

Opioid Dosing Policy: Pharmacological Considerations Regarding Equianalgesic Dosing

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Introduction

As the United States grapples with the public health crisis of opioid misuse, abuse, addiction, and overdose deaths, one common response from policymakers and third-party payers has been to suggest (or even mandate) limits on doses of opioid analgesics. In nearly all cases, ranging from the 2010 guideline from the Washington Agency Medical Directors Group to the 2016 CDC Guideline for Prescribing Opioids for Chronic Pain, dose limits are expressed in terms of a “morphine equivalent daily dose (MEDD).” Recently, third-party payers (including Medicare and Medicaid) have begun limiting coverage for opioid analgesics beyond certain MEDD levels.

Recommended dose limits would be easy to apply if all opioid analgesics had the same potency. Unfortunately, they do not. Consequently, researchers have carried out studies to determine the relative potency of various opioids in terms of their ability to relieve pain, and have summarized their results in equianalgesic conversion tables that facilitate determining the equipotent dose of any given opioid in comparison to any other given opioid.

Unfortunately, these equianalgesic conversion tables rely on a few assumptions that commonly are ignored by prescribers, dispensers, policymakers, and payers. Among these assumptions are that: 1) all the analge-

sic effect derived from a given medication is due to its action on the mu opioid receptor; and 2) all patients respond identically to all opioid medications. One group of opioids with multiple mechanisms of action, often referred to as “atypical opioids,” illustrates the dangers that can result from erroneously accepting these assumptions. Using common equianalgesic conversion tables to determine doses of these atypical opioids is fraught with danger, and potentially can result in patients unintentionally being under-dosed or over-dosed.

This white paper explains the history of equianalgesic dosing research, explores the assumptions that underlie the concept of equianalgesic dosing, and reviews the “atypical” opioid medications and the reasons why applying MEDD restrictions to those medications is risky. Policymakers and payers are advised to consider these issues when using MEDD as a means of controlling opioid dosing.

Opioid Activity Overview

There are three endogenous opioid receptors in the brain—mu, kappa, and delta—which are responsible for various pharmacological activities and side effects. Opioids provide varying degrees of analgesic benefit through activities at these receptors, each of which has several subtypes. Prototypical full opioid agonists provide most of their analgesic effect at the mu receptor and are called mu-receptor agonists. The majority of traditional FDA-approved opioids come from this class of medications. Although the primary desirable effect of these drugs is analgesia, commonly associated corollaries include euphoria, respiratory depression, diminished cognition, constipation, and other undesirable side effects, including potential for physical tolerance, physical dependence, and addiction. Other opioids have variable mechanisms of action on the opioid receptors and/or additional mechanisms of action above and beyond their opioid activity. For these “atypical” opioids, it is difficult, if not impossible, to compare their analgesic potency to that of morphine—i.e., to calculate a morphine equivalent daily dose (MEDD). Several terms are used synonymously to refer to the concept of mor-

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phine equivalencies. These include “morphine equivalents (MEQs),” “oral morphine equivalents (OMEQ),” “morphine milligram equivalents (MME),” “morphine equivalent dose (MED)” or “morphine equivalent daily dose (MEDD).” For the purposes of this commentary, MEDD will be used throughout when discussing morphine dosing equivalents.

Scientific Validity of Equianalgesic Dose Conversions

Equianalgesia is a measure of equivalence of analgesic effect between two different opioids. Equianalgesia does not imply, nor was it ever intended to assign, an equivalent abuse or respiratory depression risk when comparing two or more opioids.¹⁻³ An equianalgesic dose is the dose at which two opioids provide the same degree of pain relief. Equianalgesic dose tables have been developed for various opioids, based primarily on single-dose studies in individuals with limited previous exposure to opioids.²

To understand the validity of equianalgesic opioid dose conversion, it is important to understand the experimental process that led to the development of equianalgesic dosing. The first equianalgesic table was published approximately 50 years ago based on collated results of numerous relative potency trials.⁴ Although many versions have been published since then, the equianalgesic dose estimates have undergone few modifications.

Most of the potencies in these tables were derived from single-dose studies in acute post-operative or cancer pain populations. In these potency studies, participants were given a low dose and a high dose of the study drug and a low dose and a high dose of the comparator drug.¹⁻³ Numeric pain assessments were conducted at baseline and after administering the study drug. Only one outcome—pain reduction—was determined using the sum of pain intensity differences (SPID) or total pain relief (TOTPAR) measures.¹ Other opioid effects were not measured, and only certain opioids were included as comparators, which we will address later. Dose-related pain reduction was calculated for each medication, and these calculated values were compared to derive relatively equivalent

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doses, hence the term, “equianalgesia.” For example, if 10mg of drug-A provided 30% pain relief, and 20mg of drug-B provided 30% of pain relief, then 10mg of drug-A would be considered equianalgesic to 20mg of drug-B. Because these studies used single doses, often in people not previously using opioids, the concept of equianalgesic dosing cannot be reliably applied to long-term opioid dosing. This concept attempts to establish linear relationships among relative dose, potency, and effect; however, it does not adequately consider differences in the ways various medications affect opioid receptors or distinct characteristics of a drug that emerge at varying doses. Relative potency studies often included patients with little opioid exposure, which explains why MEDD is not readily applicable in chronic pain. It is well established that accumulation of opioids (particularly those with active metabolites) with repeated dosing contributes to analgesic response, or lack thereof depending on an individual patient’s genetic phenotype (how many opioid receptors and what types of receptors are present, ability to metabolize or not metabolize certain drugs, and other individualized biochemical and physiological differences) and drug interactions. For example, repeated dosing of morphine in a patient with reduced kidney function may cause the active metabolite, morphine-6-glucuronide, to accumulate with resultant improved analgesia but also more respiratory depression.⁵ Further consideration of this

must be given in patients with comorbidities likely to cause accumulation of parent drug and/or metabolites, such as hepatic or renal disease.

Variability Among Equianalgesic Calculators

Despite the lack of a universally accepted opioid-conversion method,^{6,7} several states have developed their own versions of opioid conversion calculators with different MEDD cut-offs than those proposed by CDC.⁸⁻¹² Furthermore, there is wide variability among equianalgesic calculators. Shaw et al., evaluated eight online opioid dose conversion calculators and identified a percent variation of -55% to +242%.⁶ Rennick, et al. surveyed 319 health care professionals on calculating

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MEDD for several opioids and found wide variability.¹³ The study authors asked participants to calculate MEDD for hydrocodone 80mg, fentanyl 75mcg/hour (1800mcg/day), methadone 40mg, oxycodone 120mg, and hydromorphone 48mg. The calculated MEDD for fentanyl, hydrocodone, hydromorphone, methadone, and oxycodone were: 176 (\pm 117) mg, 88 (\pm 42) mg, 192 (\pm 55) mg, 193 (\pm 201) mg, and 173 (\pm 39) mg, respectively. The standard deviation from these two studies alone exceeds the CDC¹⁴ and most state recommended MEDD thresholds for consulting a pain management specialist. The bottom line is that there is no universally accepted MEDD calculator and there is significant heterogeneity in calculating MEDD among clinicians.

Limitations to Equianalgesic Dose Conversions

Aside from calculations, there are patient-specific factors that are often ignored by policy makers when establishing MEDD cut-offs. These factors include age, body surface area, organ dysfunction, drug tolerance, etiology of pain (neuropathic or nociceptive), pharmacogenetics, drug-drug interactions, and drug-food interactions.^{7,15} These factors vary greatly between individuals, as demonstrated in relative potency studies that find a wide range among study participants.^{1,2,16-19} One important consideration is that the published equianalgesic dosing is based on the mean values; however, several studies have found large variability in the potency among study participants.¹⁶⁻¹⁹ For example, one study found a mean morphine to oxycodone ratio of 1.5:1 with a range of 1.1:1 to 2.3:1.¹⁶ In a small study of participants switched from morphine to subcutaneous fentanyl infusion, the mean ratio of morphine to fentanyl was 68:1 with a range of 15:1 to 100:1.¹⁷ Relying on mean values when a wide range exists is mathematically unsound and poses major risks to patients on either end of the range when these values are used clinically.

Attempts to replicate equianalgesic doses in subsequent studies often found widely varying results.^{18,19} For example, in one study, cancer patients receiving modified-release morphine were converted to transdermal fentanyl, with a mean ratio of morphine to fentanyl of 70:1.¹⁸ A similar study yielded a 96.6:1 ratio.¹⁹ Additionally, the direction of the change influences the relative equianalgesic potency. In one retrospective trial, the morphine-to-hydromorphone ratio for patients switched from morphine to hydromorphone was 5.33:1 and for patients switched from hydromorphone to morphine was 3.8:1.¹⁶

To understand why these variabilities exist, it is important to recognize the impact of pharmacokinetics, pharmacodynamics, and pharmacogenetics on opioid

response.^{15,20} The pharmacological effect of a drug is related to the concentration at the target receptor, which depends on pharmacokinetics and various biochemical and stereochemical considerations at the target receptor.²¹ Pharmacokinetics is defined as the course of drug absorption, distribution, metabolism, and excretion, all of which vary from one individual or population (termed polymorphic variation or polymorphism) to another. In one study, the oral bioavailability of morphine ranged from 15% to 64%, which is more than a four-fold difference.²² Distribution varies among individuals based on their body habitus, adipose distribution, and lipophilicity of the drug.²¹ For example, fentanyl is very lipophilic and accumulates into skeletal muscle and adipose tissue and is released slowly into the bloodstream.²⁰ According to the package insert, the average volume of distribution (Vd) for fentanyl is 6 liters/kg (range 3-8).²³ A 70 kg individual would have a Vd of 420 liters and a 120 kg individual would have a Vd of 720 liters.

Considering the impact of genetic variation on drug metabolism, it is important to recognize that most opioids primarily rely on phase I hepatic metabolism through cytochrome P450 (CYP) with few exceptions.²⁰ The CYP activity can vary among individuals based on their liver function, pharmacogenetic make-up, and presence of drug-drug interactions.^{7, 15,20} For example oxycodone as a parent drug has analgesic activity. It is metabolized by CYP2D6 to active metabolite oxymorphone and also by CYP3A4 to inactive metabolite noroxycodone. A patient whose genetic makeup makes her a rapid CYP2D6 metabolizer would rapidly convert oxycodone to oxymorphone (a more potent metabolite) and might be expected to have an increased analgesic response at lower doses compared to a patient who is a poor CYP2D6 metabolizer, which would result in reduced conversion to the more potent metabolite (oxymorphone); this latter patient ultimately could require much higher doses for a similar analgesic effect. This is in stark contrast to the metabolism of morphine, which avoids the CYP

system, relying on phase II metabolism. As such, it is impossible to equate the dosing of morphine to that of a drug requiring phase I CYP metabolism in a patient who is a genetic outlier in terms of their ability, or lack thereof, to metabolize a drug. Consider therefore what could happen if a patient was switched from high-dose morphine, which requires no CYP metabolism, to a presumed equivalent dose of oxycodone, which relies heavily on CYP3A4 for conversion. Now imagine that the patient to be switched is genetically a poor CYP3A4 metabolizer; he/she would be unable to metabolize the oxycodone effectively, which could result in overdose. Conversely, if the same person were instead an ultra-rapid expresser of CYP3A4, it could result in opioid withdrawal or false accusations that the patient is drug-seeking. The potential scenarios are endless considering the multiple enzymes involved in various drug metabolism and possible genetic abnormalities.

Opioid elimination can vary depending on a patient's kidney function, which declines with age.²¹ Based on this factor, two patients can be taking the same dose and have significantly different blood concentrations. Even if two individuals have the same concentration of one drug at the receptor, genetic variations in the receptor make-up and/or number of receptors may lead to disparities in analgesic response.^{15,20,24} Single nucleotide polymorphisms (SNP) in the mu-opioid receptor (OPRM1) have been shown to affect analgesic response.^{24,25} Individuals with 118A>G SNP in the OPRM1 may require higher opioid doses to achieve the same analgesic effect compared to individuals carrying the 118A allele.²⁵

Opioid Agonists That Should Not Have MEDD

Mu opioid receptor agonists that have additional mechanisms of action above and beyond their traditional opioid agonist activity, otherwise known as atypical opioids, should not have MEDD (Table 1). These include methadone, tramadol, tapentadol, levorphanol, and some less commonly prescribed opioids.²⁶

Methadone and levorphanol are synthetic opioids that inhibit norepinephrine (NE) reuptake and block N-methyl-D-aspartate (NMDA) receptors. Both of these activities have inherent analgesic activities (and potential for side effects) apart from their true opioid effects.

Tramadol and tapentadol are opioid receptor agonists of the phenylpropylamine class, and inhibit NE reuptake.^{27,28} Additionally, tramadol inhibits reuptake of serotonin. Further, unlike the others listed, tramadol is a prodrug (meaning it has no analgesic activity until after it is metabolized in the body) requiring CYP2D6 enzyme metabolism to its active form. Tramadol is quite chameleonic compared to most drugs, as it is a partial agonist and has metabolites that create a substantial potential for drug interactions and variable response due to polymorphism.²⁷

Table 1: Atypical Opioids That Should not Have MEDD²⁶⁻³¹

Butorphanol
Buprenorphine
Methadone
Levorphanol
Nalbuphine
Pentazocine
Tapentadol
Tramadol

These medications' additional pharmacologic properties contribute to their overall analgesic effect independent of mu-receptor activation. For example, tapentadol was found to be 18 times less potent than morphine in binding to the mu-opioid receptor but 2-3 times less potent in providing analgesia.³² This is presumably because of its dual analgesic mechanisms of mu-receptor activation and NE reuptake inhibition. Notwithstanding, patients with neuropathic pain components are likely to require lower MEDD when prescribed tapentadol compared to pure mu-receptor agonists because neuropathic pain may respond nicely to various (non-opioid) antidepressants that specifically work by blocking norepinephrine reuptake alone. Therefore, employing MEDD as a measure of analgesia for these agents is not appropriate.

Partial mu-receptor agonists other than tramadol (i.e., buprenorphine, butorphanol, and pentazocine) exhibit different behavior at the receptor compared to full agonists.²⁰ Compared to a full agonist, partial agonists do not fit as snugly when bound to the mu receptor. Because of this, they do not provide the same level of analgesia at low-to-moderate doses and, unlike full agonists, their analgesic activity plateaus at a certain dose. At low doses, these partial agonists may provide similar effects to full agonists. As the dose of a full agonist is increased, there is a proportional increase in opioid activity. However, with partial agonists, the activity eventually plateaus where further dose increases will not provide additional analgesic effect, but may cause adverse effects.³³ Buprenorphine has a ceiling effect on carbon dioxide accumulation where respiratory depression risk plateaus at higher doses.³⁰ For this reason, it should be considered as a first option for patients requiring long-term opioid therapy prior to initiating less expensive and more readily available full agonists such as oxycodone, hydrocodone, and the like. Although many clinicians employ tramadol as their first choice, it presents several risks as outlined above. But also, noteworthy of tramadol

is that its affinity for mu-receptors is 6,000 times lower than morphine, similar to the extremely weak activity seen with the well-known over-the-counter cough syrup dextromethorphan (Robitussin DM); therefore, tramadol's opioid activity cannot account for its analgesic properties.³⁶

Special Considerations When Switching to or from Atypical Opioids

There are important considerations that impact initial dosing and titration when switching to and from the atypical opioids. Applying MEDD dosing in one step conversions from these agents to full agonists or vice versa can lead to patient harm, especially when converting a full opioid agonist. Therefore, conversions need to be done methodically and slowly. Important considerations when converting atypical opioids to or from traditional full agonist opioids are summarized in Table 2.

Methadone

Methadone has a complex pharmacokinetic profile that, if ignored, can lead to increased morbidity and mortality. This should be of no surprise considering methadone contributed to nearly 1 in 3 overdoses despite accounting for less than 2% of all prescription sales in 2009.³³ The equianalgesic dose ratio of methadone is non-linear and it becomes more potent as the methadone dose increases.³⁴ This is thought to be related to methadone's inhibitory effect on the NMDA receptor, which attenuates tolerance developed as the dose of other opioids is increased. Although counterintuitive, when converting to methadone from another opioid, the higher the dose of that other opioid, the less methadone is needed to replace it. It is critical to understand that these conversions to and from methadone are not bi-directional.

Methadone is lipophilic (fat soluble) with a large Vd and a long elimination half-life (8-59 hours) subject to high inter-individual variability, up to 150 hours in polymorphic outliers.^{31,33} Methadone relies on phase I metabolism and thus is subject to drug-drug interactions that can increase or decrease its blood concentrations. When a patient is converted to methadone, dose

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escalations should not occur more frequently than every 5-7 days. Since methadone is lipophilic, it deposits into fat and other tissues and is slowly released back into the blood. When a patient is first started on methadone, their blood methadone levels will continue to gradually rise on the same dose until tissues equilibrate with blood (i.e., steady state is reached). Rapid dose escalations can cause methadone to accumulate and could result in overdose.

When converting from methadone to another opioid, it is important to remember that methadone will have a persisting effect for a few weeks as it continues to be released from the tissues into the blood. If a patient switching from methadone to another opioid starts the full dose by "equianalgesic mathematical conversion" immediately following methadone discontinuation, they can have overlapping exposure to two opioids and potentially overdose. It can generally take up to 3 weeks for methadone to be fully cleared out of the body after discontinuation.

Buprenorphine

In addition to its mixed partial agonist/antagonist effects, buprenorphine has strong binding affinity to the mu-receptor with slow dissociation rate from the receptor, which makes it harder for other opioids to displace buprenorphine from the mu-receptor.²⁹ In other words, buprenorphine wraps tightly around the mu-receptor and makes it harder for other opioids to bind to the mu-receptor. Buprenorphine has a long elimination half-life of 24-42 hours depending on the formulation. It can generally take up to 5-7 days for buprenorphine to be cleared from the body. Therefore, when switching a patient from buprenorphine to another opioid, the patient may require higher dosing in the first few days if buprenorphine was not tapered.

Tapentadol

In the package insert of tapentadol, there is no mention of MEDD or equianalgesic conversion ratio, because it has not been studied. In pivotal trials, tapentadol ER (100 - 250 mg bid) had comparable efficacy to oxycodone CR (25 - 50 mg bid) in moderate to severe osteoarthritis pain, low back pain, and pain related to diabetic peripheral neuropathy.³⁵ These studies were either active or placebo-controlled and, to our knowledge, there are no crossover studies evaluating switching from one opioid to tapentadol or vice versa.

The equianalgesic dose ratios for tapentadol only factor in analgesic potency and not potency in regard to opioid receptor activation. As discussed previously, there is a wide disparity between tapentadol's affinity and analgesic potency, which is likely due to its additional activity on the descending pain pathway via NE reuptake inhibition. It is important to understand that tapentadol's MEDD for non-analgesic effects

Table 2: Commonly Prescribed Opioids and Conversion Risk

	Mechanism of action	Risks converting to traditional full agonist	Risks converting from traditional full agonist	CYP enzymes involved	Other
Buprenorphine	Partial mu-agonist Kappa antagonist Delta agonist Partial ORL-1 (nociceptin) agonist	Buprenorphine has a higher affinity for the mu-receptor compared to traditional opioids. As buprenorphine undergoes metabolism, risk of overdose due to higher full agonist exposure increases.	Buprenorphine prevents full opioid agonists from binding to mu-receptors, which can cause unanticipated withdrawal symptoms when full agonist is at moderate-to-high dose.	CYP3A4 (major), Moderate risk of drug interactions and genetic variation when converting doses.	Buprenorphine-induced opioid withdrawal is often misinterpreted as intolerance to buprenorphine.
Methadone	Full mu-receptor agonist NMDA inhibitor (weak) Inhibits reuptake of norepinephrine and serotonin	Methadone blood levels linger in the body tissue and blood for several days to weeks. When methadone is stopped in lieu of a new full agonist opioid, it is synonymous with giving both drugs even though methadone was discontinued. This elevates risk of overdose.	Rapid escalations due to initial poor response as methadone reaches steady state and enters body tissues. If escalation is done too rapidly (shouldn't be adjusted for 5-7 days), risk of overdose increases. pharmacokinetics of methadone is counter-intuitive; the higher the dose of methadone, the less of a traditional opioid is needed to replace it.	CYP3A4 (major) CYP2B6 (major) CYP2C8 CYP2C19 CYP2C9 CYP2D6 High risk of drug interactions and genetic variation when converting doses.	The higher the dose of methadone, the more potent it becomes.
Tapentadol	Full mu-receptor agonist Inhibits reuptake of norepinephrine	Low risk. No comparative trials have been powered to assess opioid equivalence when converting tapentadol to morphine or other full agonist opioids.	Low risk. No comparative trials have been powered to assess opioid equivalence when converting to tapentadol from morphine or other full agonist opioids.	Mostly phase II metabolism with minimal and therapeutically insignificant CYP involvement. Minimal if any risk of drug interactions and genetic variation when converting doses.	There is an assigned FDA maximum dose of 500mg per day for ER formulation, and 600mg per day for IR formulation (after day-1).

related to opioid receptor activation is theoretically less than equianalgesic doses from clinical trials. Therefore, applying equianalgesic dose conversion when switching a patient from tapentadol to a traditional full agonist opioid (i.e. oxycodone, hydrocodone, morphine) can lead to more opioid activity and potential overdose. Instead, conservative dosing should be exercised when switching patients from tapentadol to another opioid.

How to Employ MEDD in Practice

As not all opioids are created equal with regard to mechanism of action and metabolism, the concept of assigning equivalent dosing conversions is not scientifically reliable. Doing so places patients at increased risk for potentially fatal adverse effects, including but not limited to overdose. Conversely, assigning a maximum daily MEDD ignores the specific needs of patients, placing them at risk for poor outcomes and increased suffering. While MEDD should not be used as a tool for direct conversion, it can provide a guideline for end dose titration when tapering or switching from one or more opioids to another.

Conclusion

The employment of morphine milligram equivalents to create parameters for patient dosing of opioids is based on an idealistic theory and not representative of the scientific characteristics of each therapy and it ignores patient-centered parameters that should be considered for individualized therapy. The practice of setting arbitrary milligram dosing cut-offs as suggested by various regulatory agencies and legally allowed by some states is an attempt to pigeon hole providers into ignoring the approach to medicine. Rather than assigning irrational rules based on pseudoscience, the regulatory agencies including the CDC and state governments should be targeting ways to increase knowledge and education with regard to opioids to foster safe and efficacious prescribing practices.

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