (44, 108)
On-therapy days	144	160	100 (63, 172)	123 (75, 210)
Fixed observation window	123	133	82 (42, 151)	98 (51, 181)
Maximum daily dose	251	268	173 (105, 300)	200 (120, 345)
No. patients	117,804	120,724	117,804	120,724
Average on-therapy days (d)	74	74	88 (63, 92)	88 (67, 92)

IQR indicates interquartile range; MME, milligrams of morphine equivalents.

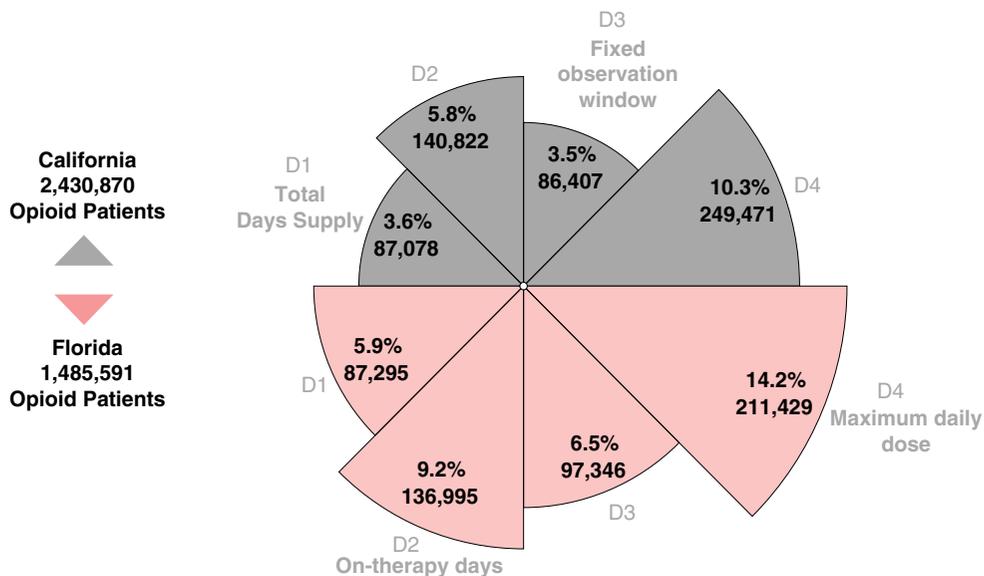


FIGURE 1. Inconsistency in identifying “high dose” patients on opioids. The proportion of patients on opioids considered “high dose” (>90 mg of morphine equivalents [MME]/day) varies by definition alone, from July to September 2018. Four definitions were identified from the literature and clinical tools. Total days supply (D1) divides the sum of MMEs by the sum of days supply, allowing the denominator to be longer than the prescribed duration. On-therapy days (D2) divides total MME by the number of calendar days. Fixed observation window (D3) uses a fixed denominator, typical 30 to 90 days in research studies. Maximum daily dose (D4) identifies the day with the highest total possible exposure.

TABLE 2. Meta-analytic Comparison of MME Definitional Variants
**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: $\chi^2 = 181, 3 df, P < 0.0001$	
CI indicates confidence interval; MME, milligrams of morphine equivalents.	

Meta-analyses

In the first meta-analysis, we compared the proportion of patients receiving “high dose” (>90 daily MME) opioids between California and Florida. MME formula was the only source of variation. While Florida consistently had more “high dose” patients, the magnitude of the difference varied solely on how daily MME was calculated: 64% or 59% or 84% or 39%. A hypothetical surveillance study or policy evaluation would reach different conclusions based on which definition was used. Meta-analytic metrics confirmed very high heterogeneity ($\chi^2 = 3257, 3 df, P < 0.0001$), with I^2 of 99.9% (Table 2).

In the second meta-analysis, we calculated mean differences in milligrams of MME per day between states. Heterogeneity was very high overall based solely on definition choice, with the extended-release only group showing the least ($I^2 = 86\%$), while the other 2 subgroups had $I^2 > 98\%$ (Table 2). A similar pattern was found using χ^2 statistics, with extended-release only showing lower relative heterogeneity arising from definition choice ($\chi^2 = 22$), followed by concurrent extended-release and immediate-release ($\chi^2 = 181$), and immediate-release only showing greatest impact from definition choice ($\chi^2 = 219$). The heterogeneity in the latter subgroup appears to be driven by Definition 3 (90-d fixed observation window) which was

markedly lower than other variants (Table 1). Patients receiving extended-release and immediate-release concurrently in Florida had consistently higher average doses than in California, however, the effect size was ambiguous: from 8.8 mg (95% CI: 8.3-9.3) to 17.2 mg (95% CI: 15.1-19.3). Definition 1 (total days supply) showed the least difference between states among patients receiving both immediate-release and extended-release opioids, but the second-highest difference in the immediate-release only subgroup. Definition 4 (maximum daily dose) consistently returned the most exaggerated result. The remaining 3 definitions changed in rank order. Further complicating the picture, patients in Florida receiving *only* extended-release opioids had lower mean MME (range: -3.3 to -10.6 mg/d) than in California. In epidemiologic terms, a claims data study using the standard incident new user design to evaluate extended-release opioids might return the opposite results to a prevalent user design.^{63,64}

Sensitivity Analysis

Both states showed boundary effects when comparing >90 daily MME to ≥90 daily MME, with a disproportionately large increase in prevalence for 1 additional milligram of MME (Table 3). Solely including the borderline unit interval: 90.0 to 90.9 increased the “high dose” proportion by 15.4% (95% CI: 15.2% to 15.7%) on average. Definition 3 (fixed observation window) was most robust to misclassification at the 90 mg borderline. With this variant, the NNH for one misclassification was 1 in 2430 in California, and 1 in 1244 in Florida. Definition 4 (maximum daily dose) was most susceptible to boundary inclusion decisions with NNH for misclassification of 1 in 67 and 1 in 30, respectively.

Data Sharing Statement

Data processing code used to construct each definition is available at www.opioiddata.org. Individual-level PDMP records are governed by state laws and requests must be made directly to those authorities; the authors are not permitted to transfer individual-level data to third parties. However, all aggregate data and code used for statistical analyses are publicly available at www.opioiddata.org and institutionally archived at the Carolina Digital Repository (<https://doi.org/10.17615/zst5-nc25>).

DISCUSSION

Over the past decade, MME have been accepted into clinical practice and adopted for opioid safety studies with limited critical assessment. 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.

Our findings preclude a universal MME formula which suits all clinical practice. The practical utility of MME in opioid management has been questioned.^{12,16} Our study further suggests that when patients are handed-off between prescribers, measurement variation could lead to inconsistent experiences for patients requiring pharmacotherapy for pain relief. MME calculations are incorporated in many clinical decision support systems, yet software interfaces and

TABLE 3. Sensitivity Analysis of Boundary Inclusion at ≥ 90 mg

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.

clinical practice rarely allow space for probing definitional nuance.⁶⁵

MMEs homogenize opioid exposure. On a policy level, the lack of definitional consensus makes it difficult to assess compliance with legislative mandates and third-party payer requirements. For example, an opioid reduction schedule was implemented by Arkansas Medicaid where beneficiaries with ≥ 250 MME per day were required to be tapered to ≤ 90 mg during an 18-month period by 50 mg intervals.⁶⁶ Since these patients are clearly not opioid naive, on-therapy days or fixed observation window may be more appropriate than the exaggerated exposure from maximum daily dose (Table 4). Without a standardized definition in this setting, choice of definition will directly impact the course of a patient’s therapy arbitrarily.

At the medicolegal interface, our work has implications for law enforcement and prescriber communication.⁶⁷ MME alert thresholds are incorporated in “doctor shopping algorithms” and automated proactive reporting, routinely devoid of diagnosis.⁶⁸ Some law enforcement use daily MME to target prescribers,⁶⁹ yet we have little reason to believe that definitions are applied with fidelity. In light of our findings, penalizing clinicians solely on the basis of 90 MME limits is problematic.⁷⁰

Of concern to epidemiologists, long-term intervention evaluation may be subject to an overlooked form of bias. This is because definition choice impacts immediate-release and extended-release opioids differentially. If the proportion of these 2 formulations changes over time, daily MME will produce biased time trends. For example, between 2012 and 2019 the number of extended-release prescriptions decreased quicker than immediate-release; the reduction was even more pronounced for extended-release opioids with properties intended to deter tampering.⁵⁹ Definition 1 is of particular concern as it exaggerates the difference in daily MME between these 2 types of formulations: Definition 1 returned one of the highest daily MMEs for immediate-release opioids, but for the lowest for extended-release. For evaluation studies with trends over time, Definition 3 may have utility since it was the most robust to misspecification, including due to overlapping prescriptions, by formulation, and at the 90 mg inclusion boundary. The mean-median inequality

also challenges assumptions in average-generating statistical models; median or geometric (eg, log-transformed) averages may be a more accurate representation because they are less prone to influence by outliers.⁷¹ The mean is not always the message; policymakers reading PDMP reports based solely on MME averages are in danger of making decisions based on metrics that are artifactually inflated. Medians and ranges may convey a more accurate picture in these scenarios.

There are standard assumptions and limitations inherent to database studies of medication use^{72,73}: perfect specification and completeness, generic equivalence,^{74,75} absence of counterfeits,⁷⁶ no external sources (eg, out-of-state, leftover, diverted, or illicitly manufactured).⁷⁷ However, these are of less concern in our study because we were not associating with biological outcomes and are independent of definition. To relax assumptions of perfect adherence, we are exploring novel parametric methods.⁷⁸ Dispensing data do not necessarily reflect actual consumption. About 60% of patients prescribed opioids retain unused medication.⁷⁹ Therefore all definitions assuming medication completion systematically overestimate biological exposure. We did not have enough information to determine how unused medications would impact each definition differently. Each definition is dependent on days supply, which is subject to variations when calculated at pharmacies; we are investigating this separately. Converting transdermal formulations to oral MME can be tricky due to dosing units measured in hours, leading to prescriber, pharmacist, and researcher variation.⁸⁰ No definition considered pain etiology or tolerance. We were not able to observe social determinants of health⁸¹ or unfilled prescriptions,⁸² and could not differentiate cancer pain. Finally, we note the debate about specific conversion factors between opioid molecules.^{16,19} We did not evaluate the impact of equianalgesic multipliers in a bid to reduce analytic complexity. Finally, the toxicologic framing of MME may have limited application for opioids where fatal toxicity does not involve respiratory depression (eg, serotonin depletion with tramadol), in the presence of atypical mu-opioid receptor agonism (eg, tapentadol, buprenorphine), or when consumed in the presence of synergistic nonopioid central nervous system depressants.

TABLE 4. Recommendations on Equianalgesic Definitional Variants

1. *Total days supply*: The least complicated calculation appears best suited when immediate-release opioids are prescribed for short discrete times. It consistently underestimated MME per day when overlapping prescriptions were present or when immediate-release and extended-release opioids were prescribed concurrently, as with 78% of patients with chronic opioid use
2. *On-therapy days*: Provides a smoothed measure useful in studies of dose-dependent adverse effects, including opioid-induced constipation or overdose in patients with opioid tolerance or who have been stable on opioids. The metric is time-varying and affords the greatest flexibility to define medication gap periods and leftover/unused medications to improve pharmacoepidemiologic studies
3. *Fixed observation window*: Most suitable for studies with a known or suspected duration of risk during which adverse events are expected to occur, such as incidence of opioid use disorder. This definition may be useful when prescriptions are filled at irregular time intervals on a as-needed basis (*pro re nata*). The definition consistently had the lowest milligrams per day for immediate-release opioids. This is the definition recommended by the Department of Health and Human Services Office of the Inspector General.⁴³ It is the most robust to misspecification, amenable to transformations, and has the least noise when constructing continuous functions.⁴⁰ However, since it assumes uniform exposure/risk within a window, there is less scope for time-varying adjustment
4. *Maximum daily dose*: A toxicological perspective may be appropriate for opioid naive patients with no tolerance and in the presence of comorbidities for respiratory depression. It appears to be best suited for immediate dose-dependent toxic effects, such as respiratory depression in opioid naive patients. This definition may have limited use if it includes opioids where fatal toxicity does not involve respiratory depression (eg, tramadol) or have atypical mu-opioid receptor agonism (eg, tapentadol, buprenorphine). The definition assumes uniform risk of adverse outcomes regardless of time on-therapy. More so than the others, this definition is prone to influence from early refills, unused medication, and how the 90 MME threshold is operationalized. This definition underlies the algorithm embedded in the CDC Opioid Guideline mobile app.⁵¹ There may be difficulty reconciling findings with studies using the other definitions because it returns a MME per day that is significantly higher

CDC indicates US Centers for Disease Control and Prevention; MME, milligrams of morphine equivalents.

Our recommendations (Table 4) will benefit from collective iteration. Definition 2 appears to have face validity with routine clinical practice. Definition 4's toxicologic focus might be useful for new opioid patients with simple regimens at risk for respiratory depression but carries the highest risk of overestimating daily MME. It remains to be seen if shifting clinical definition choice between patients may provide more practice autonomy and better patient outcomes. At a minimum, clinical guidelines, legislation, PDMP vendors, and clinical decision support systems should make formulae, conversion tables, and code explicit. Research studies should consider sensitivity analyses by definition choice, and treating MME exposure as a transformed continuous variable.⁸³ Our findings may have implications for other drug classes (eg, benzodiazepines⁸⁴ and stimulants) and the World Health Organization defined daily dose for opioids.^{80,85,86}

The sensitivity analysis showed that 15% of patients were right on the 90 to 91 mg borderline. While our study was not designed to assess prescribing motivations, the strong clustering effect suggests that this threshold might be used as a cap to appear in compliance with external mandates. There is no particular clinical reason we could identify for patients to otherwise cluster at 90 MME per day outside of policy, health system, and payer requirements. We speculate that patients who might have otherwise received higher doses are subsumed under this threshold. Definitional choices have consequences.

Despite variation in underlying definitions, the studies cited in the CDC Guideline consistently found an increased risk of fatal overdose ≥ 90 daily MME. The simplest explanation is an artifact of turning a continuous metric into one that is categorical: All but 2 studies^{30,33} we reviewed categorized MME exposure using 90 to 120 mg as the lower bound for the highest stratum. However, for fatal overdose, not all opioid molecules exhibit a dose-dependent correlation.⁸⁷ Still, our study supports FDA's contention that overdose risk with opioid analgesics is a continuous function.⁸⁸ Historically, the transition of the MME concept from pain relief to toxicology ignored the clinical concept of differential tolerance.⁸⁹ With opioid dose escalation, analgesic and unintended effects emerge asynchronously. While

90 MME may have cautionary mnemonic benefits in the midst of broad societal concern, a renewed emphasis on opioid tolerance and definitional harmonization (for daily MME and long-term therapy^{11,90}) seems overdue.

The overlooked inconsistency among daily MME definitions revealed by our study calls into question the clinical validity of a single numerical risk threshold. When measuring with inches, centimeters, and yards, the absolute number of units is arbitrary. The mix of clinical and research metrics used to calculate the 90 MME threshold is similarly convoluted. As providers, we struggle to do what we feel is right for our patients in the midst of increasing outside pressure with serious ramifications. Our findings call into question state laws and third-party payer MME threshold mandates. Without harmonization, the scientific basis for these mandates may need to be revisited. As the CDC Guideline is revised, and clinical decision tools are developed, it is critically important to reassess the evidence base in light of this previously unknown MME definitional variability.

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