

## Opioid Equianalgesic Calculations

DEBRA B. GORDON, R.N., M.S.,<sup>1</sup> KAREN K. STEVENSON, R.N., M.S.,<sup>2</sup>  
JULIANN GRIFFIE, R.N., M.S.N.,<sup>3</sup> SANDY MUCHKA, R.N., M.S.,<sup>3</sup>  
CATHY RAPP, R.N., M.S.,<sup>4</sup> and KATE FORD-ROBERTS, R.N., B.S.N.<sup>1</sup>

### ABSTRACT

Among the knowledge required by healthcare professionals to manage pain is an understanding of the differences between opioid agents and formulations. As the list of new opioid formulations continues to grow, it is increasingly important that clinicians understand the basic pharmacology of these analgesics and how to calculate equianalgesic doses. Administering an equianalgesic dose increases the likelihood that the transition to another opioid or route will be tolerated without loss of pain control or excessive side effects. Although calculation of equianalgesic doses requires relatively simple mathematical skills, few clinicians are prepared to compute them. The purpose of this article is to provide a basic review of the pharmacology of opioids, explain how to calculate an equianalgesic dose, and briefly describe some of the current controversies of the relative potencies of opioids listed in equianalgesic tables.

### INTRODUCTION

**I**NADEQUATE PAIN CONTROL continues to be a major healthcare problem. Despite the fact that most pain can be controlled with relatively simple means (eg, oral analgesics), clinical studies continue to report inadequate care.<sup>1-3</sup> Among the most frequently cited reasons for undertreatment are knowledge deficits of healthcare providers.<sup>4-6</sup> Although pharmacologic treatment is the cornerstone of pain management, many clinicians fear and misunderstand opioid analgesics. Knowledge deficits surrounding opioids include risk of tolerance

and addiction, drug choice, appropriate routes of administration, calculation of equianalgesic doses, titration of doses, and management of side effects.

Clearly, pain management is an interdisciplinary process, however many have recognized the unique and central role of the nurse.<sup>7,8</sup> The nurse is the key link in assessment, administration of interventions, and evaluation of the impact of interventions on an individual. Nurses make significant contributions to facilitate communication and decision making in pain management. To do so, nurses must process increasingly sophisticated skills

---

<sup>1</sup>University of Wisconsin Hospital and Clinics, Madison, Wisconsin.

<sup>2</sup>Wisconsin Cancer Pain Initiative, Madison, Wisconsin.

<sup>3</sup>Froedtert Hospital-East, Milwaukee, Wisconsin.

<sup>4</sup>St. Joseph's Hospital, Milwaukee, Wisconsin.

in all areas of pain management, including the choice of analgesic, dose, route, and appropriate dosing interval. However, when presented with common conversion scenarios, 56%–73% of 2135 nurses surveyed provided answers that would result in either under or over treatment.<sup>9</sup> In a separate study, one-third of nurses, who were identified as caring for patients with cancer, were unable to calculate equianalgesic doses in spite of having access to an equianalgesic table.<sup>10</sup>

Although the list of available opioids has remained relatively constant, the array of opioid formulations continues to grow. Whether for convenience or out of medical necessity, many patients need to be converted between different routes and opioids. Nurses are in a unique position to help determine the appropriate formulation, route, and dosage to meet an individual patient's needs. Calculation opioid equianalgesic conversions is an important task for nurses, in part, because other healthcare providers may be unprepared to do so. The purpose of this article is to explain equianalgesia and provide a resource to assist clinicians in learning how to calculate opioid route or drug conversions. Current controversies in equianalgesia are also examined.

## OPIOID PHARMACOLOGY

Opioids are the drugs of choice for the treatment of moderate to severe nociceptive pain. Opioid analgesics are classified as pure agonists, mixed agonist-antagonists, or antagonists, depending on which receptors they bind to and their activity at that receptor site.<sup>2</sup> Pure agonists are most commonly used to treat pain because they produce a maximal biologic response, whereas the mixed agonist-antagonists produce a submaximal response.<sup>11</sup> Pure agonists exhibit a steep dose-response curve.<sup>12</sup> In practical terms, this means as the dose is increased, so is the amount of pain relief obtained. When compared with pure agonists, mixed agonist-antagonists (buprenorphine, butorphanol, nalbuphine, pentazocine, dexocine) exhibit a "ceiling effect." This means that above a certain dose there is no more gain in analgesia. Agonist-antagonists can reduce the effect

of a pure agonist, and in some cases even precipitate withdrawal symptoms when administered concomitantly with pure agonists. Antagonists (naloxone) reverse the effects of agonists.

The most commonly used pure agonists include morphine, hydromorphone, oxycodone, hydrocodone, methadone, levorphanol, and fentanyl. Of these, morphine is the most widely available and often considered the prototype because of its well characterized pharmacokinetics and pharmacodynamics. Pharmacokinetics refers to the study of the absorption, distribution, biotransformation, and excretion of drugs.<sup>13</sup> Pharmacodynamics is the study of the biochemical effects of drugs and their mechanisms of action.<sup>13</sup> In other words, pharmacokinetics is what the body does to the drug, and pharmacodynamics is what the drug does to the body. Although all opioid agonists produce pharmacologic effects similar to morphine, their pharmacokinetics differ widely.

Important concepts of opioid pharmacodynamics include potency and equianalgesia. Potency refers to the intensity of analgesic effect for a given dose, and is based on access to the receptor and binding affinity at the receptor site.<sup>11</sup> Apparent differences in potency of various opioids are primarily the result of physiochemical and pharmacokinetic differences of individual opioids. For example, fentanyl is more potent than morphine (administered by the same route) because the dose (milligrams) of morphine required to achieve the same analgesia as fentanyl is 100 times the (milligram) fentanyl dose. Potency is a relatively unimportant factor except in situations where limited volume is an issue, such as in subcutaneous or intrathecal infusions. Potency is not the same as the efficacy of a drug, which instead refers to the maximal effect that can be produced by a drug. With the exception of codeine and dextropropoxyphene, most of the pure agonist opioids are considered to have equal maximal efficacy, that is, they are equally effective to control moderate to severe pain.<sup>12</sup>

Although the general side-effect profile of pure agonists is fairly similar, there is considerable variation among patients' responses to these drugs. Clinicians should understand that some patients will require trials of different

opioids before finding an effective and well-tolerated drug. Clinicians may need to switch opioids to improve pain control, reduce opioid toxicity or side effects, provide a more convenient treatment regimen for the patient, or to reduce the invasiveness of therapy.<sup>15,16</sup> It is also recognized that many patients may require use of multiple routes as they near end of life. In a study of 90 advanced cancer patients treated by the Supportive Care Program at Memorial Sloan Kettering Cancer Hospital, more than half required use of 2 or more routes for opioid administration, necessitating equianalgesic substitution.<sup>17,18</sup>

Two doses are considered equianalgesic if they provide approximately the same amount of pain relief. Because opioids differ from one another in potency (how much relief they provide per milligram), it is important to have some point of reference in comparing these drugs. An equianalgesic table provides a listing of opioids at doses that produce approximately the same amount of analgesia. Equianalgesic tables can be helpful when switching from one opioid to another, or when changing between the oral and parenteral route, so that the same amount of analgesia can be maintained. Equianalgesic dose calculation provides a basis for selecting the appropriate starting dose when switching opioids or changing routes.<sup>14</sup> Erroneous equianalgesic calculations can lead to needless suffering for patients, either from unrelieved pain, or from unnecessary toxicity.

Equianalgesic tables provide listings of opioid doses that produce approximately the same amount of analgesia based on bioavailability and potency. The bioavailability is the percent of drug that ends up in systemic circulation, therefore, intravenous drugs are considered to have 100% bioavailability. Bioavailability of orally administered opioids is generally one-third to one-fifth that of IV administration due to the first-pass effect.<sup>13</sup> That is, drugs taken by the oral route must first be absorbed through the gut and pass through the liver where much of the dose may be inactivated by biochemical processes that change a portion of the drug into different product metabolites. Because the bioavailability of parenterally administered drugs is different than oral formulations, the

dosage must be changed when the route is switched. Equianalgesic tables compare only the agonists, and the oral and parenteral (intravenous/subcutaneous/intramuscular) routes. When opioids are administered by other routes, such as topically, epidurally or intrathecally, other factors must be considered such as opioid lipid solubility and the proximity of drug delivery to opioid receptors.

### THE EQUIANALGESIC TABLE

The first column of Table 1 lists the generic and trade names of the most common opioid agonists. The second column lists the equianalgesic parenteral (intramuscular or subcutaneous or intravenous) doses. The third column lists the equianalgesic oral doses, followed by columns for parenteral:oral ratio, and duration of action. The duration of action is the same for the parenteral and (short acting) oral formulations. All doses listed on the table are considered approximately equal in analgesic effect. For example, 7.5 mg of oral hydromorphone is approximately equal to 10 mg of parenteral morphine in terms of providing pain relief.

It is critical to remember that the doses are approximate and most are based on single dose studies.<sup>19</sup> The doses are to be used only as a guide for calculating an initial conversion dose. The relative potency of some opioids, such as methadone and levorphanol, may increase with repetitive dosing.<sup>11</sup> Doses listed on the table were selected for the purpose of convenience to make comparisons easy. Clinicians may erroneously assume the doses listed are recommended starting doses. This is not the case. They suggest the ratio or proportion to use when calculating a new dose.

Patients can become tolerant to the analgesic and side effects of a given opioid, but not exhibit the same tolerance to another opioid. This is called incomplete cross-tolerance; meaning caution must be used when an equianalgesic dose of a different opioid is administered. When switching to a different opioid, it is recommended that only one-third to one-half of the calculated equianalgesic dose should be administered initially, particularly when pain is being controlled by the current drug.<sup>2</sup> How-

TABLE 1. EQUIANALGESIC TABLE

Drug	Parenteral	PO	Parenteral:PO ratio	Duration of action (hr)
Morphine	10	30	1:3	3-4
Hydromorphone (Dilaudid)	1.5	7.5	1:5	3-4
Oxymorphone (Numorphone)	1	10	1:10	3-4
Oxycodone <sup>o</sup> (Roxicodone, Roxicet, Percocet)	Not available in U.S.	20-30	—	3-4
Codeine	130	200 NA	1:1.5	3-4
Hydrocodone <sup>oo</sup> (Vicodin, Vicoprofen, Lortab, Lorcet)	—	30 NA	—	3-4
Propoxyphene (Wygesic, Darvocet)	—	NA*	—	4-6
Meperidine (Demerol)	75	300**	1:4	3-4
Levorphanol (Levo-Dromoran)	2	4	1:2	3-4
Methadone (Dolophine)	10	3-5***	—	4-12
Fentanyl (Sublimaze) (Duragesic <sup>^</sup> )	0.1 <sup>^</sup>	—	—	1-3 <sup>^^</sup>

Adapted from Cherny NI. *Drugs* 1996<sup>43</sup>; 51:713-737; Pasero C, Portenoy R, McCaffery M. *Pain: Clinical Manual*. St. Louis, Mosby 1999<sup>14</sup>; UW Health Pain Reference Card 4th ED, UW Board of Regents, 1998.

Duration of action based on use of short acting formulations.

NA, equianalgesic data unavailable. Codeine doses should not exceed 1.5 mg/kg because of an increased incidence of side effects with higher doses.

<sup>o</sup>These products contain 5 mg oxycodone with some combination of aspirin or acetaminophen.

<sup>oo</sup>These products contain 5, 7.5, or 10 mg of hydrocodone with some combination of aspirin, acetaminophen, or ibuprofen.

\*Long half-life. Accumulation of toxic metabolite (norpropoxyphene) with repetitive dosing. Inappropriate for use in the elderly.

\*\*Avoid multiple dosing with meperidine (no more than 48 hrs or at doses greater than 600 mg/24 hours). Accumulation of toxic metabolite normeperidine (half-life 12-16 hours) can lead to CNS excitability and convulsions. Contraindicated in patients receiving MAO inhibitors.

\*\*\*Although many equianalgesic tables list 20 mg as the PO oral methadone equianalgesic dose, recent data suggest methadone is much more potent with repetitive dosing. Ratios between PO morphine and PO methadone may range from 4-14:1.

<sup>^</sup>Transdermal fentanyl 100 µg/hr is approximately equivalent to 2-4 mg/hr of IV morphine. A conversion factor for transdermal fentanyl that can be used for equianalgesic calculation is 17 µg/hr. Roughly, the dose of transdermal fentanyl in µg/hr is approximately one-half of the 24-hour dose of oral morphine.

<sup>^^</sup>Single dose data. Continual intravenous infusion produces lipid accumulation and prolonged terminal excretion.

ever if pain is not controlled, a clinician may decide to administer the new opioid at the calculated equianalgesic dose or at a percentage increase (25%-100%) based on the severity of pain. Information other than the equianalgesic calculation should be taken into consideration in determining the new dose, including the drug's half-life, bioavailability, drug interactions, hepatic and renal clearance, the patient's type of pain and prior opioid exposure.<sup>20</sup> As always, individual patient response must be observed, and doses and intervals between doses need to be titrated according to the patient's response.

It is important to recognize that the way in which a drug is administered (eg, single dose, divided doses, or continuous dosing) is determined by the route, product formulation, clinical pharmacology of the drug, and by the clinical situation.<sup>13</sup> Because of their complete bioavailability, intravenous doses are generally provided hourly or as a continuous infusion. Although intermittent bolus doses of intramuscular and subcutaneous opioids are considered equipotent with IV dose, these modes of administration are dosed at longer intervals because they provide a slower time course due to the systemic absorption required from the

depot site.<sup>12</sup> The availability of extended release oral formulations allow for dosing of morphine as infrequently as every 12–24 hours when pain is constant and around-the-clock dosing is required. Recently, the use of a single dose of an opioid with a long duration of action for selected short pain experiences, such as migraine headache or postoperative pain, has been suggested.<sup>2</sup>

### HOW TO CALCULATE AN EQUIANALGESIC DOSE

There are a number of ways to calculate an equianalgesic dose. Choice of method is primarily one of individual preference and style of approaching math problems. When properly applied, any of the methods described below will produce the correct result (Table 2).

### RATIOS

One method to use is ratios. For example, look at Table 1 and find the oral dose listed for morphine (30 mg) and the parenteral dose (10 mg). This gives a 30:10 or 3:1 ratio for oral to parenteral morphine. This means that it takes approximately 3 times more morphine orally than parenterally to produce the same analgesic effect. One can simply multiply any IV morphine amount by 3 to determine the approximate equianalgesic oral morphine dose.

Now examine the ratio between oral hydromorphone and oral morphine. You can see from Table 1 that 7.5 mg of oral hydromorphone is equal to 30 mg of oral morphine. 7.5 mg to 30 mg is a 1:4 ratio (if you can't immediately see this ratio, divide the smaller number into the larger number, 7.5 goes into 30 four times). So a patient taking 4 mg of hydromorphone PO q4h is taking the equivalent of 16 mg of morphine PO q4h. Setting up a ratio makes it easy to view the difference between the 2 drugs. The difficulty of ratios is that there is not always a convenient one, particularly between different opioids. Take for example the ratio between oral hydromorphone (7.5 mg) and the parenteral dose of morphine (10 mg). The ratio is 7.5:10 or 3:4.

### PROPORTIONS

A second method is to set up simple math proportions using ratios. Proportions can be set up in a number of ways, and still be mathematically correct, as long as the ratios used on either side of the equation are kept parallel. For example:

*Doses from Equianalgesic Table*

*Actual Drug Doses*

$$\frac{\text{Equianalgesic table dose of current drug}}{\text{Equianalgesic table dose of new drug}} = \frac{\text{24 hr total dose of current drug}}{\text{24 hr total dose of the new drug}}$$

or

*Current Drug*

*New Drug*

$$\frac{\text{Equianalgesic table dose of current drug}}{\text{24 hr total dose of current drug}} = \frac{\text{Equianalgesic table dose of new drug}}{\text{24 hr total dose of the new drug}}$$

Both methods of setting up the proportions are equally correct. Although an equianalgesic calculation can be performed for a single dose, when a change is made it is best to convert the total 24-hour amount of opioid currently being used to the 24-hour dose of the new preferred route and drug, and then divide this amount by the appropriate dosing interval. For example, if a patient is receiving a continuous IV infusion, calculating the oral equivalent of only 1 hour of infusion would not be very helpful for determining an oral dose. Take the following example: a patient receiving an IV infusion of 7 mg of morphine per hour. Using the ratio between oral and IV morphine from Table 1 (3:1), we can see that the equivalent oral dose is approximately (7 mg × 3 =) 21 mg of morphine. However, readers would agree that we would not want to give a patient an oral dose every hour, because the duration of action of oral morphine is 3–4 hours for shorter acting preparations and 8–24 hours for extended release products. It is much easier to first add up the total 24-hour amount of IV

TABLE 2. EQUIANALGESIC CALCULATION GUIDE

<p><b>1 Add up the total amount of current drug given in 24 hours. Remember to add in both scheduled and rescue doses.</b> (If two or more different opioids have been taken, they must each be converted to the same drug and route)</p> <p><b>2 Plug numbers into the following proportion:</b> Go to equianalgesic table – find dose for current drug</p>	<p><b>Example: 1</b> Patient is taking 10mg PO morphine q4h. The patient is taking 6 doses per day: <b>6 doses × 10 mg = 60mg per day</b> Convert to oral hydromorphone:</p> <p><b>2</b> 30mg PO morphine = 60 mg PO morphine</p>
<p>Go to equianalgesic table – find dose for new drug = <math>\frac{\text{Put in 24h dose of current drug (from step 1)}}{\text{N (the 24h dose of the new drug)}}</math></p>	<p>7.5mg PO hydromorphone = <math>\frac{\text{N (the 24h dose of PO hydromorphone)}}{\text{N}}</math></p>
<p><b>Shortcut tip:</b> Look at the left side of the proportion above as a fraction. If possible, reduce the fraction. This new fraction provides the ratio and applies to the relationship between the 24h doses, and may immediately show you the value of N. If can see this, skip to step 4.</p>	<p>30mg morphine = <math>\frac{4}{1}</math> = <math>\frac{60\text{mg morphine}}{\text{N}}</math> 7.5mg hydromorphone</p>
<p><b>3 Solve for N by cross multiplying:</b> <b>A</b> Equianalgesic table dose of current drug = <math>\frac{24\text{h dose of current drug}}{\text{N}}</math></p>	<p><b>3</b> <b>A</b> 30mg morphine = <math>\frac{60\text{mg morphine}}{\text{N}}</math> 7.5mg hydromorphone</p>
<p><b>B</b> Equianalgesic table dose of new drug = <math>\frac{\text{N}}{\text{Equianalgesic table dose current drug}} \times \text{24h dose current drug}</math></p> <p><b>C</b> 24h dose current drug X Equianalgesic table dose new drug = N</p>	<p><b>B</b> 60mg morphine X 7.5mg hydromorphone = 30mg morphine X N</p> <p><b>C</b> 60mg morphine X 7.5mg hydromorphone = N 30mg morphine</p>
<p><b>D</b> Answer! “N” will be the 24h dose of the new drug</p> <p><b>E</b> Does this answer make sense? Double check. Plug answer into the proportion in step A, cross multiply and the numbers should be equal.</p>	<p><b>D</b> 15mg hydromorphone = N</p> <p><b>E</b> 30mg morphine = <math>\frac{60\text{mg morphine}}{15\text{mg hydromorphone}}</math> 7.5mg hydromorphone</p>
<p><b>4 Look up the duration of action (the dosing interval) of the new drug in the equianalgesic table and determine how many doses the patient should take each day. Divide N by the number of dose per day. This gives the amount for each scheduled dose of the new opioid.</b></p>	<p><b>4</b> Hydromorphone can be given every 4h, which is 6 doses per day. To give 15mg of hydromorphone in a day, divide the 24h dose by 6. <b>2.5mg hydromorphone q4h</b> Since hydromorphone comes in 2,4, and 8mg tablets, the dose would be rounded up or down depending on the clinical situation.</p>

This guide illustrates one method of changing from one opioid or route of administration to another. Clinicians must be able to identify appropriate opioid doses when a patient requires a change of opioid and/or route of administration. Mastering this skill enables you to determine a dose of a new opioid that is approximately equal in analgesic effect to the dose of a former opioid to ensure continued pain relief.

morphine the patient is currently receiving ( $7 \text{ mg} \times 24 \text{ hours} = 168 \text{ mg IV morphine}/24 \text{ hours}$ ). Again, using the ratio method, multiply this total by 3 to determine the approximate amount of oral morphine required in 24 hours ( $3 \times 168 \text{ mg} = 504 \text{ mg}$ ). The new 24-hour total can then be divided by the appropriate dosing interval based on the duration of action of the product being used (eg, for short-acting oral morphine divide by 6 dosing intervals, and administer every 4 hours; for 12-hour formulations such as MS-Contin™ or Oramorph™ divide by 2 dosing intervals and administer every 12 hours; for 24-hour formulations such as Kadian™ (Zeneca Pharmaceuticals, Wilmington, DE) the 24-hour dose does not need to be divided and can be administered as a single dose).

### CONTROVERSIES

Recent data from crossover studies have questioned the validity of widely published equianalgesic tables.<sup>22</sup> Among a number of equianalgesic doses currently under question, are the relative doses of methadone to morphine and hydromorphone, hydromorphone to morphine, and oral oxycodone to morphine. In addition, the development of novel formulations for new systemic routes of administration (eg, transdermal, transmucosal, inhaled) brings new challenges to equianalgesic conversions.

### METHADONE

Methadone is known for a wide ranging and unpredictable plasma half-life (13 to 50 hours), and for its progressive duration of analgesia with chronic dosing. Whereas the duration of analgesia is often only 4 to 8 hours in the first few days of therapy, with repetitive dosing, the drug is known to accumulate, lengthening dosing interval requirements to only once or twice a day.<sup>12</sup>

Some equianalgesic tables propose a dose ratio of 1:1 between oral and parenteral morphine and methadone.<sup>13,23</sup> Others, propose a morphine-methadone ratio of 4:1 for the oral route and 2.7:1 for the parenteral route.<sup>2</sup> A number of authors<sup>24-27</sup> have more recently reported

major differences in the dose of methadone required to maintain control of cancer pain when compared to previous doses of morphine and hydromorphone. In all studies, methadone was found to be much more potent than was suggested by single-dose studies.

Although most equianalgesic tables propose a parenteral hydromorphone to oral methadone dose ratio ranging from 1:6 to 1:10, data from a retrospective study of opioid rotations of 65 cancer patients<sup>28</sup> whose median total equivalent morphine dose before opioid change was 1185 mg, found the ratio between subcutaneous hydromorphone and oral methadone to be 1.14:1. This is approximately 6 to 10 times higher than previously suggested. Although the dose ratio did not change according to the previous opioid dose, it was correlated with the total opioid dose. It is also been reported, that contrary to what one might expect, toxicity from methadone appears to occur frequently in patients previously exposed to high doses of other opioids than in patients previously receiving low doses.<sup>26</sup> The findings indicate that the ratio between methadone and other opioid agonists may vary widely and change as a function of the previous dose exposure.<sup>26</sup>

### HYDROMORPHONE

Although short-term studies<sup>29</sup> support a morphine to hydromorphone equivalency ratio of 7:1 or 5:1, data from more recent long-term studies<sup>30</sup> suggest that the morphine/hydromorphone equivalency ratio changes over time and may be more close to 3:1. Data from another retrospective study of opioid rotations in cancer patients,<sup>31</sup> suggest that hydromorphone is 5 times more potent than morphine when given second, but only 3.7 times more potent when given first. In other words, the opioid to which the patient is rotated is relatively more potent.

### ORAL OXYCODONE TO MORPHINE

Package inserts for slow release oxycodone suggest an equivalency ratio of 2:1 for oral mor-

phine to oral oxycodone. This ratio is derived from comparison, double-blind, randomized, parallel-group assays of oxycodone to codeine and morphine,<sup>32,33</sup> and is considered conservative by some, who instead, recommend a milligram to milligram conversion for oral morphine to oral oxycodone (1:1). It has also been suggested to use a slightly different ratio depending on which direction the switch is being made (eg, from oral morphine to oral oxycodone 1.5:1, or 20 mg of oxycodone for every 30 mg of morphine, and from oral oxycodone to oral morphine use 1:1).<sup>14</sup> Ratios of 1:1 and 1.3:1 (oral oxycodone to oral morphine) have both been found to be safe and effective in studies of both chronic advanced cancer pain<sup>34</sup> and postoperative patients.<sup>35</sup>

### TRANSDERMAL FENTANYL

If not the most controversial, perhaps the most challenging opioid formulation for which to calculate an equianalgesic dose is transdermal fentanyl. Fentanyl is generally considered 50–150 times more potent than morphine and is well known for its use in anesthesia.<sup>36</sup> Transdermal fentanyl patches capitalize on the drug's lipid solubility and contain a rate-controlling membrane that allows for continuous 72-hour systemic drug delivery through percutaneous absorption.<sup>37</sup> As mentioned previously, equianalgesic tables traditionally compare only per os and parenteral doses. However, as interest and use in newer formulations such as transdermal fentanyl grow, there is a demand for equianalgesic doses of novel routes such as transdermal, transmucosal, and inhalation.

Although the pharmacokinetics of transdermal fentanyl are fairly well defined, the recommended range of equianalgesic doses is considerably variable. Package inserts lists the recommended conversion for 25  $\mu\text{g/hr}$  of transdermal fentanyl at 45–134 mg of oral morphine per day.<sup>38</sup> Many clinicians use a 2:1 ratio between oral morphine and transdermal fentanyl. By dividing the current 24-hour total dose of oral morphine by two, one can easily determine the approximate microgram starting dose of transdermal fentanyl. For example, a

patient taking 400 mg of oral morphine in 24 hours would be switched to 200  $\mu\text{g/hr}$  patch of transdermal fentanyl Q72 hours. Clinical studies continue to report that either method (package insert or ratio) is conservative, with up to 50% of patients requiring upward dose titration after initial application.<sup>39–40</sup>

### CONCLUSIONS

From their earliest use,<sup>41</sup> equianalgesic tables have been recognized for several weaknesses. Many of the relative potencies listed on equianalgesic tables are derived from single-dose or short-term studies with limited control on subject differences such as psychological characteristics, previous degree of opioid exposure, nature and severity of pain, random fluctuations in pain severity, age, and sex. The pioneering studies by Houde and colleagues<sup>42</sup> from which most equianalgesic values are derived, were developed to address the pharmaceutical industry's needs to know the dose to use when introducing new analgesics into practice,<sup>20</sup> not for clinicians to determine treatment decisions. In a recent editorial, Foley and Houde<sup>20</sup> discuss the increasing confusion and misinterpretation of equianalgesic dose tables as data from opioid rotation studies is added. They caution, that if such tables are to be used clinically, we must carefully define how the ratios are established, and the confidence limits for each study utilized. In addition, although pharmacokinetic factors and pharmacodynamics studies can be used to help predict equianalgesia, psychological factors will also influence the analgesic effectiveness of an opioid<sup>12</sup> and should be considered in treatment decisions.

Providing quality pain management continues to be a major healthcare challenge. As science and collective clinical experience converge, more information is available to help guide clinicians in decisions about analgesic therapy. Equianalgesic calculation is a quintessential skill for all clinicians, who for many reasons, may need to switch opioid agents or routes for patients in pain. The process of switching from one opioid to another is complex and much more than performing a simple mathematical calculation based on an equianal-



gesic conversion table. Exact conversion factors and procedures for switching are still unknown.

Many of the commonly accepted equianalgesic ratios are coming under question and re-examination. It is unlikely we will ever know with precision, an exact formula to predict a certain outcome. As in all aspects of pain management, individual characteristics and response must be carefully considered and assessed. Even with experienced clinicians, use of recommended ratios may result in undertreatment or the reverse, side effects and toxicity. More information and carefully controlled studies are needed.

### ACKNOWLEDGMENTS

We wish to thank and acknowledge June Dahl, Ph.D. and David Weissman, M.D. for their guidance and leadership in teaching equianalgesic calculation in the Cancer Role Model Program, and for their support in preparation of this manuscript.

### REFERENCES

1. Agency for Health Care Policy and Research (AHCPR): Acute pain management: Operative or medical procedures and trauma. Publication No. 92-0032, Rockville, MD: AHCPR, 1992.
2. Agency for Health Care Policy and Research (AHCPR): Management of cancer pain. Publication No. 94-0592, Rockville, MD: AHCPR, 1994.
3. Cleeland SC, Gonin R, Hatfield AK, Edmonson JH, Blum RH, Stewart JA, Pandya KJ: Pain and its treatment in outpatients with metastatic cancer. *N Engl J Med* 1994;330:592-596.
4. Ferrell BR, McCaffery M, Rhiner M: Pain and addiction: An urgent need for changing nursing education. *J Pain Symptom Manage* 1992;7:117-124.
5. VanRoenn JH, Cleeland CS, Gonin R, Hatfield AK, Pandya KJ: Physician attitudes and practice in cancer pain management. *Ann Intern Med* 1993;119:121-126.
6. McCaffery M, Ferrell BR: Nurses' knowledge about cancer pain: A survey of five countries. *J Pain Symptom Manage* 1995;10:356-369.
7. NIH Consensus Development Conference: The integrated approach to the management of pain. *J Pain Symptom Manage* 1987;2:35-44.
8. Spross JA, McGuire DB, Schmitt RM: Oncology Nursing Society Position Paper on cancer pain. Part I: Introduction and background. *Oncology Nurs Forum* 1990a;17:595-614.
9. McCaffery M, Ferrell BR: Opioid analgesics: nurses' knowledge of doses and psychological dependence. *J Nurs Staff Dev* 1992;8:77-84.
10. Ferrell BR, McCaffery M: Nurses' knowledge about equianalgesia and opioid dosing. *Cancer Nurs* 1997;20:201-212.
11. Ferrante FM: Principles of opioid pharmacotherapy: Practical implications of basic mechanisms. *J Pain Symptom Manage* 1996;11:265-273.
12. Inturrisi CE, Hanks F: Opioid analgesic therapy. In: Doyle D, Hanks GWC, MacDonald N (eds): *Oxford Textbook of Palliative Medicine*. Oxford, New York, Toronto: Oxford University Press, 1993, pp. 166-182.
13. Benedetti C, Butler SH: Systematic analgesics. In: Bonica JJ (ed.) *The Management of Pain*. Volume II. 2nd ed. 1990, pp. 1640-1675.
14. Pasero C, Portenoy R, McCaffery M: Opioid analgesics. In: McCaffery M, Pasero C (eds): *Pain: Clinical Manual*. St Louis: Mosby, 1999, pp. 161-299.
15. Cherny NI, Chang V, Frager G, Ingham JM, Tiseo PJ, Popp B, Portenoy RK, Foley KM: Opioid pharmacotherapy in the management of cancer pain: A survey of strategies used by pain physicians for the selection of analgesic drugs and routes of administration. *Cancer* 1995;76:1283-1293.
16. Noemi DD, Bruera E, Suarez-Almazor M: Opioid rotation for toxicity reduction in terminal cancer patients. *J Pain Symptom Manage* 1995;10:378-384.
17. Coyle N, Adelhart J, Foley K, Portenoy RK: Character of terminal illness in the advanced cancer patient: Pain and other symptoms during the last four weeks of life. *J Pain Symptom Manage* 1990;5:83-93.
18. De Stoutz ND, Burera E, Suarez-Almazor S: Opioid rotation for toxicity reduction in terminal cancer patients. *J Pain Symptom Manage* 1995;10:378-384.
19. Houde RW, Wallenstein SL, Roger A: Clinical pharmacology of analgesics: A method of assaying analgesic effect. *Clin Pharmacol Ther* 1960;1:163-174.
20. Foley KM, Houde RW: Methadone in cancer pain management: Individualize dose and titrate to effect. *J Clin Oncol* 1998;16:3213-3215.
21. Sunshine A, Olson NX, Colon A, Rivera J, Kaiko RF, Fitzmartin RD, Reder RF, Goldenheim PD: Analgesic efficacy of controlled-release oxycodone in postoperative pain. *J Clin Pharmacol* 1996;36:595-603.
22. Cherny NI: Raising the Standard of Care in Cancer Pain Management. American Pain Society 16th Annual Scientific Meeting Symposia. New Orleans, Louisiana, October 25, 1997.
23. Health and Welfare Canada: Cancer Pain: A Monograph on the Management of Cancer Pain. Ottawa, Canada, Health & Welfare, Minister of Supply and Services, H42-2/5, 1984E.
24. Ventafridda V, Ripamonti C, Bianchi M, Sbanotto A, De Conno F: A randomized study of oral administration of morphine and methadone in the treatment of cancer pain. *J Pain Symptom Manage* 1986;9:203-207.
25. DeConno F, Groff L, Brunelli C, Zecca E, Ventafridda V, Ripamonti C: Clinical experience with oral methadone administration in the treatment of 196

- advanced cancer patients. *J Clin Oncol* 1996;14:2836-2842.
26. Ripamonti C, Zecca E, Bruera E: An update on the clinical use of methadone for cancer pain. *Pain* 1997;70:109-115.
  27. Mandredi PL, Borsook D, Chandler SW, Payne R: Intravenous methadone for cancer pain unrelieved by morphine and hydromorphone: Clinical observations. *Pain* 1997;70:99-101.
  28. Bruera E, Pereira J, Watanabe S, Belzile M, Kuehn N, Hanson J: Opioid rotation in patients with cancer pain: a retrospective comparison of dose ratios between methadone, hydromorphone, and morphine. *Cancer* 1996;78:852-857.
  29. Coda B, Tanaka A, Jacobson RC, Donaldson G, Chapman CR: Hydromorphone analgesia after intravenous bolus administration. *Pain* 1997;71:41-48.
  30. Dunbar PJ, Chapman CR, Buckley FP, Gavrin JR: Clinical analgesic equivalence for morphine and hydromorphone with prolonged PCA. *Pain* 1996;68:265-270.
  31. Lawlor P, Turner K, Hanson H, Bruera E: Dose ratio between morphine and hydromorphone in patients with cancer pain: A retrospective study. *Pain* 1997;72:79-85.
  32. Beaver WT, Wallenstein SL, Rogers A, House RW: Analgesic studies of codeine and oxycodone in patients with cancer. Comparisons of oral with intramuscular oxycodone and of oral with intramuscular morphine and codeine. *Pharmacol Ther* 1978;207:101-108.
  33. Kaiko RF, Benzinger DP, Fitzmartin RD, Burke BE, Reder RF, Goldenheim PD: Pharmacokinetic-pharmacodynamic relationship of controlled release oxycodone. *Clin Pharmacol Ther* 1996;59:52-61.
  34. Glare RA, Walsh TD: Dose-ranging study of oxycodone for chronic pain in advanced cancer. *J Clin Oncol* 1993;11:973-978.
  35. Ginsberg B, Sinatra R, Crews J, Hord A, Adler L, Lockhar E: Conversion from IV PCA morphine to oral controlled-release oxycodone tablets for postoperative pain management. 72nd Clinical and Scientific Congress, International Anesthesia Research Society, Orlando, Florida, March 7-11, 1998.
  36. Stanley TH: The history and development of the fentanyl series. *J Pain Symptom Manage* 1992;7:S3-S7.
  37. Sandler A: Transdermal fentanyl: Acute analgesic clinical studies. *J Pain Symptom Manage* 1992;7:S27-S35.
  38. Wakefield B, Hohanson JA, Kron-Chalupa J, Paulsen L: A research-based guideline for appropriate use of transdermal fentanyl to treat chronic pain. *Oncol Nurse Forum* 1998;25:1505-1513.
  39. Simonds MA, Richenbacher J: Transdermal fentanyl: Long term analgesic studies. *J Pain Symptom Manage* 1992;7:S36-S39.
  40. Donner B, Zenz M, Tryba M, Strumpf M: Direct conversion from oral morphine to transdermal fentanyl: a multicenter study in patients with cancer pain. *Pain* 1996;527-534.
  41. Keele KD: The pain chart. *Lancet* 1948;2:6-12.
  42. Houde RW, Wallenstein SL, Beaver WT: Clinical measurement of pain. In: deStevens G (ed): *Analgesics*. New York, NY: Academic Press, 1965, pp. 75-127.
  43. Cherny NI: Opioid analgesics: Comparative features and prescribing guidelines. *Drugs* 1996;51(5):713-737.

Address reprint requests to:

Deb Gordon, R.N., M.S.

University of Wisconsin Hospital & Clinics

3330 University Avenue, Suite 300

Madison, WI 53705

E-mail: db.gordon@hosp.wisc.edu

**This article has been cited by:**

1. José H. Jiménez-Almonte, Cody C. Wyles, Saranya P. Wyles, German A. Norambuena-Morales, Pedro J. Báez, Mohammad H. Murad, Rafael J. Sierra. 2015. Is Local Infiltration Analgesia Superior to Peripheral Nerve Blockade for Pain Management After THA: A Network Meta-analysis. *Clinical Orthopaedics and Related Research*® . [\[CrossRef\]](#)
2. Junyoung Ahn, Daniel D. Bohl, Ehsan Tabaraee, Khaled Aboushaala, Islam M. Elboghday, Kern Singh. 2015. Preoperative narcotic utilization: accuracy of patient self-reporting and its association with postoperative narcotic consumption. *Journal of Neurosurgery: Spine* 1-9. [\[CrossRef\]](#)
3. A.R. Valentine, B. Carvalho, T.A. Lazo, E.T. Riley. 2015. Scheduled acetaminophen with as-needed opioids compared to as-needed acetaminophen plus opioids for post-cesarean pain management. *International Journal of Obstetric Anesthesia* 24, 210-216. [\[CrossRef\]](#)
4. Junyoung Ahn, Daniel D. Bohl, Islam Elboghday, Khaled Aboushaala, Hamid Hassanzadeh, Kern Singh. 2015. Postoperative Narcotic Consumption in Workman's Compensation Patients Following a Minimally Invasive Transforaminal Lumbar Interbody Fusion. *Spine* 40, 1284-1288. [\[CrossRef\]](#)
5. Stavros G. Memtsoudis, Daniel Yoo, Ottokar Stundner, Thomas Danninger, Yan Ma, Lazaros Poultsides, David Kim, Mary Chisholm, Kethy Jules-Elysee, Alejandro Gonzalez Della Valle, Thomas P. Sculco. 2015. Subsartorial adductor canal vs femoral nerve block for analgesia after total knee replacement. *International Orthopaedics* 39, 673-680. [\[CrossRef\]](#)
6. Yaowu Bai, Timothy Miller, Mingjuan Tan, Lawrence Siu-Chun Law, Tong Joo Gan. 2015. Lidocaine patch for acute pain management: a meta-analysis of prospective controlled trials. *Current Medical Research and Opinion* 31, 575-581. [\[CrossRef\]](#)
7. Andrew A. Gassman, Alfred P. Yoon, Justin B. Maxhimer, Ivan Sanchez, Harleen Sethi, Kevin W. Cheng, Charles Y. Tseng, Jaco H. Festekjian, Andrew L. Da Lio, Chris A. Crisera. 2015. Comparison of Postoperative Pain Control in Autologous Abdominal Free Flap versus Implant-Based Breast Reconstructions. *Plastic and Reconstructive Surgery* 135, 356-367. [\[CrossRef\]](#)
8. Louise Wen, Gillian Hilton, Brendan Carvalho. 2015. The impact of breastfeeding on postpartum pain after vaginal and cesarean delivery. *Journal of Clinical Anesthesia* 27, 33-38. [\[CrossRef\]](#)
9. Barbara A. Rakel, Bridget M. Zimmerman, Katharine Geasland, Jennie Embree, Charles R. Clark, Nicolas O. Noiseux, John J. Callaghan, Keela Herr, Deirdre Walsh, Kathleen A. Sluka. 2014. Transcutaneous electrical nerve stimulation for the control of pain during rehabilitation after total knee arthroplasty: A randomized, blinded, placebo-controlled trial. *Pain* 155, 2599-2611. [\[CrossRef\]](#)
10. J. David Prologo, Matthew Passalacqua, Indravadan Patel, Nathan Bohnert, David J. Corn. 2014. Image-guided cryoablation for the treatment of painful musculoskeletal metastatic disease: a single-center experience. *Skeletal Radiology* 43, 1551-1559. [\[CrossRef\]](#)
11. Qing Liu, Jacques E. Chelly, John P. Williams, Michael S. Gold. 2014. Impact of Peripheral Nerve Block With Low Dose Local Anesthetics on Analgesia and Functional Outcomes Following Total Knee Arthroplasty: A Retrospective Study. *Pain Medicine* n/a-n/a. [\[CrossRef\]](#)
12. Mary F. Chisholm, Heejung Bang, Daniel B. Maalouf, Dorothy Marcello, Marco A. Lotano, Robert G. Marx, Gregory A. Liguori, Victor M. Zayas, Michael A. Gordon, Jason Jacobs, Jacques T. YaDeau. 2014. Postoperative Analgesia with Saphenous Block Appears Equivalent to Femoral Nerve Block in ACL Reconstruction. *HSS Journal* ® 10, 245-251. [\[CrossRef\]](#)
13. C.S. Zin, L.-C. Chen, R.D. Knaggs. 2014. Changes in trends and pattern of strong opioid prescribing in primary care. *European Journal of Pain* n/a-n/a. [\[CrossRef\]](#)
14. S. Singh, S. Dhir, K. Marmai, S. Rehau, M. Silva, C. Bradbury. 2013. Efficacy of ultrasound-guided transversus abdominis plane blocks for post-cesarean delivery analgesia: a double-blind, dose-comparison, placebo-controlled randomized trial. *International Journal of Obstetric Anesthesia* 22, 188-193. [\[CrossRef\]](#)
15. Jean-Pierre Estebe, Michel Olivier. 2013. Comment prendre en charge l'analgésie d'un patient sous traitement opiacé chronique. *Le Praticien en Anesthésie Réanimation* 17, 140-146. [\[CrossRef\]](#)
16. Gavin M. Langille, Gordon O. Launcelott, Ricardo A. Rendon. 2013. Access to the Extrapleural Space at the Time of Surgery for Continuous Paravertebral Block After Flank Incision: Description of the Technique and Case Series. *Urology* 81, 675-678. [\[CrossRef\]](#)

17. C.M. Ortner, M. Granot, P. Richebé, M. Cardoso, L. Bollag, R. Landau. 2013. Preoperative scar hyperalgesia is associated with post-operative pain in women undergoing a repeat Caesarean delivery. *European Journal of Pain* 17:10.1002/ejp.2013.17.issue-1, 111-123. [[CrossRef](#)]
18. J.Y. Wong, B. Carvalho, E.T. Riley. 2013. Intrathecal morphine 100 and 200µg for post-cesarean delivery analgesia: a trade-off between analgesic efficacy and side effects. *International Journal of Obstetric Anesthesia* 22, 36-41. [[CrossRef](#)]
19. Jaishankar Raman, Sven Lehmann, Kenton Zehr, Brian J. De Guzman, Lishan Aklog, H. Edward Garrett, Heber MacMahon, Brian M. Hatcher, Michael S. Wong. 2012. Sternal Closure With Rigid Plate Fixation Versus Wire Closure: A Randomized Controlled Multicenter Trial. *The Annals of Thoracic Surgery* 94, 1854-1861. [[CrossRef](#)]
20. Brendan Carvalho, Harry J. Lemmens, Vicki Ting, Martin S. Angst. 2012. Postoperative Subcutaneous Instillation of Low-Dose Ketorolac but Not Hydromorphone Reduces Wound Exudate Concentrations of Interleukin-6 and Interleukin-10 and Improves Analgesia Following Cesarean Delivery. *The Journal of Pain* . [[CrossRef](#)]
21. Barbara A. Rakel, Nicole Petsas Blodgett, Bridget M. Zimmerman, Nyla Logsden-Sackett, Charles Clark, Nicolas Noiseux, John Callaghan, Keela Herr, Katharine Geasland, Xiaoyan Yang, Kathleen A. Sluka. 2012. Predictors of postoperative movement and resting pain following total knee replacement. *Pain* 153, 2192-2203. [[CrossRef](#)]
22. Ralph J. Mobbs, Praveenan Sivabalan, Jane Li. 2012. Minimally invasive surgery compared to open spinal fusion for the treatment of degenerative lumbar spine pathologies. *Journal of Clinical Neuroscience* 19, 829-835. [[CrossRef](#)]
23. Tim Geary, Anna Negus, Brian J. Anderson, Boris Zernikow. 2011. Perioperative management of the child on long-term opioids. *Pediatric Anesthesia* no-no. [[CrossRef](#)]
24. Lynn Webster, Randall Brewer, David Morris, Jody Cleveland, Beatrice Setnik. 2011. Opioid Titration and Conversion in Patients Receiving Morphine Sulfate and Naltrexone Hydrochloride Extended Release Capsules. *Postgraduate Medicine* 123, 155-164. [[CrossRef](#)]
25. Robert A Moore, Róisín J Ní Mhuirheartaigh, Sheena Derry, Henry J McQuay. 2011. Mean analgesic consumption is inappropriate for testing analgesic efficacy in post-operative pain: analysis and alternative suggestion. *European Journal of Anaesthesiology* 28, 427-432. [[CrossRef](#)]
26. Lindsey Atkinson Ralls, David R. Drover, Claudia F. Clavijo, Brendan Carvalho. 2011. Prior Epidural Lidocaine Alters the Pharmacokinetics and Drug Effects of Extended-Release Epidural Morphine (DepoDur®) After Cesarean Delivery. *Anesthesia & Analgesia* 1. [[CrossRef](#)]
27. Jacques T. YaDeau, Spencer S. Liu, Matthew C. Rade, Dorothy Marcello, Gregory A. Liguori. 2011. Performance Characteristics and Validation of the Opioid-Related Symptom Distress Scale for Evaluation of Analgesic Side Effects After Orthopedic Surgery. *Anesthesia & Analgesia* 1. [[CrossRef](#)]
28. Brendan Carvalho, David J. Clark, David C. Yeomans, Martin S. Angst. 2010. Continuous Subcutaneous Instillation of Bupivacaine Compared to Saline Reduces Interleukin 10 and Increases Substance P in Surgical Wounds After Cesarean Delivery. *Anesthesia & Analgesia* 111, 1452-1459. [[CrossRef](#)]
29. Kathleen A. Puntillo, Shoshana Arai, Neal H. Cohen, Michael A. Gropper, John Neuhaus, Steven M. Paul, Christine Miaskowski. 2010. Symptoms experienced by intensive care unit patients at high risk of dying\*. *Critical Care Medicine* 38, 2155-2160. [[CrossRef](#)]
30. Mellar P. Davis, Mary Lynn McPherson. 2010. Tabling Hydromorphone: Do We Have It Right?\*. *Journal of Palliative Medicine* 13:4, 365-366. [[Citation](#)] [[Full Text HTML](#)] [[Full Text PDF](#)] [[Full Text PDF with Links](#)]
31. Howard Smith Role of Opioid Rotation and Tapering in Managing Opioid-Induced Hyperalgesia 134-163. [[CrossRef](#)]
32. Christina Ullrich, Joanne Wolfe Pediatric Pain and Symptom Control 1097-1105. [[CrossRef](#)]
33. Brendan Carvalho, David J. Clark, Martin S. Angst. 2008. Local and Systemic Release of Cytokines, Nerve Growth Factor, Prostaglandin E2, and Substance P in Incisional Wounds and Serum Following Cesarean Delivery. *The Journal of Pain* 9, 650-657. [[CrossRef](#)]
34. Douglas J. Weschules, Kevin T. Bain. 2008. A Systematic Review of Opioid Conversion Ratios Used with Methadone for the Treatment of Pain. *Pain Medicine* 9:10.1111/pme.2008.9.issue-5, 595-612. [[CrossRef](#)]
35. Brendan Carvalho, Laura M. Roland, Larry F. Chu, Vincent A. Campitelli, Edward T. Riley. 2007. Single-Dose, Extended-Release Epidural Morphine (DepoDur???) Compared to Conventional Epidural Morphine for Post-Cesarean Pain. *Anesthesia & Analgesia* 105, 176-183. [[CrossRef](#)]
36. Enno Freye, Astrid Anderson-Hillemacher, Ingrid Ritzdorf, Joseph Victor Levy. 2007. Opioid Rotation from High-Dose Morphine to Transdermal Buprenorphine (Transtec ♦ ) in Chronic Pain Patients. *Pain Practice* 7:10.1111/ppr.2007.7.issue-2, 123-129. [[CrossRef](#)]

37. 2007. Recommandations pour l'indication et l'utilisation de la PCA à l'hôpital et à domicile pour l'administration de morphine chez le patient atteint de cancer et douloureux, en soins palliatifs – mars 2006. *Médecine Palliative : Soins de Support - Accompagnement - Éthique* 6, 114-143. [[CrossRef](#)]
38. R MULARSKI. 2004. Pain management in the intensive care unit. *Critical Care Clinics* 20, 381-401. [[CrossRef](#)]
39. Margaret Wootton. 2004. Morphine is not the only analgesic in palliative care: literature review. *Journal of Advanced Nursing* 45, 527-532. [[CrossRef](#)]
40. Arnold R. Gammaitoni, Perry Fine, Nancy Alvarez, Mary Lynn McPherson, Suzette Bergmark. 2003. Clinical Application of Opioid Equianalgesic Data. *The Clinical Journal of Pain* 19, 286-297. [[CrossRef](#)]
41. Robert Arnold, David E. Weissman. 2003. Calculating Opioid Dose Conversions #36. *Journal of Palliative Medicine* 6:4, 619-620. [[Citation](#)] [[Full Text PDF](#)] [[Full Text PDF with Links](#)]
42. G. Gazelle, Perry G. Fine. 2003. Methadone for the Treatment of Pain #75. *Journal of Palliative Medicine* 6:4, 620-621. [[Citation](#)] [[Full Text PDF](#)] [[Full Text PDF with Links](#)]
43. Susannah Hall, Rollin M. Gallagher, Edward Gracely, Calvin Knowlton, Douglas Wescules. 2003. The Terminal Cancer Patient: Effects of Age, Gender, and Primary Tumor Site on Opioid Dose. *Pain Medicine* 4, 125-134. [[CrossRef](#)]
44. Arnold R. Gammaitoni, Perry Fine, Nancy Alvarez, Mary Lynn McPherson, Suzette Bergmark. 2003. Clinical Application of Opioid Equianalgesic Data. *The Clinical Journal of Pain* 286. [[CrossRef](#)]
45. Bruce Nicholson. 2003. Responsible Prescribing of Opioids for the Management of Chronic Pain. *Drugs* 63, 17-32. [[CrossRef](#)]
46. R Anderson. 2001. Accuracy in Equianalgesic Dosing Conversion Dilemmas. *Journal of Pain and Symptom Management* 21, 397-406. [[CrossRef](#)]