Pain Medicine

Pain Medicine 2012; 13: 562–570
Wiley Periodicals, Inc.

OPIOIDS, SUBSTANCE ABUSE & ADDICTIONS SECTION

Review Article

Review and Critique of Opioid Rotation Practices and Associated Risks of Toxicity

Lynn R. Webster, MD,* and Perry G. Fine, MD†

*Lifetree Clinical Research, Salt Lake City, Utah;

†Pain Research and Management Centers, Department of Anesthesiology, School of Medicine, University of Utah, Salt Lake City, Utah, USA

Reprint requests to: Lynn R. Webster, MD, FACPM, FASAM, Lifetree Clinical Research, 3838 South 700 East, #202, Salt Lake City, UT 84106-6102, USA. Tel: 801-892-5140; Fax: 801-261-3341; E-mail: lrwebstermd@gmail.com.

Disclosure: Lynn Webster, MD, has received funding from the following companies as compensation for clinical research or as honoraria: Adolor, Alkermes, Allergan, AlphaBioCom, American Academy of Pain Medicine, American Board of Pain Medicine, AstraZeneca, Bayer, BioDelivery Sciences International, Boston Scientific, Cephalon, Collegium Pharmaceuticals, Covidien, Eisai, Elan Pharmaceuticals, Gilead Sciences, GlaxoSmithKline, Identigene (Sorenson), King Pharmaceuticals, Meagan Medical, Medtronic, Merck, Naurex, Nektar Therapeutics, NeurogesX, Nevro Corporation, Novartis, Pfizer, SchaBar, Shionogi USA, St. Renatus, SuCampo Pharma Americas, Takeda, TEVA Pharmaceuticals, Theravance, Vanda, Vertex, and Xanodyne Pharmaceuticals.

Perry Fine, MD, over the last 12 months has received honoraria for serving on advisory boards for Ameritox, Archimedes, Nuvo, Covidien, Purdue Pharma, and Pricara/OrthoMcNeil, and he has received consulting fees for medical-legal consultation for Johnson & Johnson, Cephalon, and Mylan.

Abstract

Objectives. A dramatic increase in unintentional deaths from opioids has occurred over the past decade with strong inference that many of these deaths may be resulting from prescriber's error. Recent evidence suggests that the use of dose conversion ratios published in equianalgesic tables may lead to fatal or near-fatal opioid overdoses. The objective of this review was to determine whether the current practice of opioid rotation may be contributing to high rate of unintentional deaths.

Methods. We performed a focused literature review to identify reports of fatal or near-fatal outcomes that have occurred in conjunction with opioid rotation, to evaluate clinician competence in opioid rotation, and to identify inconsistencies in published protocols for opioid rotation. Further information was obtained by reviewing dosing instructions contained in product labels for extended-release formulations of several opioids.

Results. An increasing body of literature suggests that widely used opioid rotation practices, including the use of dose conversion ratios found in equianalgesic tables, may be an important contributor to the increasing incidence of opioid-related fatalities. These errors may be due, in part, not only to inadequate prescriber's competence but also to proliferation of inconsistent guidelines for opioid rotation, conflation of equianalgesic tables as conversion tables, and limitations inherent in the equianalgesic dose tables.

Conclusions. Most of the fatal outcomes occurring during opioid rotation are preventable. The current process being used for opioid rotation has important flaws that must be corrected.

Key Words. Opioid Rotation; Equianalgesic Dose Tables; Opioid Dose Conversion

Introduction

Chronic pain affects more than 100 million people in the United States and has a considerable impact on overall health, functional capacity, and quality of life [1–5]. While many people with moderate to severe pain achieve adequate analgesia with a specific opioid regimen, some may suffer from intolerable adverse events, tolerance, and/or inadequate pain relief. For these patients, opioid rotation (or opioid switching)—defined as a change in opioid drug or route of administration with the goal of

improving outcomes [6]—has become a widespread practice. In fact, available data suggest that 50–80% of patients with chronic pain who respond poorly to one opioid improve after being rotated to another opioid [7,8]. Another study of patients with chronic noncancer pain found that 81% of patients (N = 86) required a switch to another opioid with as many as five different extended-release opioids in succession to establish an effective level of pain control with a tolerable side-effect profile [9].

Unfortunately, a dramatic increase in unintentional poisoning deaths from opioids has occurred in recent years [10–13]. A recent report by the United States Centers for Disease Control and Prevention (CDC) noted that nearly 15,000 people die every year as a result of overdoses involving prescription painkillers and that the number of overdose deaths now exceeds the number of deaths from heroin and cocaine combined [10]. A review of all serious adverse events and medication errors in the United States reported to the United States Food and Drug Administration (FDA) found that 5 of the 15 drugs most frequently named in fatal outcomes were opioids, including oxycodone, fentanyl, morphine, methadone, and acetaminophen/hydrocodone [14]. Although most of the deaths are due to polysubstance abuse, opioids have been cited as a major factor contributing to many of the deaths. Unintentional deaths from opioids are not only related to diversion for nonmedical use and misuse by patients, but by prescriber's error as well. A study in which researchers examined medical records of 208 patients who were hospitalized 304 times found that opioids had the highest predictive value of prescribing discrepancies for adverse events with a positive prediction value (PPV) of 0.28 [15]. The next highest prescriber error rates were found for metronidazole (PPV of 0.16), non-opioid analgesics (PPV of 0.14), and levothyroxine (PPV of 0.12) with the PPV for all other drugs or drug classes $\leq$0.08.

Although data are not yet sufficient to elucidate all of the reasons for prescribing errors or their relationship to increases in unintentional opioid-related deaths, evidence suggests that the use of dose conversion ratios published in equianalgesic tables may be an important associated and contributing factor, especially—but not only—when patients are converted to methadone [16,17]. Several reviews have recently drawn attention to limitations inherent in the construction of equianalgesic dose tables [18–20]. In an effort to further examine the extent to which the current practice of opioid rotation may be contributing to the unacceptable rate of unintentional deaths, a literature review was performed to identify reports of fatal or near-fatal outcomes that have occurred in conjunction with opioid rotation, to evaluate clinician competence in opioid rotation, and to identify inconsistencies in published protocols for opioid rotation.

Methods

An extensive literature search was performed in the Medline database using PubMed to identify articles. The terms searched included various combinations of "opioid rotation," "opioid switching," "equianalgesic," "medication errors," "education," "deaths," and "side effects." Further information was obtained by reviewing product labels for extended-release formulations of several opioids. Additional articles were identified by a manual search of the reference lists of retrieved articles. English language articles published from 1970 to November 2011 were reviewed. All articles describing deaths or life-threatening events that occurred during opioid rotation were included. Most of these articles described case reports or events that occurred during clinical trials. All relevant articles that addressed clinician competence or education in opioid rotation were included. Additional articles, particularly systematic reviews, were selected based on their quality and relevance to the subject with a focus on opioid conversion practices, equianalgesic dose tables, and incomplete cross-tolerance to opioids. This literature was collated, reviewed, and critiqued with the goal of elucidating the important inconsistencies and weaknesses of the evidence basis for guiding safe and effective medical practice when rotating opioid analgesia for chronic pain related to both cancer and noncancer conditions.

Results and Discussion

Protocols for Opioid Rotation Using Dose Conversion Ratios

There are several proposed protocols for opioid rotation with most protocols involving the use of equianalgesic dosing tables to convert the dose of the original opioid to a putative equivalent dose of morphine, then convert the dose of morphine to the new opioid, and then incorporate a safety margin by reducing the calculated equianalgesic dose. The most widely accepted guideline for opioid rotation was developed by an interdisciplinary panel of clinical and research experts in opioid pharmacology [6]. This guideline has been a major contribution to the field; however, it has never been formally validated for safety or efficacy. Methodologically sound studies of opioid rotation protocols with well-defined outcomes are lacking. Although opioid rotation has been shown to be of benefit to many patients [7,9], systematic reviews of opioid rotation have concluded that well-founded recommendations for opioid rotation practices are difficult to make due to insufficient evidence and serious limitations in the designs of opioid rotation studies [21–24].

Dose Conversion Ratios Found in Equianalgesic Dose Tables Are Arguable

Several factors contribute to limitations in the utility of currently available opioid equianalgesic tables for opioid rotation. Exhaustive reviews have recently been published detailing the shortcomings of equianalgesic tables and dose conversion ratios [18,19,23]. Limitations of equianalgesic tables include the fact that most studies used single dose or a relatively limited range of doses of a specific route and therefore may not generalize to chronic dosing or other routes; study designs were intended to increase the study's sensitivity to finding differences

between drugs and doses and therefore acquisition of data lacked broad generalizability; and studies were performed in non-opioid-tolerant patients [18,23]. Patients in these studies usually had no concurrent illness or organ dysfunction, and studies did not account for responses based on ethnicity, advanced age, concomitant medication use, or comorbidities [18,23]. Studies did not necessarily assess the direction of switching from one drug to another, and for several drugs, the potency varies depending on the direction of the switch [18,23]. Lastly, and very importantly, most opioid equianalgesic dose studies were performed prior to recognition of significant opioid receptor polymorphism, with its implications for major interindividual differences in opioid responsiveness.

Incomplete Cross-Tolerance Limits Generalizability of Dose Conversion Ratios

Even if dose ratios contained in the equianalgesic dose table were accurate within an individual, it is impossible for these tables to account for the large variability in interpatient responses to opioids. Recent research has demonstrated incomplete cross-tolerance when patients are switched from one mu-opioid to another due to genetic factors [25–27], causing the pharmacokinetics and pharmacodynamics of different opioids to vary unpredictably among patients. Figure 1 shows how differing receptor selectivity can lead to complete, partial, or no cross-tolerance of mu-opioid analgesics [25]. Demographic differences such as race, age, and gender as well as major organ dysfunction—such as renal, hepatic, and adrenal impairment—can also cause unpredictable differences in the relative potency, effectiveness, and safety of opioids. These factors alone preclude safe use of the tables even by the most experienced clinicians. Although much is being discovered about the role of pharmacogenetics and interpatient response to opioids, there are no available tests or measures to inform most daily clinical decisions. Knowing whether a patient metabolizes opioids poorly would require genetic testing, which is not currently the standard care for patients undergoing opioid rotation. Therefore, for safety's sake, clinicians must assume that every patient is at risk for overdose when instituting opioid therapy for pain.

Methadone: A Particularly Challenging Drug

The use of equianalgesic tables when converting patients to methadone is particularly dangerous due to the unique pharmacokinetic/pharmacodynamic profile of methadone (i.e., long and highly variable half-life with shorter duration of analgesia). This can contribute to unpredictable accumulation of methadone during the early days and weeks of treatment, leading to potentially life-threatening, and in many cases fatal, respiratory depression, particularly during sleep. Moreover, because it can take several days to achieve meaningful analgesia when methadone is initiated, patients may tend to self-escalate dosing to obtain relief, leading to respiratory failure. Therefore, relying on tables derived from single-dose studies is especially problematic with repeated dosing of methadone.

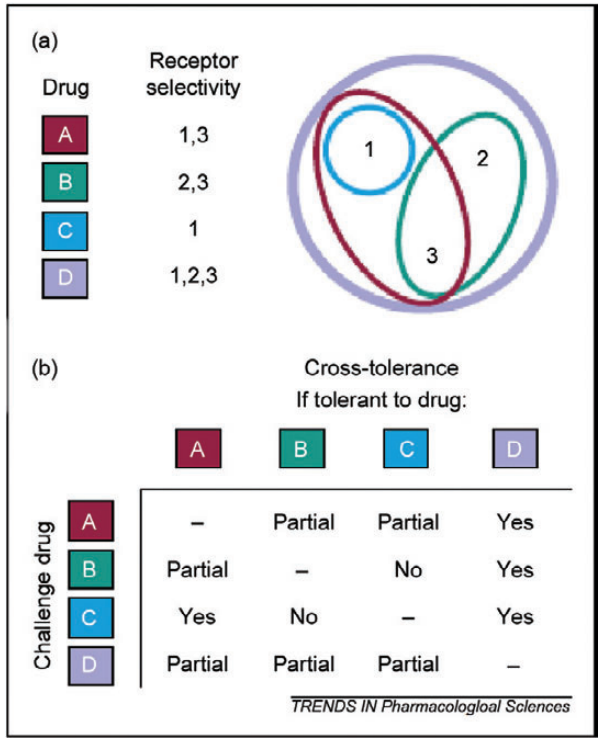

Figure 1 Incomplete cross-tolerance. (a) Drugs A–D can act on one or more of the receptors 1–3. (b) These drugs can show complete, partial, or no cross-tolerance when tested against each other. Extension of this model illustrates how incomplete cross-tolerance among analgesics acting at the mu-opioid peptide (MOP) receptor could reflect differing selectivity profiles of drugs for the MOP receptor subtypes. Reproduced with permission from Pasternak [25]. (From: Pasternak 2001/p69/figure 4).

Methadone-related deaths have been documented during methadone induction when being used to treat opioid dependence as well as chronic pain [28–32]. In fact, the FDA published a public health advisory regarding death and life-threatening changes in breathing and heart rate that were occurring in patients newly starting methadone [32]. Prescribing information for use of methadone for detoxification and maintenance treatment of opiate dependence recommends an initial single dose of 20–30 mg with the total daily dose of methadone on the first day of treatment not exceeding 40 mg (Dolophine® Package Insert, 2009; Roxane Laboratories, Inc. Columbus, OH, USA). However, consensus now exists that methadone induction protocols should initiate doses less than 30 mg due to the risk of fatal respiratory depression [31].

Deaths or Near Misses Occurring During Opioid Rotation When Dose Conversion Ratios Are Used

Several case reports suggest that opioid-related deaths or near misses may occur when clinicians switch patients from one opioid to another using a dose conversion ratio [33–35]. Hunt and Bruera reported on a 61-year-old cancer patient who had been switched from 84 mg/day of subcutaneous hydromorphone to 90 mg/day of oral methadone [33]. The authors noted that the conversion rate they used was 1:20 subcutaneous hydromorphone to oral morphine, giving a morphine equivalent daily dose equal to 1,680 mg of oral morphine. At the time of publication, the authors noted that the literature favored a 1:1 conversion of parenteral morphine to parenteral methadone, although they acknowledged there was a growing debate. The authors were using a dose ratio of 5:1. Because of the patient's recent adverse reactions to opioids, they cautiously prescribed a much lower dose of methadone (30 mg orally every 8 hours). On this dose, the patient developed respiratory depression and noncardiogenic pulmonary edema that responded to subcutaneous naloxone and methadone discontinuation. Regnard and Pelham described a 70-year-old patient with drowsiness and mild confusion who was converted from controlled-release morphine 50 mg 12 hourly to 25 μg/h transdermal fentanyl [34]. Approximately 36 hours after starting the fentanyl, the patient became sedated with pinpoint pupils and developed central cyanosis with a respiratory rate less than 6 breaths/min. Respiratory depression abated with removal of the transdermal fentanyl. Fishbain and colleagues described a case of a chronic pain patient who was rotated from controlled-release oxycodone to methadone for detoxification purposes [35]. The oxycodone 60 mg/day the patient had been receiving was discontinued and a methadone taper was initiated with a first step of 35 mg twice a day. Approximately 11 hours after the first dose of methadone was administered, the patient was found in cardiopulmonary arrest with resuscitation unsuccessful.

Studies in which patients were rotated from one opioid to another have also reported deaths during rotation [36,37]. Twycross stopped a study prematurely when it was discovered that patients being rotated to methadone from diamorphine-cocaine had a lower survival rate than patients who remained on the diamorphine-cocaine [36]. The authors had selected a potency ratio of methadone : diamorphine of 1:1 based, in part, on literature that had been published up to 10 to 20 years prior to their study [38,39]. Moksnes and colleagues evaluated two protocols for rotating cancer patients from morphine or oxycodone to methadone: a stop-and-go strategy (i.e., the original opioid was immediately replaced by methadone using dose-dependent conversion ratios, N = 16), and a 3-day switching strategy (i.e., the original opioid dose was reduced stepwise by 1/3 every day and substituted with 1/3 of a putative equianalgesic dose of methadone over 3 days, N = 19) [37]. The dose-dependent conversion ratios used were 4:1 for patients on 91–300 mg morphine, 7.5:1 for patients on 301–600 mg morphine, 11.7:1 for patients on 601–1,000 mg morphine, and 14.2:1 for patients on >1,000 mg morphine. Two patients died and one experienced severe sedation in the stop-and-go group. No serious adverse events occurred in the 3-day switching group [37].

An analysis of the root causes for opioid-related deaths in the United States was recently published [40]. For this analysis, a panel of experts in pain medicine and public policy were convened to review results from a search of PubMed and state and federal government sources to assess frequency, demographics, and risk factors for opioid-related overdose deaths from the previous decade. The panel of experts concluded that clinicians' overreliance on published equianalgesic conversion tables, particularly when converting to methadone from another opioid, was one important contributor to opioid-related deaths caused by physician's error [40].

Dose Conversion Ratios Found in Equianalgesic Tables Are Not Consistently Supported by Research

In addition to the articles cited previously with respect to deaths or near misses, several other authors have described problems they encountered while using published dose conversion ratios. For example, some patients have been found to require far lower doses of the second opioid than predicted by equianalgesic tables. A case report of a 48-year-old patient with hyperalgesia who was switched from fentanyl to methadone required an "exaggeratedly low" dose of the second opioid (about 1/10 of the initial dose calculated), which the authors attributed to reversal of hyperalgesia that had been induced by fentanyl [41]. Unfortunately, a clinician cannot predict which patients will require these "exaggeratedly low" doses *a priori*. A report of four patients with neuropathic pain or a neuropathic component to their pain found that effective pain relief was produced by a much lower dose of transdermal buprenorphine than the equianalgesic tables proposed [42]. Again, there is no way for even an experienced pain specialist to predict who these patients will be. For these patients, reliance upon equianalgesic tables can be dangerous, leading to potentially life-threatening dosing errors.

A study of opioid rotation in 118 patients found no relationship between the starting opioid dose and dose at stabilization after switching ($P = 0.810$) or time to achieve stabilization ($P = 0.064$) with patients switching to methadone requiring more changes in doses (about three dose changes) than those switching to transdermal fentanyl or buprenorphine [8]. A retrospective study of clinical experience with transdermal and orally administered opioids in 354 palliative care patients found that pain relief was achieved with lower equianalgesic morphine doses but higher equianalgesic hydromorphone doses than predicted based on equianalgesic tables, for which the authors had no clear explanation [43].

Studies in acute pain have also demonstrated limitations inherent in the use of equianalgesic tables. A recent study comparing the efficacy of a low-dose methadone tapering

schedule to a high-dose methadone tapering schedule in pediatric intensive care unit patients exposed to fentanyl infusions demonstrated that the methadone dose must be adjusted to each patient's response because of the risks of both withdrawal and oversedation with any fixed methadone schedule [44]. In this study, the researchers were unable to predict success with the low or high methadone group based on clinical characteristics. For example, the researchers had anticipated a higher incidence of withdrawal in the low-dose methadone group and a higher incidence of oversedation in the high-dose methadone group—neither scenario occurred. They also anticipated that patients who had been on prolonged infusions of fentanyl would be more likely to fail the low-dose methadone taper—this also did not occur.

Inconsistent Guidelines Including Varying Dose Conversion Ratios and Recommendations Regarding the Use of Rescue Medication

Contributing to the confusion surrounding opioid rotation is the widespread availability of numerous published equianalgesic tables containing inconsistent and variable conversion ratios (Table 1). A recent survey of commercially available educational materials for equianalgesic tables found that opioid route conversion ratios of oral to parenteral morphine ranged from 3:1 to 2:1 to 6:1; ratios for oral to parenteral hydromorphone ranged from 2:1 to 5:1; and oral to parenteral methadone ratios varied from 2:1 to 10:1 and 4:1 [20]. In the same study, ratios for opioid rotation within the same route also varied with parenteral methadone to parenteral morphine ratios varying from 1:10 to 6.7:10 to 1:1; modified-release oxycodone to modified-release morphine ratios ranged from 1:1 to 1:2; ratios between oral morphine and hydromorphone varied from 40–60:6.5–7.5 to 10:2.5 [20].

Published protocols for how opioid rotation itself should be performed also vary. For example, one review article distinguished between opioid switching and opioid rotation and provided unique instructions for each regarding the use of the equianalgesic table [45]. Specifically, opioid switching was defined as occurring soon after opioid initiation because of a poor initial response and opioid rotation was defined as occurring during chronic opioid treatment because of declining efficacy and/or increasing adverse effects. For opioid switching, the author noted that "equianalgesic tables can generally be used without modification because conversion from the ineffective or poorly tolerated opioid occurs early in treatment before tolerance emerges," and for opioid rotation, the author noted that "the computed conversion dose must be adjusted to account for incomplete cross-tolerance between the previous and substitute opioid." Other guidelines make no distinction between opioid switching and opioid rotation [6].

Dose conversion guidelines found in package inserts for opioids, particularly the newer extended-release opioids, are also inconsistent and potentially dangerous. For example, language in the Exalgo® (Mallinckrodt Brand Pharmaceuticals, Inc. Hazelwood, MO, USA) package insert for extended-release hydromorphone states: "In general, start Exalgo therapy by administering 50% of the calculated total daily dose of Exalgo (see conversion ratio table below) every 24 hours. The initial dose of Exalgo can be titrated until adequate pain relief with tolerable side effects has been achieved." Assuming a patient is on 200 mg of extended-release morphine daily, the equivalent dose of extended-release hydromorphone would be 40 mg (200 mg × 0.2 = 40 mg). Using the guideline suggested in the package insert, the patient would be started on 50% of 40 mg, or 20 mg. However, because extended-release hydromorphone is only formulated in 4, 8, 12, and 16 tablets, the prescriber would be inclined to prescribe either 16 mg tablets or 2 × 12 mg tablets (24 mg). This conversion would create one of three clinical situations: 1) the conversion underestimates the amount

Table 1 Approximate equivalent oral doses in various equianalgesic dose tables

Drug	APS. Principles of Analgesic Use in the Treatment of Acute Pain and Cancer Pain	Online Opioid Analgesic Converter*	Narcotic Equivalence Converter†	EXALGO Package Insert	OPANA ER Package Insert	OxyContin‡
Morphine	30 mg	30–60 mg	30 mg	60 mg	30 mg	60 mg
Hydromorphone	7.5 mg	7.5 mg	3.8 mg	12 mg	—	7.5 mg
Hydrocodone		20–30 mg	2.5–5 mg	30 mg	20 mg	33.3 mg
Methadone	10 mg	2–20 mg (short-term use: 20 mg) Chronic dosing: 2–4 mg (3 mg)	10 mg	20 mg	20 mg	20 mg
Oxycodone	20 mg	15–30 mg (20 mg)	2.5–5 mg	30 mg	20 mg	30 mg
Oxymorphone	—	10 mg		20 mg	10 mg	—
Codeine	—	200 mg	100 mg	200 mg	—	200 mg

* http://www.globalrph.com/narcoticonv.htm. These conversion data are also used for Epocrates MedTools.
† http://www.medcalc.com/narcotics.html.
‡ The approximate equivalent dose was not presented in the package insert, only oral conversion ratios.

of extended-release hydromorphone necessary for adequate analgesia; 2) the conversion overestimates the amount of extended-release hydromorphone necessary for analgesia and the patient is subjected to increased risk of overdose; or 3) the conversion is within a reasonable window and would not need an adjustment. Underestimating the dose of the new opioid might seem to be safe but, in fact, may lead to self-medication in an attempt to find adequate relief or to treat withdrawal symptoms induced by the conversion. This could represent a subset of patients where this type of error could be fatal. Inadequate analgesia during opioid rotation may be especially problematic in patients who have difficulty controlling their drug use, such as patients with substance use disorders or patients with chronic pain.

Guidelines for initiation of methadone found in the current package insert are also concerning. The package insert for methadone states that patients may be started on methadone doses up to 30 mg/day. Although a starting dose up to 30 mg/day may be safe for some patients, it may be lethal for patients who are slow methadone metabolizers or have comorbid medical conditions such as sleep-disordered breathing associated with obesity. A recent review of medical records of 20 patients with chronic pain who died from overdose found methadone to be responsible for 10 of these deaths. Some of these patients were receiving less than 30 mg methadone/day. Of the 20 deaths, 13 occurred within the first week after a change in opioid prescription dosage, suggesting that some early opioid-associated deaths are due to too high of a starting dose and/or too rapid of a dose titration [46].

Recommendations for the use of rescue medication with a short-acting opioid are also inconsistent, particularly in product labeling for extended-release opioids. Some, but not all, package inserts encourage the use of rescue dosing with short-acting opioids during rotation. For example, rescue dosing is encouraged in package inserts for Avinza® (King Pharmaceuticals, Inc. Bristol, TN, USA), Kadian® (Actavis Kadian, LLC Morristown, NJ, USA), MS Contin® (Purdue Pharma L.P., Stamford, CT, USA), Oramorph® (Xanodyne Pharmaceuticals, Inc. Newport, KY, USA), and Oxycontin® (Purdue Pharma). However, no mention of rescue dosing is included in the package inserts for Dolophine®, Exalgo®, and Opana®. Due to FDA regulations, when no mention of rescue dosing is made in the product labeling, manufacturers of opioids are prohibited from educating physicians on the importance of using a rescue medication when rotating patients from another opioid to their drug as this is outside the confines of approved labeling.

Opioid Rotation, Including Use of Dose Conversion Ratios, Is Confusing to Prescribers

Not surprisingly, clinician's competence in opioid rotation has been found to be woefully inadequate [47–54]. A survey of 182 pharmacists found that almost 39% of respondents found it difficult to calculate opioid dosages in the case of opioid rotation, and 18% were unable to calculate the correct dosage when asked to do so using the existing tables [47]. In a randomized, crossover study designed to compare a Web-based individualized opioid conversion calculator with manual calculation using a written table by 72 graduate students with little experience in opioid conversion, 81% of participants answered the question correctly when using the calculator and 68% answered correctly when using the table, revealing that 19–32% of the time doses were erroneously calculated [48]. In another study, when residents in internal medicine programs were asked four multiple choice questions on basic aspects of opioid analgesia, three of which pertained directly to opioid conversion, only 20% of residents answered all questions correctly [49]. Approximately one-half (51%) of residents could not convert an intravenous morphine infusion regimen to an equivalent regimen of immediate-release oral morphine and 59% could not make the same conversion to an equivalent regimen of long-acting oral morphine.

Buss et al. conducted a survey of palliative care and non-palliative care topics in hematology/oncology fellows [50]. Fellows rarely reported receiving explicit education on when to rotate opioids (33%). When given an equianalgesic chart and asked to perform an opioid conversion from oxycodone to long-acting morphine with reduction for incomplete cross-tolerance, 77% answered incorrectly. Fellows who completed a palliative care rotation were twice as likely to report explicit education on opioid rotation (49% vs 27%). When a group of 406 nonpain specialist physicians (182 general practitioners, 110 geriatrics care physicians, and 112 clinical specialists) were surveyed about their knowledge of opioid rotation, 59% said they had difficulties calculating opioid dosages when rotating and 46% were interested in education about opioid rotation [51]. When asked to convert a daily dose of 60 mg oxycodone to a fentanyl patch, the response "don't know" was given by 41% of clinical specialists, 28% of general practitioners, and 17% of geriatrics care physicians. Of particular interest was the fact that the researchers were forced to provide two correct answers (25 and 50 μg/h) because different guidelines give different conversions, which lead to two different answers. Also of concern was the finding that although 62% of respondents reported sometimes or often rotating opioids in practice, 59% reported that they find calculating opioid dosages when rotating difficult. Nurses also find opioid rotation to be difficult, with one study reporting that 73% of nurses were unable to provide a correct response to an equianalgesic route conversion question [52]. A more recent study found that nurses had the most difficulty answering questions relating to pharmacology of opioids and the authors suggested that nurses may perceive physicians and pharmacists to be the experts and rely on their expertise with analgesia regimens [53].

Even after educational interventions to improve opioid rotation skills are instituted, competence remains inadequate. A study of an educational intervention to improve pain management practices by internal medicine residents found that although opioid conversion skills improved fol-

lowing the intervention, competence was still relatively low [54]. Prior to the intervention, 37% of residents knew the relative potency of parenteral to oral morphine, 26% were able to convert a fixed immediate-release morphine to a long-acting morphine, and 43% were able to convert oral morphine to oral hydromorphone. Following the intervention, 67%, 37%, and 57% of residents were able to answer the three questions correctly, respectively. Before and after the intervention, 54% and 43% of residents, respectively, reported being unfamiliar with equianalgesic tables. Clearly, the type of education or "intervention" was not sufficient to lead to competence. Notwithstanding that issue, competence, as defined by answering test questions or accurate use of conversion tables (mathematically), may not correlate with safety.

As might be expected with low prescriber's competence, serious errors have been reported when clinicians believe that equianalgesic doses are being prescribed. For instance, one report [55] describes a situation in which an internist prescribed intravenous hydromorphone 4 mg for an opioid-naïve patient with a migraine. When questioned by the pharmacist, it was discovered that the physician believed the hydromorphone to be relatively equivalent to morphine on a milligram-for-milligram basis (in actuality, hydromorphone is putatively 8–10 times more potent than morphine). Crosby reported an error in switching a patient from oral morphine to subcutaneous diamorphine [56]. The patient had been switched from 80 mg controlled-release oral morphine daily to a syringe driver with 120 mg diamorphine in 24 hours (equivalent to a 360 mg of oral morphine daily). A dose of 25 mg diamorphine in 24 hours was found to be sufficient for the patient.

Conclusions

Opioids are an important component of a pain control regimen when more effective or safer options are not available. However, based on increasing levels of morbidity and mortality with the use of opioids in the management of chronic pain, and serious concerns about current opioid rotation practices, prescribing guidelines and opioid conversion methods must be carefully re-examined. An increasing body of scientific literature suggests that widely used opioid rotation practices, including the use of dose conversion ratios found in equianalgesic tables—mostly developed nearly a half century ago—may be an important contributor to the increasing incidence of opioid-related fatalities. Moreover, prescriber's competence is shockingly inadequate. There is no acceptable level of medically prescribed opioid dosing error, especially when toxicity can and does lead to fatality. Guidelines for opioid rotation must eliminate the risk of inadvertent harm to all patients, but the growing toll of opioid-related fatalities demonstrates that the current system is not working.

Fatal outcomes can occur during opioid rotation even when prescribers have not deviated from published opioid rotation guidelines. Prescribing errors, regardless of cause (inadequate education, confusion, lack of attention to detail, calculation error, etc.), are an increasingly common impetus for litigation and clinicians who make these errors can suffer dire consequences. Unfortunately, a punitive approach by which clinicians are blamed for errors overlooks the more pressing and overt system's problem: that clinicians have "bought into" use of opioid conversion charts that are inherently flawed when used in the context of opioid rotation, which can lead to fatal outcomes. Many physicians who are trained and very comfortable using "expert-consensus" clinical algorithms for other clinical conditions may be lulled into believing that conversion tables are safe and appropriate, particularly clinicians who do not specialize in pain medicine. In many cases, prescribers feel reassured or protected from liability when using published guidelines such as these. The recognition of this problem calls for a systematic approach to re-evaluate currently promulgated methods for opioid rotation, starting with cautionary notes included in all prescribing information for opioids.

In conclusion, fatal outcomes are occurring during opioid rotation, most of which could likely be prevented. The current processes for opioid rotation have important flaws that must be corrected. All patients who have indications for opioid therapy must be assured that routine clinical practices are safe and have an evidentiary basis. It is time for professional societies, government agencies, and industry to work together to ensure this goal is attained.

Acknowledgment

The authors acknowledge the contribution of Lynne Pauley, MS, contract medical writer, Salt Lake City, Utah, for her assistance performing the literature review and preparing this article.

References

1 American Pain Society (APS) Bulletin. Pain hurts—Individuals, significant others, and society! Volume 16(1), Winter 2006. Available at: http://www.ampainsoc.org/pub/bulletin/win06/pres1.htm (accessed March 1, 2012).

2 Center for Disease Control and Prevention. Prevalence of disabilities and associated health conditions among adults—United States, 1999. MMWR Morb Mortal Wkly Rep 2001;50(7):120–5. Available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5007a3.htm (accessed March 1, 2012).

3 Stewart WF, Ricci JA, Chee E, Morganstein D, Lipton R. Lost productive time and cost due to common pain conditions in the US workforce. J Am Med Assoc 2003;290:2443–54.

4 Turk DC, Dworkin RH, Revicki D, et al. Identifying important outcome domains for chronic pain clinical trials: An IMMPACT survey of people with pain. Pain 2008;137:276–85.

5 Institute of Medicine. Relieving Pain in America: A Blueprint for Transforming Prevention, Care,

Education, and Research. Washington, DC: The National Academies Press; 2011.

6 Fine PG, Portenoy RK, Ad Hoc Expert Panel on Evidence Review and Guidelines for Opioid Rotation. Establishing "best practices" for opioid rotation: Conclusions of an expert panel. J Pain Symptom Manage 2009;38:418–25.

7 Mercadante S, Bruera E. Opioid switching: A systematic and critical review. Cancer Treat Rev 2006;32: 304–15.

8 Mercadante S, Ferrera P, Villari P, et al. Frequency, indications, outcomes, and predictive factors of opioid switching in an acute palliative care unit. J Pain Symptom Manage 2009;37:632–41.

9 Quang-Cantagrel ND, Wallace MS, Magnuson SK. Opioid substitution to improve the effectiveness of chronic noncancer pain control: A chart review. Anesth Analg 2000;90:933–7.

10 Center for Disease Control and Prevention. Prescription painkiller overdoses in the US. CDC Vital Signs, November 2011. Available at: http://www.cdc.gov/VitalSigns/PainkillerOverdoses/index.html (accessed March 1, 2012).

11 Bohnert AS, Valenstein M, Bair MJ, et al. Association between opioid prescribing patterns and opioid overdose-related deaths. J Am Med Assoc 2011;305: 1315–21.

12 Dhalla IA, Mamdani MM, Sivilotti ML, et al. Prescribing of opioid analgesics and related mortality before and after the introduction of long-acting oxycodone. CMAJ 2009;181:891–6.

13 Paulozzi LJ, Budnitz DS, Xi Y. Increasing deaths from opioid analgesics in the United States. Pharmacoepidemiol Drug Saf 2006;15:618–27.

14 Moore TJ, Cohen MR, Furberg CD. Serious adverse drug events reported to the Food and Drug Administration, 1998–2005. Arch Intern Med 2007;167: 1752–9.

15 Boockvar KS, Liu S, Goldstein N, et al. Prescribing discrepancies likely to cause adverse drug events after patient transfer. Qual Saf Health Care 2009;18:32–6.

16 American Pain Foundation, Pain Safe Program. Frequently asked questions about opioid safety. 2011. Available at: http://www.painfoundation.org/painsafe/healthcare-professionals/pharmacotherapy/opioids/faqs-about-opioids.html (accessed March 1, 2012).

17 Webster LR, Cochella S, Dasgupta ND, et al. An analysis of the root causes for opioid-related overdose deaths in the United States. Pain Med 2011;12:S26–35.

18 Knotkova H, Fine PG, Portenoy RK. Opioid rotation: The science and the limitations of the equianalgesic dose table. J Pain Symptom Manage 2009;38:426–39.

19 Mercadante S, Caraceni A. Conversion ratios for opioid switching in the treatment of cancer pain: A systematic review. Palliat Med 2011;25:504–15.

20 Shaheen PE, Walsh D, Lasheen W, Davis MP, Lagman RL. Opioid equianalgesic tables: Are they all equally dangerous? J Pain Symptom Manage 2009;38:409–17.

21 Dale O, Moksnes K, Kaasa S. European palliative care research collaborative pain guidelines: Opioid switching to improve analgesia or reduce side effects. A systematic review. Palliat Med 2011;25:494–503.

22 Chou R, Fanciullo GJ, Fine PG, et al. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. J Pain 2009;10:113–30.

23 Patanwala AE, Duby J, Waters D, Erstad BL. Opioid conversions in acute care. Ann Pharmacother 2007;41:255–66.

24 Quigley C. Opioid switching to improve pain relief and drug tolerability. Cochrane Database Syst Rev 2004;(3):D004847.

25 Pasternak GW. Incomplete cross tolerance and multiple mu opioid peptide receptors. Trends Pharmacol Sci 2001;22:67–70.

26 Pasternak GW. Molecular insights into mu opioid pharmacology: From the clinic to the bench. Clin J Pain 2010;26:S3–9.

27 Pasternak GW. Multiple opiate receptors: Déjà vu all over again. Neuropharmacology 2004;47:312–23.

28 Caplehorn JR. Deaths in the first two weeks of maintenance treatment in NSW in 1994: Identifying cases of iatrogenic methadone toxicity. Drug Alcohol Rev 1998;17:9–17.

29 Center for Substance Abuse Treatment. Methadone-Associated Mortality: Report of a National Assessment, May 8–9, 2003. SAMHSA Publication. NO.04-3904. Rockville, MD: Center for Substance Abuse Treatment, Substance Abuse and Mental Health Services Administration, 2004.

30 Cousins G, Teljeur C, Motterlini N, et al. Risk of drug-related mortality during periods of transition in methadone maintenance treatment: A cohort study. J Subst Abuse Treat 2011;41:252–60.

31 Modesto-Lowe V, Brooks D, Petry N. Methadone deaths: Risk factors in pain and addicted populations. J Gen Intern Med 2010;25:305–9.

32 US Food and Drug Administration. Public Health Advisory: Methadone use for pain control may result in death and life-threatening changes in breathing and heart beat. November 27, 2006. Available at: http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm124346.htm (accessed March 1, 2012).

33 Hunt G, Bruera E. Respiratory depression in a patient receiving oral methadone for cancer pain. J Pain Symptom Manage 1995;10:401–4.

34 Regnard C, Pelham A. Severe respiratory depression and sedation with transdermal fentanyl: Four case studies. Palliat Med 2003;17:714–6.

35 Fishbain DA, Cutler RB, Cole B, et al. Medico-legal rounds: Medico-legal issues and alleged breaches of "standards of medical care" in opioid rotation to methadone: A case report. Pain Med 2003;4:195–201.

36 Twycross RG. A comparison of diamorphine-with-cocaine and methadone. [Letter]. Br J Clin Pharmacol 1977;61:691–3.

37 Moksnes K, Dale O, Rosland JH, et al. How to switch from morphine or oxycodone to methadone in cancer patients? A randomised clinical phase II trial. Eur J Cancer 2011;47:2463–70.

38 Eddy NB, Halbach H, Braenden OJ. Synthetic substances with morphine-like effect: Clinical experience; potency, side-effects, addiction liability. Bull World Health Organ 1957;17:569–863.

39 Beaver WT, Wallenstein SL, Houde RW, Rogers A. A clinical comparison of the analgesic effects of methadone and morphine administered intramuscularly, and of orally and parenterally administered methadone. Clin Pharmacol Ther 1967;8:415–26.

40 Webster LR, Brewer R, Morris D, Cleveland JM, Setnik B. Opioid titration and conversion in patients receiving morphine sulfate and naltrexone hydrochloride extended release capsules. Postgrad Med 2011;123:155–64.

41 Mercadante S, Arcuri E. Hyperalgesia and opioid switching. Am J Hosp Palliat Care 2005;22:291–4.

42 Likar R, Krainer B, Sittl R. Challenging the equipotency calculation for transdermal buprenorphine: Four case studies. Int J Clin Pract 2008;62:152–6.

43 Clemens KE, Klaschik E. Clinical experience with transdermal and orally administered opioids in palliative care patients. Jpn J Clin Oncol 2007;37:302–9.

44 Bowens CD, Thompson JA, Thompson MT, et al. A trial of methadone tapering schedules in pediatric intensive care unit patients exposed to prolonged sedative infusions. Pediatr Crit Care Med 2011;12:540–11.

45 Slatkin NE. Opioid switching and rotation in primary care: Implementation and clinical utility. Curr Med Res Opin 2009;25:2133–50.

46 Rich BA, Webster LR. A review of forensic implications of opioid prescribing with examples from malpractice cases involving opioid-related overdose. Pain Med 2011;12(suppl 2):s59–65.

47 Borgsteede SD, Rhodius CA, De Smet PAGM, et al. The use of opioids at the end of life: Knowledge level of pharmacists and cooperation with physicians. Eur J Clin Pharmacol 2011;67:79–89.

48 Plagge H, Ruppen W, Ott N, et al. Dose calculation in opioid rotation: Electronic calculator vs manual calculation. Int J Clin Pharm 2011;33:25–32.

49 Chaitowitz M, Tester W, Eiger G. Use of a comprehensive survey as a first step in addressing clinical competence of physicians-in-training in the management of pain. J Opioid Manage 2005;1:98–108.

50 Buss MK, Lessen DS, Sullivan AM, et al. Hematology/oncology fellows' training in palliative care: Results of a national survey. Cancer 2011;117:4304–11.

51 Rurup ML, Rhodius CA, Borgsteede SD, et al. The use of opioids at the end of life: The knowledge level of Dutch physicians as a potential barrier to effective pain management. BMC Palliat Care 2010;9:23–34.

52 McCaffery M, Ferrell BR. Opioid analgesics: Nurses' knowledge of doses and psychological dependence. J Nurs Staff Dev 1992;8:77–84.

53 Lewthwaite BJ, Jabusch KM, Wheeler BJ, et al. Nurses' knowledge and attitudes regarding pain management in hospitalized adults. J Contin Educ Nurs 2011;42:251–7.

54 Scott E, Borate U, Heitner S, et al. Pain management practices by internal medicine residents—A comparison before and after educational and institutional interventions. Am J Hosp Palliat Care 2009;25:431–9.

55 Hanks S. The law of unintended consequences: When pain management leads to medication errors. P T 2008;33:420–5.

56 Crosby VL, Corcoran R. Modes of administration of morphine in cancer pain. Some doctors lack basic knowledge about prescribing morphine. Br Med J 1996;313:687.