



Clinical Review: Morphine Equivalent Daily Dose to Prevent Opioid Overuse

Learning Objectives:

- Define morphine equivalent daily dose (MEDD) and how it is being used to indicate potential dose-related risk for prescription opioid overdose.
- Describe high-risk prescribing of prescription opioids within the Medi-Cal fee-for-service program.
- Summarize best practices for responsible opioid prescribing.

Key Points:

- While there is no completely safe dose of opioids, MEDD can be used as an indicator of potential dose-related risk for adverse drug reactions, including overdose.
- While there are differing opinions as to the maximum MEDD threshold that should trigger additional action by clinicians, the Medical Board of California (MBC) recommends proceeding cautiously once the MEDD reaches 80 mg.
- In the Medi-Cal fee-for-service population, the vast majority (87%) of paid claims for opioids were well under the 80 mg MEDD threshold recommended by the MBC for a yellow flag warning.
- Online MEDD calculators are available to help clinicians determine morphine milligram equivalency. These calculators are not intended for dosage conversion from one product to another, but can be used to assess the comparative potency of opioids using a morphine equivalency standard.
- All providers who prescribe opioids need to enroll in and access California's prescription drug monitoring program, available on the [Controlled Substance Utilization Review and Evaluation System \(CURES\)](#) Web page of the Office of the Attorney General website. In order to be most effective, MEDD calculations need to include all opioid prescriptions written for a patient, including those written by other providers.

Background

Each day in the United States, 46 people die from an overdose of prescription opioid or narcotic pain relievers.¹ The Centers for Disease Control and Prevention (CDC) describes the following groups as particularly vulnerable to prescription opioid overdose: 1) people who obtain multiple controlled substance prescriptions from multiple providers; 2) those who take high daily dosages of prescription painkillers and those who misuse multiple abuse-prone prescription drugs, especially other CNS depressants, such as benzodiazepines, carisoprodol, or other sedatives; 3) low-income people and those living in rural areas; and 4) people with mental illness and/or those with a history of substance abuse.²

Morphine Equivalent Daily Dose (MEDD)

Recent studies demonstrate that a patient's cumulative MEDD is an indicator of potential dose-related risk for adverse drug reactions to opioids, including overdose.^{3,4} The terminology for daily morphine equivalency may vary depending on the resource used, and may be described as MEDD, morphine equivalent dose (MED), or morphine milligram equivalents (MME). **Daily morphine milligram equivalents are used to assess comparative potency, but not to convert a particular opioid dosage from one product to another.** The calculation to determine morphine milligram equivalents includes drug strength, quantity, days' supply and a defined conversion factor unique to each drug. By converting the dose of an opioid to a morphine

equivalent dose, a clinician can determine whether a cumulative daily dose of opioids approaches an amount associated with increased risk.

Online calculators are available to estimate MEDD. **It should be noted again that these calculators are not intended for dosage conversion from one product to another, but only to assess the comparative potency of opioids.** Furthermore, calculated morphine equivalency may vary between tools for certain drugs, depending on the algorithm used. Commonly used websites that offer MEDD calculators include the following:

- [Washington State Agency Medical Directors' Group](#)
- [Prescription Drug Monitoring Program Training and Technical Assistance Center \(PDMP TTAC\)](#)
- [The New York City Department of Health and Mental Hygiene](#)

Equianalgesic dose ratios are only approximations and do not account for genetic factors, incomplete cross-tolerance between various opioids, and variable pharmacokinetics that may affect relative potency. If used to estimate a conversion, it is recommended that after calculating the appropriate conversion dose, the prescribed dose be reduced by 25 – 50% to assure patient safety.⁴

Compared with patients receiving an MEDD of 1 – 20 mg, who had a 0.2% annual overdose rate, patients receiving an MEDD of 100 mg or more had almost nine times as much risk of overdose and a 1.8% annual overdose rate as compared to the lowest doses.³ The CDC review of opioid prescribing and overdose found that among patients who are prescribed opioids, an estimated 80% are prescribed low doses (<100 mg MEDD) by a single provider, and these patients account for an estimated 20% of all prescription drug overdoses. Another 10% of patients are prescribed high doses (≥100 mg MEDD) of opioids by single prescribers and account for an estimated 40% of prescription opioid overdoses. The remaining 10% of patients seek care from multiple doctors, are prescribed high daily doses, and account for another 40% of opioid overdoses.⁵

While there are differing opinions among experts and organizations as to the maximum MEDD threshold that should trigger additional action by clinicians (Table 1), the MBC recommends proceeding cautiously (a yellow flag warning) once the MEDD reaches 80 mg.⁶ There is no completely safe opioid dose.

Table 1. Selected Organizations' MEDD Thresholds and Recommended Actions

Year	Organization	MEDD Threshold (mg/day)	Recommended Action at MEDD Threshold
2010	American Academy of Pain Medicine ⁷	>200	Increase frequency and intensity of monitoring
2010	Utah State Clinical Guidelines ⁸	>120 – 200	Increase clinical vigilance
2010	Veterans Affairs/Department of Defense ⁹	>200	Refer or consult
2010, 2015	Washington State Agency Medical Directors' Group ⁴	>120	Consult from pain management expert
2011	Canadian Guidelines ¹⁰	>200	Reassess or monitor
2011, 2014	American College of Occupational and Environmental Medicine ¹¹	≥50	Follow up frequently; document improved function
2011	New York City Department of Health and Mental Hygiene ¹²	>100	Reassess pain status or consider other approaches
2012	American Society of Interventional Pain Physicians ¹³	>91	Consider pain management consultation
2012	Centers for Medicare and Medicaid Services ¹⁴	>120	Consider case management
2014	Medical Board of California ⁶	≥80	Proceed cautiously and consider referral to specialist when higher doses are contemplated
2015	California Division of Workers' Compensation ¹⁵	≥80	Increase clinical monitoring, consider specialty referral, attempt to wean to lower dose.

In addition, as of federal fiscal year 2013 (FFY 2013), nine state Medicaid programs reported having an established policy with a recommended maximum MEDD (Table 2).¹⁶

Table 2. State Medicaid Drug Use Review (DUR) Programs with Established Recommendations for Maximum MEDD

State	MEDD Threshold (mg/day)	Additional Information
Delaware	120	All long-acting opioids require prior authorization. The total dose for all narcotic therapy must be <120 mg MEDD.
Kansas	200	
Massachusetts	360	Individual dose limits for each opioid were determined based on utilization trends.
Maine	30	Prior authorization is required for any dose over 30mg; maximum allowable dose 300 mg
Michigan	30	
North Carolina	750	Maximum allowable dose
Oregon	120	
Washington	120	Based on Agency Medical Directors Association Interagency Guidelines
Wyoming	120	

Both Massachusetts and Washington have described in detail the impact of implementing an established policy and predetermined maximum MEDD threshold for triggering a detailed patient review.^{17,18} Massachusetts defined a specific maximum MEDD for oxycodone, fentanyl, morphine,

and methadone (they selected two standard deviations outside the mean dose noted in their drug utilization review). In addition to requiring prior authorization for the specified dose, a multidisciplinary team including a physician, pharmacist, and behavioral specialist reviewed high-dose utilization profiles every two weeks. The team participated in phone interventions for clarification of prior authorization requests, treatment care plans, or specific restrictions. Over a three-year period (2002 – 2005), the number of unique utilizers decreased by 17.8% (p <0.0001) and the number of claims by 4.1% (p <0.0001).¹⁷ Claims for oxycodone decreased by 34.9% and claims for fentanyl decreased by 25%.¹⁷

In 2007, the Washington State Agency Medical Directors' Group, which represents all public payers in Washington, developed a collaborative interagency guideline on opioid dosing (updated in June 2015).⁴ The guideline recommends that at an MEDD of 120 mg providers must obtain consultation from a pain medicine expert for patients whose pain and function have not substantially improved as a result of opioid treatment. An evaluation of the impact of the guideline was conducted through 2010, and showed the number of prescriptions for Schedule II opioids plateaued during 2006 – 2008, and then declined sharply in 2009 and 2010.⁷ The total number of paid prescriptions for Schedule III opioids had peaked in 1999 (93,550), then declined through 2008 (79,882), 2009 (63,808) and 2010 (52,499).⁷ The average MEDD among beneficiaries declined from a peak of 144.7 in 2002 to 105 in 2010.¹⁸

MEDD in the Medi-Cal Fee-For-Service Population

A retrospective cohort study was conducted to calculate the MEDD for all paid pharmacy claims for prescription opioid medications in the Medi-Cal fee-for-service population (dates of service between July 1, 2014, and June 30, 2015). The National Drug Code (NDC), days supply, and drug quantity fields were extracted from Medi-Cal pharmacy claims data and matched (via NDC) to the drug strength and MME conversion factor using the Morphine Equivalent Calculator Tool developed by the PDMP TTAC at Brandeis University, in collaboration with the CDC.

The following equation was used to calculate MEDD:

$$\frac{(\text{Drug Strength}) \times (\text{Drug Quantity}) \times (\text{MME Conversion Factor})}{(\text{Days Supply})}$$

All instructions for MEDD calculation were followed using the technical assistance guide provided by the PDMP TTAC.¹⁹

An additional analysis was performed on a subset of Medi-Cal fee-for-service beneficiaries who were continuously eligible in the Medi-Cal fee-for-service program between January 1, 2015, and June 30, 2015, and who had at least one paid claim for a prescription opioid medication between April 1, 2015, and June 30, 2015 (the measurement period). Medical and pharmacy claims data were reviewed for all beneficiaries in the study population with a calculated cumulative morphine equivalent dose >120 mg for at least one day during the measurement period. Data fields specifying diagnostic codes and place of service were extracted from medical claims data and were used to identify those beneficiaries in the study population who had a primary or secondary diagnosis of cancer and/or who were receiving hospice care.

Descriptive statistics were used to summarize MEDD values and claims data. Data analyses were performed using IBM® SPSS®, version 23.0 (Chicago, IL).

Results

Between July 1, 2014, and June 30, 2015, a total of 529,681 paid pharmacy claims for prescription opioid medications were filled by a total of 262,017 Medi-Cal fee-for-service beneficiaries. The summary of paid claims exceeding MEDD thresholds of 80 mg, 100 mg, and 120 mg for all paid claims is shown in Table 3. Also shown in Table 3 is the distribution among a subset of paid claims with a days supply >14 days, as over half (56%) of all paid claims for opioids between July 1, 2014, and June 30, 2015, were for a days supply ≤7 days.

Table 3. Total Paid Claims Exceeding Recommended MEDD Thresholds in the Medi-Cal Fee-For-Service Population (Dates of Service Between July 1, 2014, and June 30, 2015)

	Recommended MEDD Thresholds		
	>80 mg/day	>100 mg/day	>120 mg/day
Total paid claims (n = 529,681)	71,236 (13.4%)	58,741 (11.1%)	47,769 (9.0%)
Total paid claims >14 days supply (n = 237,106)	62,596 (26.4%)	54,060 (22.8%)	43,865 (18.5%)

The vast majority of paid claims for opioids were well under the 80 mg/day threshold recommended by the MBC for a yellow flag warning (87% of all paid claims and 74% of paid claims >14 days supply). However, during one year there were 47,769 paid claims identified that exceeded 120 mg MEDD.

As the CDC identified people who obtain multiple controlled substance prescriptions from multiple providers as one of the high-risk groups for opioid overdose, a summary of the total number of prescribers and pharmacies is shown in Table 4 for all Medi-Cal fee-for-service beneficiaries who had a paid claim for an opioid during that same year.

Table 4. Crosstabulation of Total Prescribers and Total Pharmacies for Opioid Paid Claims in the Medi-Cal Fee-For-Service Population (Dates of Service Between July 1, 2014, and June 30, 2015)

Total Utilizing Beneficiaries (n = 262,017)		Total Pharmacies					
		1	2	3	4	5 – 9	10+
Total Prescribers	1	208,071	8,131	886	129	24	0
	2	18,113	13,079	1,434	269	66	0
	3	2,952	3,104	1,467	288	113	0
	4	648	790	533	249	102	1
	5-9	300	403	365	241	208	7
	10+	2	5	3	5	22	7

The majority of these beneficiaries (n = 208,071; 79%) had only one paid claim for a prescription opioid medication during this one-year period. However, a total of 3,611 beneficiaries (1%) had paid claims for opioids from three or more prescribers and filled these claims at three or more pharmacies.

A total of 22,505 beneficiaries were included in an analysis of cumulative MEDD. Each of these beneficiaries was continuously eligible in the Medi-Cal fee-for-service program between January 1, 2015, and June 30, 2015, and had at least one paid claim for a prescription opioid medication between April 1, 2015, and June 30, 2015. This 90-day window was selected in order to identify the distribution of beneficiaries who exceeded a cumulative total of >120 mg MEDD for at least one of those days, and to identify beneficiaries who exceeded >120 mg MEDD for the entire 90 days, which would make this group at high-risk for overdose due to sustained high-dose opioid use over time.

As shown in Table 5, a total of 3,904 beneficiaries (17%) were identified in this group with at least one day out of 90 that exceeded >120 mg cumulative MEDD. Results are stratified by those who had a primary or secondary diagnosis of cancer and/or who were receiving hospice care, and those who did not have a primary or secondary diagnosis of cancer and no indication of hospice care in the medical claims data.

Table 5. Summary of Medi-Cal Fee-For-Service Beneficiaries Days >120 mg Cumulative MEDD (Dates of Service Between April 1, 2015, and June 30, 2015)

Days with MEDD >120 mg	Cancer/Hospice (n = 1,306)	Non-cancer/ Non-hospice (n = 21,199)	Total (n = 22,505)
0	1,078 (83%)	17,523 (83%)	18,601 (83%)
≥1	228 (17%)	3,676 (17%)	3,904 (17%)
≥2	225 (17%)	3,648 (17%)	3,873 (17%)
≥3	223 (17%)	3,593 (17%)	3,816 (17%)
≥10	217 (17%)	3,467 (16%)	3,684 (16%)
≥30	178 (14%)	2,778 (13%)	2,956 (13%)
≥60	120 (9%)	1,900 (9%)	2,020 (9%)
≥90	65 (5%)	963 (5%)	1,028 (5%)

Of the 1,028 beneficiaries that exceeded >120 mg cumulative MEDD for all 90 days, almost half (n = 410; 40%) had only one prescriber and one pharmacy for all opioid claims, while 49 beneficiaries (5%) had paid claims for opioids from three or more prescribers and filled these claims at three or more pharmacies. There was no statistically significant difference between the number of days that exceeded >120 mg cumulative MEDD when stratified by cancer/hospice status.

Conclusion/Discussion

While there is no completely safe dose of opioids, the ability to calculate morphine equivalent dose adds an additional assessment tool to combat potential opioid overdose and/or overuse. Federal and state agencies should provide guidelines and instructions for calculation of MEDD and promote case management and, as needed, referrals to appropriate pain specialists as higher doses of opioids are considered. Finally, all providers who prescribe opioids need to enroll in and access California's prescription drug monitoring program, CURES. In order to be most effective, MEDD calculations need to include all opioid prescriptions written for a patient, including those written by other providers.

Clinical Recommendations

- Review materials and resources for preventing prescription drug abuse available through the [California State Board of Pharmacy](#), [Medical Board of California](#), and the [California Department of Public Health](#).
- Weigh the benefits and risks of opioid therapy, especially for opioid therapy when alternative treatments are ineffective.
- Discuss with patients the risks and benefits of pain treatment options, including those that do not involve prescription painkillers.
- Follow best practices for responsible opioid prescribing, including:
 - Consult CURES initially and at every subsequent visit
 - Conduct a physical exam, urine drug test, and document pain history prior to prescribing opioids
 - Screen for substance abuse, mental health problems, and other physical conditions that are contraindicated for opioid use
 - Advise against concomitant use of alcohol, sedatives, and hypnotics
 - Implement pain treatment agreements

- Prescribe the lowest effective dose of short-acting opioid producing analgesia and improved function (no more than 80 mg MEDD) in a limited supply with no refills
- Regularly evaluate the role of opioid therapy beyond 3 months for non-cancer chronic pain
 - ❖ Use tapering (not abrupt cessation) to discontinue or reduce dose of opioids
- Track and document levels of pain and function at every visit
- Exercise vigilance at high doses
 - ❖ Consider prescribing naloxone as a rescue medication in the event of a potentially life-threatening overdose and instruct caregivers on proper use and administration. For detailed information on dosing and administration of naloxone, please go to the [Prescribe to Prevent](#) website
- Enroll in and access CURES reports to establish whether or not an individual is receiving controlled substances from multiple prescribers. The CURES report should be requested frequently for patients who are being treated for pain and/or addiction.

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