Opioid analgesics have long been the mainstay, both domestically and abroad, for treating moderate to severe pain from a variety of etiologies. Morphine has been the first-line opioid agent. Today, it is the standard to which all other opioids are measured due to its ubiquity, availability for essentially every possible route of administration, and clinician familiarity. Morphine demonstrates those attributes most coveted in a drug therapy: it undergoes straightforward pharmacokinetics with two well-elucidated metabolites; is effective, inexpensive, and widely available; and it has been safely used for nearly 200 years in Western medicine. Although morphine once stood prominently at the center of the opioid analgesic toolkit, it is now beset by new opioid agents, reformulations of erstwhile agents, new non-opioid therapies, and new insights into the enigmatic world of pain management.

The importance of a broad and variable assortment of formulations, mechanisms, and pharmacokinetic profiles is clear to any pain management clinician. For although morphine may be the established gold standard, the majority of chronic pain patients with moderate to severe pain will not be controlled and maintained on their initial opioid

**Mathematical Model For Methadone Conversion Examined**

A new model aims to better mirror the continuity that prescribing physicians may expect to occur over a range of dosing conversions.

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analgesic, and often will receive medications with varying pharmacological mechanisms to maximize therapeutic benefit. There is a considerable degree of inter-patient variability in response to opioid therapy and in an effort to maximize efficacy and reduce opioid-related toxicity and drug interactions, numerous agents are frequently tried before a patient reaches their pain management goals.

The Role of Methadone

As clinicians and researchers attempt to expand their pain management repertoire to better treat the specific nuances of each patient, it is not just toward the future that they gaze. Methadone, a µ-opioid agonist with a unique N-methyl-D-aspartate (NMDA) receptor antagonist profile, was developed in Germany in 1937 and expropriated to the Allies following World War II. In 1947, Eli Lilly and Company purchased the rights to the compound for $1, and methadone became widely available in the United States. Perhaps to its detriment, methadone originally found its niche in the treatment of opioid dependence, a stigmatization that follows the drug to this day. Nonetheless, methadone has grown in popularity as a viable option for the treatment of moderate to severe chronic pain.

The myriad benefits to methadone therapy for severe chronic pain are clear. It is relatively inexpensive, has excellent oral bioavailability, high potency, no known active metabolites, and a receptor activity profile unique enough to allow for effective analgesia in patients intolerant or unresponsive to many other opioids. Methadone has potent µ-opioid analgesia, but is unique for NMDA receptor antagonism and modest norepinephrine reuptake inhibition. The benefit of NMDA receptor antagonism in neuropathic pain has been well established, allowing methadone particular usefulness in chronic pain with neuropathic components.

Unfortunately, these benefits must be weighed against an intimidating combination of concerns that limit methadone’s use among inexperienced practitioners. The elimination half-life of methadone is significantly longer than its analgesic effect, which may potentiate toxic drug accumulation with too frequent dosing or attempts at rapid escalation. Methadone requires slow dose escalation for several days or weeks to achieve optimal analgesic response. Even at unchanged doses, one may not realize benefit for several days because of the complex pharmacokinetics including high and variable volume of distribution, long half-life, and resultant time to steady state. Methadone is partially metabolized through the cytochrome-P450 enzyme system, which may cause a fluctuation in serum concentrations in response to concomitant inducers or inhibitors of the same enzymes. In addition, methadone is extensively protein-bound, with the active drug being free in the serum. Other extensively protein-bound drugs have the potential to displace methadone from its binding sites.

Methadone may prolong the QTc interval in some patients, particularly those who are receiving high methadone doses combined with tricyclic antidepressants and/or other agents that may affect myocardium electroconductivity. Compounding these concerns, perhaps the most pressing to inexperienced practitioners is accurate and safe dosing, or more specifically, how to convert from another opioid analgesic to methadone or from methadone to another opioid. Unfortunately, conversion to or from methadone is not bi-directional. After discontinuing methadone, it remains in the serum for several days. Therefore, an abrupt switch to an alternate opioid will result in double dosing even in the absence of further methadone doses.

There has been some contention regarding the equianalgesic dose ratio (EDR) between oral morphine and oral methadone within the literature. Different authors have reported three varying methadone conversion schematics, all of which have been based on small sample sizes. There is a great deal of genetic polymorphism resulting in broadly varying inter-patient variability both pharmacodynamically and pharmacokinetically with opioids, including methadone. For these reasons, no specific formula or methadone conversion guidelines are sanctioned due to lack of replicated data in larger-scale controlled studies for which a priori power analyses have been done. Notwithstanding, these schematics have been routinely employed by clinicians in an attempt to titrate methadone. Although the authors caution and discourage endorsing any specific methadone conversion strategy, each previous attempt may certainly provide tentative starting points.

The first of these conversion strategies was published by Ripamonti et al in 1998. Being one of the first widely distributed studies of morphine to methadone conversion, it provided useful guidance, but had several significant limitations. As of 1998, methadone’s use for analgesia was limited predominantly to cancer-related pain and heroin maintenance, the former of which is reflected in the investigators’ population. In addition, the sample size included only 38 patients. Despite this, the study offered a tentative starting point and clearly established that the equianalgesic dose ratio between morphine and methadone was significantly more capricious than previously thought. The median dose ratio was found to be 7.75:1,
with a 1:1 ratio found to be inappropriate for any patient, regardless of previous morphine requirements. The findings from the investigators’ study are summarized in Table 1.

In 2000, Ayonrinde and Bridge published their own morphine to methadone conversion strategy created from the results of a small prospective study conducted at Royal Perth Hospital in Washington.16 In response to a near-fatal toxicity experienced by one of their methadone patients, the study was initiated to assess each consecutive patient deemed appropriate for a conversion to methadone over a 6-month period. The study included just 14 patients with predominantly neuropathic pain as methadone’s unique receptor profile may assuage severe pain of neuropathic etiology to an extent that µ-opioid activity alone may not. Just as Ripamonti et al had discovered, Ayonrinde and Bridge’s patients experienced significantly improved analgesia within several days of the conversion. However, investigators proposed a conversion ratio with six breakpoints, in contrast to Ripamonti et al’s three breakpoints. The morphine to methadone conversion ratios proposed by Ayonrinde and Bridge are summarized in Table 1.

In 2001, Mercadante et al proposed their own morphine to methadone conversion ratios based on a study conducted between July 1998 and May 2000 in palliative care units located in Palermo and Milan, Italy.17 This 52-patient prospective study was the largest of its kind and utilized inclusion criteria, methods, and analysis similar to its predecessors. The initial conversion ratios were based upon the data published by Ripamonti and colleagues in 1998 and the results of the study were very similar and strongly supportive of this strategy. Mercadante et al’s findings are also summarized in Table 1.
Beyond narrow inclusion criteria, small sample sizes, and polymorphic considerations, the greatest mathematical limitation of these previously published conversion strategies is due to the equianalgesic dose ratio breakpoints. When evaluated graphically at methadone increments of 2.5 mg over several hundred milligrams, this flaw becomes clear (Figure 1). Because Ripamonti et al’s 1998 publication was utilized as a basis for Mercadante et al’s 2001 study, their two equianalgesic dose ratios almost seamlessly superimpose. Yet, both strategies fail at the 100 mg and 300 mg oral morphine equivalent breakpoints (Table 1 and Figure 1). For example, using Ripamonti and investigators’ ratio, a patient currently maintained on 90 mg per day of oral morphine (or equivalent) would require 24 mg per day of methadone, yet a patient maintained on 105 mg per day of oral morphine (or equivalent) would require 13.5 mg of methadone per day. It is counterintuitive to believe that 15 mg more of morphine in this case would require 10.5 mg less of methadone. These and other dosage inconsistencies at select ratio breakpoints are summarized in Table 2.

Ayonrinde and Bridge’s proposed morphine-methadone conversion ratios demonstrate the largest inconsistencies upon graphing. As opposed to the three ratio breakpoints that Ripamonti et al and Mercadante et al proposed, Ayonrinde and Bridge proposed six. Intuitively, this may have appeared to offer a more accurate conversion strategy, but as demonstrated in Figure 1 and Table 2, each breakpoint causes a precipitous drop in methadone equivalence per very small changes in oral morphine dosage. This causes Ayonrinde and Bridge’s proposed conversion strategy to swing inconsistently between highs and lows, compounded by having the least conservative ratios of the presented strategies. A significant danger of this is elucidated when utilizing certain online conversion calculators that heretofore and currently utilize previously accepted methadone conversion schematics. GlobalRPh, perhaps one of the most frequently utilized online opioid calculators, relies heavily on Ayonrinde and Bridge’s proposed conversion ratios for methadone equivalency calculations.18

In response to these issues, a mathematical model was derived (Figure 2) to eliminate the significant peaks and troughs at dose interval breaks (Figure 3), and to take the most conservative dosing approach at morphine equivalents greater than or equal to 300 mg per day. This newly developed equation was anticipated to eliminate the

### Table 2. Morphine to Methadone Conversions At Select Ratio Breakpoints

<table>
<thead>
<tr>
<th>Oral Morphine Equivalents</th>
<th>90 mg/d</th>
<th>105 mg/d</th>
<th>290 mg/d</th>
<th>305 mg/d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ripamonti et al</td>
<td>24 mg</td>
<td>13.5 mg</td>
<td>37.5 mg</td>
<td>25 mg</td>
</tr>
<tr>
<td>Mercadante et al</td>
<td>22.5 mg</td>
<td>13 mg</td>
<td>36 mg</td>
<td>25.5 mg</td>
</tr>
<tr>
<td>Ayonrinde et al</td>
<td>30 mg</td>
<td>21 mg</td>
<td>58 mg</td>
<td>30 mg</td>
</tr>
<tr>
<td>Fudin</td>
<td>19 mg</td>
<td>19 mg</td>
<td>30 mg</td>
<td>30 mg</td>
</tr>
</tbody>
</table>

Doses shown are daily oral morphine equivalents and daily oral methadone in milligrams.

\[ \text{Methadone (mg)} = \frac{x}{37.5} \times \left( 5.7 - 3 \times \sin \left( \frac{\pi/2}{\left( \frac{110 \times x}{\pi} + 1 \right)} \right) - \sin \left( \frac{\pi/2}{\left( \frac{120 \times x}{\pi} + 1 \right)} \right) \right) \]

Figure 2. Fudin equation, where the sine function appears as radians.

\( x = \text{morphine (mg)} \)

Figure 3. Morphine to methadone equianalgesic dosing ratios including Fudin equation.
Mathematical Model For Methadone Conversion Examined

Formula Development

As a starting point, the previous models were graphed to show the relationship between morphine dosing and methadone dosing. This led to three distinct linear areas of conversion: 0-100 mg of morphine, 101-300 mg of morphine, and 301 mg or greater of morphine. To represent this graphically, a formula was derived using sine functions to follow the saw tooth pattern seen across these conversion dosages. Formula 1 was used, where “x” is the morphine dosage in mg and the sine functions are in degrees (see Figure 2, where sine function appears in radians). This produces a more fluid curve that better represents conversion factors across the entire range of possible dosing. We ultimately chose to obligate the sine function in degrees instead of radians because degrees are more commonly preprogrammed into calculators routinely used by pharmacy clinicians during daily practice.

Since the final derived equation is mathematically cumbersome, therefore presenting an inherent risk for error by miscalculation, publication of the formula was deferred by the developers (since 2005) until an electronic version became available in 2012.19 Practical Pain Management (PPM) recently developed an online calculator that uses the formula; therefore, widespread dissemination and applicability are now possible (Table 3).

As with the previously published conversion strategies, the equation presented here has inherent limitations. Most importantly, the equation is based upon the previously published conversion strategies, which included limited sample sizes and relatively homogenous patient populations. Data from large prospective studies are still lacking for methadone conversion. Another limitation is the complexity of the equation itself. This may dissuade manual calculation or create the opportunity

Table 3. Common Morphine to Methadone Conversions Based on Fudin Equation

<table>
<thead>
<tr>
<th>Morphine (mg/day)</th>
<th>Methadone Equivalent (mg/day)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>5</td>
</tr>
<tr>
<td>40</td>
<td>10</td>
</tr>
<tr>
<td>60</td>
<td>15</td>
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<td>90</td>
<td>20</td>
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<td>120</td>
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<td>200</td>
<td>25</td>
</tr>
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<td>300</td>
<td>30</td>
</tr>
</tbody>
</table>

*Rounded to the nearest available strength
for mathematical error when manually calculated. This potential has been largely obviated by the PPM calculator, but the concern remains for practitioners whom are unable or unwilling to utilize this service. Still, because of complex pharmacokinetics, polymorphic variability, and significant risk of drug interactions with methadone, even with an improved mathematical model measured against previous schematics, only experienced clinicians should attempt to convert to or from methadone. In all cases, the calculated dose should serve as a guide towards a postulated target dose after slow and careful titration.

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Dr. Fudin is on speakers’ bureaus for Jansen Pharmaceuticals, Inc., and Purdue Pharma. This commentary was not prepared as part of Dr. Fudin’s official government duty as clinical pharmacy specialist. He is a consultant to Practical Pain Management in the development of an online opioid analgesic calculator. Dr. Marcoux and Mr. Fudin have no financial information to disclose.

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