Variability in Opioid Equivalence Calculations

Article *in* Pain Medicine · September 2015

DOI: 10.1111/pme.12920

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Original

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Disclosures: Amanda Rennick: Nothing to disclose; Timothy Atkinson: Nothing to disclose; Nina Cimino: Nothing to disclose; Jeffrey Fudin: Consultant to Practical Pain Management in development of online opioid conversion calculator, Consultant to Zogenix and Millennium Health; Speakers' Bureaus for Millennium Health and Astra Zeneca; Mary Lynn McPherson: Nothing to disclose; Scott Strassels: Employee of Mallinckrodt Pharmaceuticals; contribution to this article occurred prior to joining company.

Abstract

Objective. Equianalgesic conversion methods are commonly used to switch patients from one opioid to another due to suboptimal pain relief or adverse events. There is no universally accepted opioid conversion method, however, and there is often significant variability between conversion resources. As a result, patients are at risk for undertreated pain and serious adverse events. The purpose of this survey was to compare the equianalgesic conversion estimates between nurse practitioners, pharmacists, and physicians for commonly prescribed opioids.

Methods. A survey form was developed using Survey Monkey. Participation was solicited by providing a link to the survey via social media (e.g., Facebook, Twitter, LinkedIn, etc.) and emailing professional organizations for sharing with their members and followers. Data collected included demographics and estimated morphine equivalents (MEQs) of hydrocodone 80 mg, fentanyl transdermal patches 1,800 mcg (as 75 mcg/hour), methadone 40 mg, oxycodone 120 mg, and hydromorphone 48 mg. Participants were also asked to provide their choice of reference utilized to complete the conversions, including personal knowledge. Descriptive analyses were performed using measures of central tendency. Hypothesis testing was performed using Pearson's chi-squared and Fisher's Exact Test for categorical data and the Kruskal–Wallis equality of populations rank test for continuous data to assess differences between median opioid doses by professional groups.

Results. The total number of respondents included in the analysis was 319. Physicians, pharmacists, and nurse practitioners/physician assistants comprised 25.4%, 56.7%, and 16.3%, respectively, of respondents. The overall mean (± standard deviation) MEQ doses for fentanyl, hydrocodone, hydromorphone, methadone, and oxycodone were: 176 (±117) mg, 88 (±42) mg, 192 (±55) mg, 193 (±201) mg, and 173 (±39) mg, respectively. For fentanyl, the mean (±standard deviation) MEQ doses were 180 (±122) mg, 178 (±128) mg, and 157 (±68) mg, for physicians, pharmacists, and nurse practitioners/physician assistants, respectively. For all three groups of clinicians, the median MEQ dose for fentanyl was 150 mg. The mean (±standard deviation) MEQ

doses of methadone for physicians, pharmacists, and nurse practitioners/physician assistants were: 214 (±142) mg, 171 (±107) mg, and 185 (±129) mg, respectively. The median MEQ dose for methadone was 160 mg for each of the clinician groups.

Conclusions. As evidenced by large standard deviations, there was significant variation in mean opioid conversions to MEQ doses within each profession type, particularly for fentanyl and methadone. The median MEQ doses provided for opioid conversions were the same among each profession. No universal method exists that allows each of the five studied opioids to be accurately and consistently converted to another opioid (i.e., morphine).

Key Words. Variability; Opioid; Equivalence; Conversion

Introduction

Opioid overdoses in the U.S. quadrupled from 1999 to 2010 with a corresponding increase in prescriptions for opioids driven mainly by increased prescribing for chronic noncancer pain (CNCP) [1]. Prescription opioids are responsible for almost 15,000 overdose deaths annually, and now cause more overdose deaths than cocaine and heroin combined [2]. In addition, opioid analgesics were associated with 75% of all prescription overdose deaths [1]. Opioids, including oxycodone, methadone, hydrocodone/acetaminophen, fentanyl, and morphine, account for five of the top 15 drugs shown to contribute to overdose fatalities [3]. Exploration and close scrutiny by clinicians, public health experts, and lawmakers alike have attributed the root cause of the increase in opioid overdoses to increased access of prescription opioids. According to the Joint Commission, opioids are one of the most commonly used drug classes associated with adverse events [4]. Lack of knowledge regarding differences in potency is one of the reasons given by the Joint Commission for the common implication of opioids in adverse events [4].

While nonmedical use and abuse of opioids may be a contributing factor to the rise in prescription opioid-related deaths, one cannot discount the possibility that some of these fatalities may be influenced by inappropriate opioid conversion. According to Webster and Fine, "Recent evidence suggests that the use of dose conversion ratios published in equianalgesic tables may lead to fatal or near-fatal opioid overdoses."[5] A 2012 CDC report states that methadone accounted for less than 2% of dispensed opioid prescriptions but was responsible for nearly one-third of opioid-related deaths [6]. Methadone conversion schematics present an even greater risk compared to other opioid conversions because of heightened polymorphic variability, complex pharmacokinetics, and mathematical conversions that are not bidirectional [7]. Although switching between opioid analgesics can be challenging and pose a safety risk if done inappropriately, it is frequently necessary when caring for patients with pain. Reasons for changing a patient from one or more opioids to another include lack of efficacy, tolerance, development of side effects, and/or hyperalgesia, among others [8,9]. Patients who respond poorly to one opioid are often switched to another opioid in hopes of improving pain relief [10]. Up to 80% of these patients experience a positive response when switching agents [5]. Equianalgesic opioid conversion tables and online opioid conversion calculators are readily available to aid clinicians in dosing when converting patients from one or more opioid analgesics to another opioid. However, as prescribing of opioids has become more prevalent and deaths from opioid overdoses have increased congruently, so too does the concern for the accuracy and reliability of such conversion resources [5].

At present, several states have passed laws setting maximum daily thresholds for opioids while others have published guidelines suggesting appropriate daily limits [11,12]. Third party payers are also beginning to limit coverage to a certain maximum morphine equivalent dose including Medicaid in a couple of states [13,14]. However, if any maximum dosage is placed on opioids, the potential for substantial confusion exists because there is no officially acceptable method of converting between opioids, and there is significant variability among the various conversion sources. The lack of consensus regarding appropriate opioid conversion therefore raises the potential for adverse patient care outcomes and confusion regarding public policy and regulation.

The purpose of this survey was to compare the results of opioid conversion calculations provided by various clinician types (physicians, pharmacists, nurse practitioners, and physician assistants) and to ascertain the variability among these results. Survey participants were asked to perform conversion calculations for five preselected opioids to oral morphine equivalent doses. The five preselected opioid doses were: hydrocodone 80 mg, fentanyl transdermal patches 1,800 mcg (as 75 mcg/hour), methadone 40 mg, oxycodone 120 mg, and hydromorphone 48 mg; these opioids and doses were selected because the practitioners may encounter them in everyday practice.

The primary hypothesis was that there would be a statistically significant difference in the mean oral morphine dose calculated as equivalent to each of the five preselected opioids. This was previously demonstrated on a small sample size of pharmacy students from the Albany College of Pharmacy & Health Sciences, however, no information is available on whether differences in opioid conversions are observed among clinicians, and whether or not the results of opioid conversion calculations vary according to practitioner type (physicians, pharmacists, nurse practitioners, and physician assistants) [15].

Table 1 Participants' professional characteristics n (column %).

	Nurse Practitioners (n = 69)	Pharmacists (n = 213)	Physicians (n = 129)	*P*-value
Specialty	N = 67	N = 201	N = 123	<0.001
Ambulatory Care (n = 151)	12 (17.9)	100 (49.8)	39 (31.7)	
Pain & Palliative Care (n = 240)	55 (82.1)	101 (50.3)	84 (68.3)	
Board Certified	N = 68	N = 213	N = 129	<0.001
No	37 (54.4)	203 (95.3)	63 (48.8)	
Yes	31 (45.6)	10 (4.7)	66 (51.2)	
Conversion resource	N = 48	N = 126	N = 93	0.082
Journal table	1 (2.1)	12 (9.5)	2 (2.2)	
Online calculator	17 (35.4)	32 (25.4)	34 (36.6)	
Personal Knowledge	19 (39.6)	64 (50.8)	41 (44.1)	
Textbook table	11 (22.9)	18 (14.3)	16 (17.2)	

Methods

Data for this study was derived from an online survey that was developed using SurveyMonkey® to collect estimated equianalgesic doses of five commonly prescribed opioids to their corresponding daily morphine equivalent oral doses: fentanyl 1,800 mcg/24 hour transdermal (as 75 mcg/hour); hydrocodone 80 mg oral; hydromorphone 48 mg oral; methadone 40 mg oral; and oxycodone 120 mg oral. Respondents were also asked for demographic information, such as their profession and practice area(s), board certifications, year of licensure, location of practice, and resources used to complete the conversion problems. An advanced version of Survey Monkey was purchased with funds accrued from vouchers at the Albany College of Pharmacy and Health Sciences for training Student Pharmacists. This advanced survey form allowed for an unlimited number of collected responses and the ability to transfer data directly into Microsoft Excel.

The final survey was posted on Facebook, Twitter, other social media sites and various pain management websites, including practicalpainmanagement.com and paindr.com. Additionally, a link to the survey was emailed to several professional organizations, including the American College of Clinical Pharmacy (ACCP) and the Reserve Officers' Training Corps (ROTC) for sharing with their members. Survey respondents were asked to indicate their profession (physician, pharmacist, physician assistant, and nurse practitioner) and specialty area of practice, if applicable. Survey respondents who did not practice as one of the healthcare professionals listed above were able to identify themselves as "patients and others" to discourage respondents from misrepresenting themselves. However, only data from nurse practitioners, pharmacists, and physicians were included in the survey analysis, as only 12 physician assistants responded. Other reasons for exclusion included respondents who did not belong to one of the three groups of clinicians, selected multiple professions and specialties, or those who did not provide any answers to the conversion problems.

Data were assessed using the mean, median, standard deviation, and range for continuous variables, and proportion for categorical variables. For continuous variables, hypothesis testing of the differences between medians was done using the Kruskal–Wallis equality of populations rank test. This test is the nonparametric analog to the Analysis of Variance. For categorical variables, hypothesis testing was done using the Pearson's chi-squared and Fisher's exact tests for cells in which the expected count was less than 5. All persons in the dataset were included, and analyses were performed using STATA MP 12.1 (StataCorp LP, College Station, TX).

Results

The survey was open from September 2013 and closed in December 2013. Of the 471 respondents, 60 were excluded, leaving a total sample size of 411. Physicians, pharmacists, and nurse practitioners comprised 31.4%, 51.8%, and 16.8%, respectively, of respondents. Approximately half of the pharmacists who participated in the survey identified a specialty of

Table 2 Mean estimated morphine equivalents by profession (median, SD, range, n)

	Nurse Practitioners (n = 69)	Pharmacists (n = 213)	Physicians (n = 129)	*P*-value
Fentanyl 75 mcg/hourr	n = 68 186.9 (150, 152.4, 15–1,113)	n = 210 180.7 (150, 119.3, 5.6–1,500)	n = 128* 186.1 (150, 152.2, 5–1,350)	0.9193
Hydrocodone 80 mg	n = 69 81.5 (80, 36.0, 20–320)	n = 210 88.6 (80, 43.6, 26.7–400)	n = 126 91.8 (80, 43.0, 10–320)	0.2389
Hydromorphone 48 mg	n = 69 181.2 (192, 67.4, 12–336)	n = 213 191.5 (192, 41.3, 7–384)	n = 129 198.7 (192, 67.1, 12–576)	0.0253
Methadone 40 mg	n = 68 202.8 (170, 134.0, 7–400)	n = 203 177.5 (160, 110.5, 4–600)	n = 122 198.3 (160, 132.4, 10–800)	0.6413
Oxycodone 120 mg	n = 69 169.7 (180, 48.5, −18–360)	n = 213 177.1 (180, 35.0, 40–360)	n = 128 174.8 (180, 39.9, 60–360)	0.4107

Hypothesis testing was done using the Kruskal–Wallis equality-of-populations rank test (nonparametric analog to ANOVA; test of medians) using Stata/MP 12.1.

* One physician estimated that fentanyl 75 mcg/hour was equivalent to morphine 22,500 mg. We excluded this point as it was fifteen times the next highest estimate.

pain and palliative care, while over 80% of NPs and nearly 70% of physicians identified specialties in this area. However, only 66 of the total 411 participants noted an official board certification in pain and palliative care (Table 1).

A total of 124 (46%) respondents identified using personal knowledge as a resource for their conversion problems, followed by use of an online calculator at 83 (31%), a textbook table at 45 (17%), and a conversion table from a journal at 15 (6%) (Figure 1).

The overall mean [± standard deviation] MEQ doses for fentanyl, hydrocodone, hydromorphone, methadone, and oxycodone were: 183 [± 136] mg, 88 [± 42] mg, 192 [± 55] mg, 188 [± 122] mg, and 176 [± 38] mg, respectively. For fentanyl, the mean [± standard deviation] MEQ doses were 186 [± 152] mg, 181 [± 119] mg, and 187 [± 153] mg, for physicians, pharmacists, and nurse practitioners, respectively. For all three groups of clinicians, the median MEQ dose for fentanyl was 150 mg.

The mean [± standard deviation] MEQ doses of methadone for physicians, pharmacists, and nurse practitioners were: 198 [± 132] mg, 178 [± 111] mg, and 203 [± 134] mg, respectively. The median MEQ dose for methadone was 160 mg for physicians and pharmacists and was 170 mg for nurse practitioners (Table 2).

Discussion

Converting patients from one opioid to another may be necessary for a variety of reasons including suboptimal analgesia, occurrence or risk of adverse events, development of tolerance, drug interactions, or opioid-induced hyperalgesia, among others. There are a variety of equianalgesic conversion methods used in clinical practice, however there is no standard method widely accepted or considered best practice. Further, it is generally recognized that different conversion methods can result in different results, which may have important clinical consequences. To demonstrate this, we invited healthcare professionals to perform 5 opioid conversions at set doses to their morphine equivalent or equianalgesic doses utilizing any source available to them.

The results presented in this report provide evidence that the clinical utility of commonly used conversion methods is uncertain. For example, across all practitioner types, although median estimated doses were very similar, mean doses varied widely, the ranges were wide, and standard deviations large, indicating that estimates were skewed and widely dispersed. The most alarming result in the current study was the vast differences in conversions for fentanyl and methadone, which are so extreme that these findings could contribute to harm or death. The median fentanyl conversion was similar for all practitioners, but the variability as measured by their standard deviation was (± 152) mg, (± 119.3) mg, and (± 152.4) mg, for physicians, pharmacists, and nurse practitioners respectively. The methadone results were also highly variable with standard deviations of (± 132.4) mg, (± 110.5) mg, and (± 134) across the same groups. At inappropriately low doses, patients are at risk of uncontrolled pain, while at high doses, patients are at increased risk of opioid-related adverse events, toxicity, and overdose.

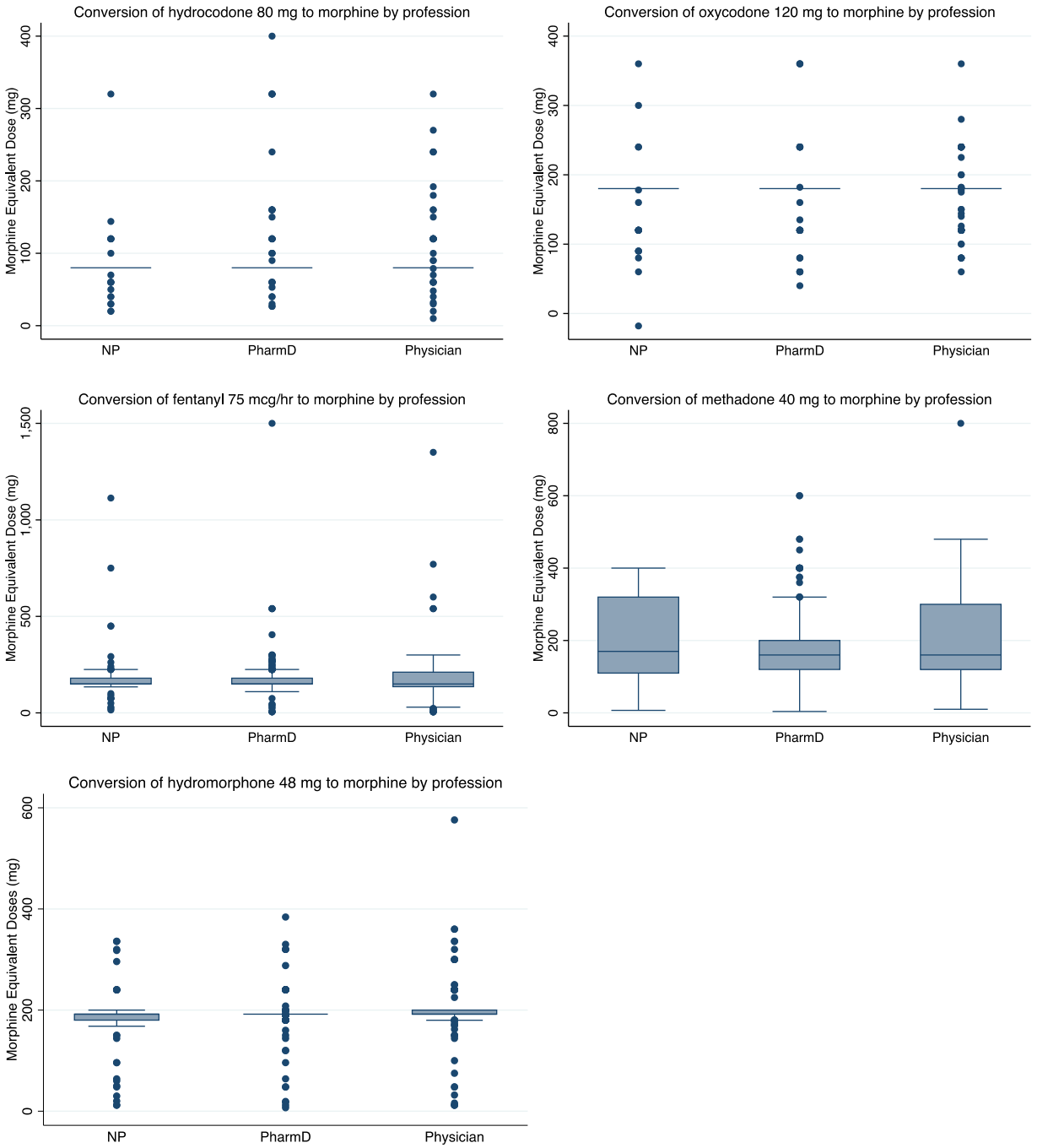

Figure 1 Box and Whisker Plots of Conversion Data by Profession. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

This finding also helps explain why methadone consistently results in more opioid-related overdose deaths than any other opioid despite representing a small fraction of opioid prescriptions [3,7,16].

Establishing consistency in clinical practice for specific opioid equivalence and conversions is difficult for a number of reasons. Few randomized controlled clinical trials directly compare different doses of opioids, so while some equivalencies are evidenced-based, many are extrapolated. Existing opioid conversion ratios are typically based on single dose studies [15]. Standardization conversion ratios do not exist in part because pain societies and government agencies are

hesitant to endorse a particular conversion ratio as "official" due to an evidence deficit and a lack of validation. As a result, available opioid equivalence tables vary between authors and institutions based upon limited clinical data and adopted expert opinion. The source of information appears to have a significant impact on the variability between providers. For example, in our study 23% of practitioners said they used a textbook, institutional table, or journal article as their source for opioid equivalency to perform conversions. Over 30% of practitioners reported using online opioid calculators to convert between opioids, however online conversion calculators have been shown to introduce substantial variability and in some cases drastically overestimate conversions particularly with fentanyl (100%) and methadone (242%) [17]. The remaining 46% of practitioners relied upon personal knowledge to make opioid conversions.

Results were similar across all three major practitioner groups responding to our study (nurse practitioners, NP; pharmacists, PharmD or RPh; physicians, MD, or DO) as demonstrated by similar median conversions but immense variability within each group. The majority of participants heard about the study from pain management websites or email LISTSERVS and this is reflected in the demographics of respondents. Almost two-thirds (62%) of respondents indicated pain management as their specialty with the approximate remaining one-third (38%) in general practice. Although the majority of survey respondents self-identified as pain specialists, the profound inconsistency and wide variability in opioid conversion calculations reflects the widespread nature of this problem. This may be a reflection of overconfidence in equianalgesic tables, source inconsistency, and reliance on personal knowledge by pain specialists.

The lack of consistency for opioid conversion calculations among clinicians observed in this survey likely represents variability in clinical practice. This variability may place patients at increased risk of opioid adverse effects or conversely, under-treatment of pain. More studies are necessary to directly assess relative equivalencies, if plausible, particularly with the opioids having the highest degree of variability (i.e., fentanyl and methadone). Although determining precise opioid equivalencies is limited by a range of patient-specific factors such as age, genetics, comorbid disease states, and medications, more robust data expanding upon the currently available literature could certainly provide more insight into the accuracy of existing conversion ratios and perhaps better inform clinicians as to which additional clinical factors should be considered when calculating equivalent doses of opioids. Best practice guidelines are available for opioid conversions but the strategies recommended are based upon expert opinion and should be validated in additional studies to confirm safety and efficacy [18]. Studies are available converting from morphine to fentanyl or methadone, however, there is a dearth of studies illuminating appropriate conversions back to morphine leading practitioners to incorrectly assume these conversions are bidirectional. Conversions that are conservative in one direction are liberal, aggressive, and potentially disastrous if applied in reverse [17,19]

Even in a perfect world, universal equivalents still wouldn't account for patient-specific details such as current level of pain control, body surface area, drug interactions, pharmacogenetics, age, and organ dysfunction. As with all studies, this effort has several limitations, including the potential for selection bias and low generalizability due to the methods used to identify participants and collect the data. Using an online survey requires reliance on good faith efforts of respondents. Additionally, no patient-specific factors were provided to help guide study participants in their estimates. Despite these limitations, these data provide evidence that wide variability in opioid conversions exists among clinicians. As opioid conversions are commonly required in pain management practice, improved equianalgesic conversion methods would likely improve pain management practice by providing effective analgesia while minimizing risk during opioid conversions.

Conclusion

The results of this survey suggest large variability exists among clinicians when converting various opioids to oral morphine equivalents. While the median morphine equivalent dose provided for each opioid conversion was not significantly different between physicians, pharmacists, and nurse practitioners, large variations in MEQ doses were demonstrated within each clinician group. Large standard deviations in the MEQ dose provided for each of the five opioid conversions, particularly fentanyl and methadone, reflect the wide range of MEQ doses provided by clinicians. While the majority of survey representatives were pharmacists, variability in opioid conversions was demonstrated by all clinician groups surveyed, suggesting a variation in opioid conversion practices within and between clinician groups. The lack of standardization for converting between opioids is reflected in the variability of these survey results, and suggests that clinicians may be in need of guidance to ensure that patients are neither over- nor under-dosed when converting between opioids.

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