



## Clinical Review Update: Morphine Equivalent Daily Dose

### Learning Objectives:

- Describe morphine equivalent daily dose (MEDD) and how it is being used to indicate potential dose-related risk for prescription opioid overdose.
- Summarize best practices for prescribing opioids.
- Identify resources available that promote responsible opioid prescribing, including online and mobile applications for calculation of morphine milligram equivalency.
- Describe recent legislation in California related to prescription opioids.

### 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.
- The Medical Board of California (MBC) recommends proceeding cautiously at 80 mg MEDD. Referral to an appropriate specialist should be considered when higher doses are contemplated.
- In the Medi-Cal fee-for-service population, the vast majority (97.4%) of paid claims for opioids were well under the 80 mg MEDD threshold recommended by the MBC for a yellow flag warning.
- Online and mobile application 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.
- In order to be most effective, MEDD calculations need to include all opioid prescriptions written for a patient, including those written by other providers. Effective October 2, 2018, it is mandatory to consult the [Controlled Substance Utilization Review and Evaluation System \(CURES\) 2.0](#) database prior to prescribing, ordering, administering, or furnishing a Schedule II – IV controlled substance.
- Effective January 1, 2019, California prescribers are now required to offer a prescription to a patient for either naloxone or another drug approved by the U.S. Food and Drug Administration (FDA) for the complete or partial reversal of opioid-induced respiratory depression when certain conditions are present, including when the prescription dosage for the patient is  $\geq 90$  mg MEDD.

## Background

Each day in the United States, 46 people die from an overdose of prescription opioid or narcotic pain relievers.<sup>1</sup> While the amount of opioids prescribed in the United States began to decrease in 2011,<sup>2</sup> in 2017, prescription opioids were still involved in more than 35% of all opioid overdose deaths.<sup>1</sup> 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 and pharmacies; 2) people who take high daily dosages of prescription painkillers and those who misuse multiple abuse-prone prescription drugs, especially other central nervous system (CNS) depressants, such as benzodiazepines, carisoprodol, or other sedatives; 3) people with a low income who live in rural areas; and 4) people with mental illness and/or those with a history of alcohol or other substance abuse.<sup>3</sup>

## Morphine Equivalent Daily Dose (MEDD)

While there is no completely safe opioid dose, a patient's cumulative MEDD is one indicator of potential dose-related risk for adverse drug reactions to opioids, including overdose.<sup>4-6</sup> 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 equivalent (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. 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 ensure patient safety.<sup>4-6</sup>

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.<sup>4</sup> 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.<sup>6</sup>

Online and mobile application 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. Web-based calculators are offered by several agencies, including the [Washington State Agency Medical Directors' Group](#) and the [Oregon Health Authority](#).

The CDC also offers the CDC Opioid Guideline application, which is available for free download on [Google Play](#) (Android devices) and in the [Apple Store](#) (iOS devices). This mobile application is designed to help providers apply the recommendations of CDC's Guideline for Prescribing Opioids for Chronic Pain and includes an MEDD calculator, summaries of key recommendations and a link to the full Guideline, and an interactive motivational interviewing feature to help providers practice effective communications skills and prescribe with confidence.

While there are differing opinions among experts and organizations regarding 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.<sup>7</sup> In addition, effective January 1, 2019, California prescribers are now required to offer a prescription to a patient for either naloxone or another drug approved by the FDA for the complete or partial reversal of opioid-induced respiratory depression when the following conditions are met:

- The prescription dosage for the patient is  $\geq 90$  mg MEDD.
- An opioid medication is prescribed concurrently with a prescription for a benzodiazepine.
- The patient presents with an increased risk for overdose, including a patient with a history of overdose, a patient with a history of substance use disorder, or a patient at risk for returning to a high dose of opioid medication to which the patient is no longer tolerant.

**Table 1. Selected Organizations' MEDD Thresholds and Recommended Actions**

Year	Organization	MEDD Threshold (mg/day)	Recommended Action at MEDD Threshold
2014	Medical Board of California <sup>7</sup>	$\geq 80$	Proceed cautiously and consider referral to specialist when higher doses are contemplated
2015	Washington State Agency Medical Directors' Group <sup>6</sup>	$> 120$	Consult from pain management expert
2015	California Division of Workers' Compensation <sup>8</sup>	$\geq 80$	Increase vigilance and clinical monitoring, consider specialty referral, attempt to wean to lower dose
2016	American College of Occupational and Environmental Medicine <sup>9</sup>	$\geq 50$	Increase vigilance
2017	American Society of Interventional Pain Physicians <sup>10</sup>	$\geq 91$	Consider pain management consultation
2017	Canadian Guidelines <sup>11</sup>	$\geq 90$	Referral to a colleague for a second opinion regarding the possibility of increasing the dose
2017	Veterans Affairs/Department of Defense <sup>12</sup>	$> 90$	Evaluate for tapering to reduced dose or to discontinuation
2018	New York City Department of Health and Mental Hygiene <sup>13</sup>	$> 90$	Reassess pain status and treatment plan
2019	Centers for Medicare and Medicaid Services <sup>14</sup>	$\geq 90$	Real-time opioid care coordination safety edit at the time of dispensing as a proactive step to engage both patients and prescribers about overdose risk and prevention

As of federal fiscal year 2017, a total of 24 state Medicaid programs reported having an established policy with a recommended maximum MEDD, which ranged from 300 mg (Colorado) to 30 mg (Maine).<sup>15</sup> Seven states and the District of Columbia reported plans to implement a maximum MEDD during federal fiscal year 2018.<sup>15</sup> Of note, states with higher maximum MEDD often reported using a scheduled tapering protocol, where the maximum MEDD allowed without authorization is decreased at set intervals (typically every 6 months).<sup>15</sup> Patients undergoing active cancer, palliative, and end-of-life care are usually excluded from MEDD maximum requirements.

### 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 from January 1, 2018, through December 31, 2018). 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 provided by the CDC. As the CDC identified people who obtain multiple controlled substance prescriptions from multiple providers as one of the high-risk groups for opioid overdose, an evaluation of the total number of prescribers and pharmacies was also conducted.

All instructions for MEDD calculation were followed using the [Toolkit: Using Data Analysis To Calculate Opioid Levels and Identify Patients At Risk of Misuse or Overdose](#), developed by the Office of Inspector General, U.S. Department of Health and Human Services.<sup>16</sup> Descriptive statistics were used to summarize MEDD values and claims data. Data analyses were performed using IBM® SPSS®, version 25.0 (Chicago, IL).

### Results

Between January 1, 2018, and December 31, 2018, a total of 487,835 paid pharmacy claims for prescription opioid medications were filled by a total of 189,583 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 2. Almost half (n = 219,300; 47.9%) of these paid claims for opioids between January 1, 2018, and December 31, 2018, were for a days' supply ≤7 days, so also shown in Table 3 is the distribution among a subset of paid claims with a days' supply >14 days.

**Table 2. Total Paid Claims Exceeding Recommended MEDD Thresholds in the Medi-Cal Fee-for-Service Population (dates of service between January 1, 2018, and December 31, 2018)**

	Recommended MEDD Thresholds		
	>80 mg/day	>100 mg/day	>120 mg/day
<b>Total paid claims (n = 487,835)</b>	12,795 (2.6%)	8,420 (1.7%)	6,465 (1.3%)
<b>Total paid claims &gt;14 days' supply (n = 174,569)</b>	7,970 (4.6%)	5,782 (3.3%)	4,520 (2.6%)

The vast majority of paid claims for opioids were well under the 80 mg MEDD threshold recommended by the MBC for a yellow flag warning (97.4% of all paid claims and 95.4% of paid claims >14 days' supply). However, during one year there were 4,520 paid claims identified for a days' supply >14 days that exceeded 120 mg MEDD prescribed to a total of 1,487 beneficiaries. A review of ICD-10-CM data for 2018 found the majority of these beneficiaries (n = 1,284; 86.3%) did not have diagnosis codes indicating they were receiving active cancer treatment, palliative, or end-of-life care.

Table 3 summarizes the total number of prescribers and pharmacies for all Medi-Cal fee-for-service beneficiaries who had a paid claim for an opioid during that same year.

**Table 3. Total Prescribers and Total Pharmacies for Opioid Paid Claims in the Medi-Cal Fee-for-Service Population (dates of service between January 1, 2018, and December 31, 2018)**

Total Utilizing Beneficiaries (n = 189,583)		Total Pharmacies				TOTAL
		1	2	3	4+	
Total Prescribers	1	152,706	6,603	1,048	331	160,688
	2	12,444	8,277	1,116	383	22,220
	3	1,934	1,753	775	241	4,703
	4+	585	680	407	300	1,972
TOTAL		167,669	17,313	3,346	1,255	189,583

The majority of these beneficiaries (n = 167,669; 88.4%) had only one paid claim for a prescription opioid medication during this one-year period. However, a total of 1,255 beneficiaries (0.7%) had paid claims for opioids from three or more prescribers and filled these claims at three or more pharmacies.

### Conclusion/Discussion

While there is no completely safe dose of opioids, the ability to calculate the morphine equivalent dose adds an additional assessment tool to combat potential opioid overdose and/or overuse. Health care providers should follow CDC and MBC guidelines for use of opioids and calculation of MEDD, promote case management and, as needed, referrals to appropriate pain specialists as higher doses of opioids are considered, and offer a prescription for naloxone (or similar drug) as indicated by new California regulations. Finally, all providers who prescribe opioids are now required to enroll in and access California's prescription drug monitoring program, [CURES 2.0](#). 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:

- Follow the [CDC Guideline for Prescribing Opioids for Chronic Pain](#), which includes the following recommendations:
  - Use opioids only when benefits are likely to outweigh risks.
  - Start with the lowest effective dose of immediate-release opioids. For acute pain, prescribe only the number of days that the pain is expected to be severe enough to require opioids.
  - Reassess benefits and risks if considering dose increases.
- Review the [Guideline Resources](#) available on the CDC website, which include clinical tools and materials for patients.
- Review materials and resources for preventing prescription drug abuse that are available through the [California State Board of Pharmacy](#), [Medical Board of California](#), and the [California Department of Public Health](#).

- Offer a prescription for naloxone or another drug approved by the FDA for the complete or partial reversal of opioid-induced respiratory depression to a patient when one or more of the following conditions are present:
  - The prescription dosage for the patient is  $\geq 90$  mg MEDD.
  - An opioid medication is prescribed concurrently with a prescription for a benzodiazepine.
  - The patient presents with an increased risk for overdose, including a patient with a history of overdose, a patient with a history of substance use disorder, or a patient at risk for returning to a high dose of opioid medication to which the patient is no longer tolerant.
- For detailed information on naloxone dosage and administration, providers may visit the [Prescribe to Prevent](#) website.
- Follow best practices for responsible opioid prescribing, including:
  - Consult the [CURES 2.0](#) database 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 three 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.
- If opioid use disorder is suspected based on patient concerns, patient behaviors, findings in prescription drug monitoring program data, or findings from urine drug testing, health care providers should discuss their concerns with their patients and provide an opportunity for the patient to disclose related concerns or problems.
  - Health care providers should assess for the presence of opioid use disorder or arrange for a substance use disorder treatment specialist to assess for the presence of opioid use disorder.
  - For patients meeting criteria for opioid use disorder, health care providers should offer or arrange for patients to receive evidence-based treatment, including medication-assisted treatment (MAT) with buprenorphine in combination with behavioral therapies.

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