PPM Launches Online Opioid Calculator

One of the daily challenges facing healthcare providers is how to safely and accurately calculate appropriate opioid doses—either for opioid-naïve patients or when switching from one agent to another. *Practical Pain Management* asked three pain experts to take on the momentous task of developing their "ideal" opioid conversion calculator—one based on the latest medical evidence—that would be easy to use at the point of care. The result is the *PPM* Opioid Conversion Calculator, which is now available at no charge at www.PracticalPainManagement.com. Here to discuss the calculator's development and unique features are its three developers:

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PPM What are the challenges facing physicians when prescribing [dosing] opioids, or switching from one opioid to another? In other words, why is there a need for an opioid conversion calculator?

Dr. Brennan: In the 21st century, we've come to recognize that people respond differently to different medications. This tool has taken the most current data collected on individual drugs, and provided an easy-to-use, readily available tool for clinicians—whether pharmacists, physicians, or nurses—at the point of care so we can safely and effectively switch patients from one drug to another, with a significant emphasis on safety. Safety is trumping all other efforts with this.

So, why is this necessary? There are a variety of reasons a patient may need to switch opioids: from loss of insurance, change of insurance, or an insurance plan changing its prescription formulary to side effects, etc. Very often patients are sitting in the examination room when a clinician finds out their patient can no longer take a certain medicine. So, by having this Website and this tool, clinicians will be able to—with the patient in the room—do a safe calculation based on the best published and available data. As such, physicians will have the ability to switch their patient from one medication to another that might better benefit the patient in an easy, scientifically based, state-of-the-art approach.

Dr. Perkins: One benefit of the *PPM* opioid calculator is that it makes calculating equivalent doses very easy. One problem with conversions is knowing the equivalent doses. The conversions can involve complex mathematical equations. The calculator can easily and accurately make these calculations quickly. Another reason for developing an opioid calculator is to address the complexity of converting from a long-acting agent to a shorter-acting agent. For example, morphine is the gold standard—it is what every other opioid is compared to. Some of the opioids have much longer half-lives than morphine, and people don't realize that. If you're transitioning from an opioid with a long half-life to something like morphine with a short half-life, there are risks involved, and you need to be aware of those risks to avoid respiratory depression. We have outlined these risks under the "Tips and Warnings" sections when conversions to or from a specific opioid are performed.

PPM What are some of the safety issues surrounding opioid dosing?

Dr. Fudin: There are a number of issues. One issue is inter-patient variability, not only among populations—for example, an Asian versus Caucasian population—but also physiological differences between those populations (polymorphism). But besides that, there are genetic differences even within populations. So, for instance, if you convert from one opioid to another, even if it was an exact science, when you convert to the desired opioid, the patient may actually need a far, far lower dose. So, even if we could create a perfect calculator, there are still going to be inter- and intra-patient variables the prescriber needs to consider. That's a huge challenge.

Dr. Brennan: I agree. One of the things we've learned in the last 25 years is different people have different sensitivities not only to side effects, but to potencies of drugs. And that's based on a number of genetic and experiential factors. So, we recognize that, and have incorporated a number of warnings and provisos into the new tool. We have given some flexibility to the clinician that will allow for a safe switch or rotation from one drug to another. What's been done is that, based on size of the patient, and based on best published data on the relative strengths of drugs, a safety level has been built in to err on the side of caution for converting from drug A to drug B.

On top of that, we've given clinicians added wiggle room to make it an even more conservative conversion. This is vital, because most clinicians have had inadequate training on how to switch drug doses. The tools that have been in doctors' offices mostly are tools developed by pharmaceutical companies to allow one brand of narcotic to be switched to another brand of narcotic. Well, those are one-way conversions. So, by giving clinicians an unbiased, non-branded kind of format [which includes all opioids], we think we're enabling them to make safer and easier switches with this algorithm and formula.

Dr. Perkins: We tried to be conservative with dosing, especially when switching to a long-acting agent like fentanyl transdermal patches. Patches can be a convenient method of drug delivery because they don't require IV access and patients don't have to swallow a pill. If you start at a conservative dose, you can always supplement with as-needed medication, but if you start with too high of a dose, you can't get it back. So, we tried to provide conservative, yet reasonable, dosing—not too conservative, so patients won't get pain control, but conservative enough to take side effect profiles into account.

PPM Is the calculator then useful for physicians who might be initiating pain medications in an opioid-naïve patient?

Dr. Fudin: Absolutely. In fact, as Dr. Brennan noted, many of the current guidelines for opioid dosing have starting doses that are not very conservative at all. The one prime example is methadone. Therefore, methadone should only be prescribed by a physician who is thoroughly trained in its use. In many guidelines—which can be found on the Internet, in textbooks, and in journals—the starting dose of methadone is listed as 10 to 20 mg every eight hours in an opioid-naïve patient. The reason for that is because that's what appeared in the PDR [*Physicians' Desk Reference*] many years ago and the companies that first manufactured methadone used that dose.

Well, we now recognize that if you start an opioid-naïve patient on that dose, it could be fatal. With our calculator, instead of 10 to 20 mg every eight hours, if you want to get the correct dose of methadone for an adult patient weighing 50 kg or greater, it's going to tell you 10 to 20 mg in 3-4 divided doses over 24 hours. So, in other words, instead of giving an answer of 20 mg three times a day, you're going to get an answer that's about 25% of that.

A far as I can tell, and I've looked at seven different calculators, the other calculators are basing their doses on old information that has been accumulated through the years and has become habit. What we did for the initial dosing is base it on the most conservative starting point.

PPM Let's talk a little more about methadone. I understand that Dr. Fudin created a unique formula for how to convert patients from any opioid to methadone. Dr. Fudin, can you explain a little bit about how you developed this formula and why it's unique?

Dr. Fudin: Sure. Most conversions are based on a model developed by Ripamonti et al and published in 1998.[1] Basically, the calculations he developed required clinicians to use a lower methadone ratio as the dose of morphine increased. In other words, the higher the morphine dose, the less methadone needed to replace it. For example, if a patient was taking between 0 and 90 mg of morphine or its equivalent in another drug, the conversion ratio to methadone was 3.7:1; for 91 mg to 300 mg of morphine or its equivalent, the conversion ratio to methadone was 7.75:1; and for 301 mg to infinity of morphine equivalents, it was 12.25:1. Over the years, a lot of people used variations of that formulation.

When I graphed out this formula, I noticed that when the curve got to 90 mg, it dropped and then started to go up again, and as it got to 300 mg, it just dropped (see Figure 1). I was thinking, "How does the body know I took 90 or 91 mg of morphine, and when it got to 91 mg, all of a sudden, it dropped?" It didn't make sense.

So, my son Jason, who was an engineering student at McGill University at the time, and I came up with a formula that eliminated these dips in the graph (see Figure 2). Now, the graph goes up gradually from lower to higher doses, and even beyond 300 mg. We called it the Methadone Fudin Factor. To test its accuracy, we conducted a retrospective study (unpublished) several years ago in more than 100 patients. It seemed to be right on the money. This different formula really makes this calculator unique in terms of methadone conversions (see Figure 3).

Dr. Perkins: Methadone is very, very tricky for a number of reasons. As you take methadone, the half-life changes and it accumulates in the body. As Dr. Fudin pointed out, depending on the equivalent number of milligrams of morphine you were on, you would use a different formula to calculate the dose of methadone to switch to. So, switching to methadone is very complicated. And, again, methadone is one of those agents that's used for hospice patients, because it's very inexpensive, it has a long half-life so you don't have to give it that often, and it comes in a variety of forms. How do you know what dose to switch to when the literature gives you three different values depending on the dose of morphine? What do you do if the dose of morphine is between 90 mg and 100 mg? Well, the equation that Dr. Fudin and his son developed takes all of that into account, without leaving a gap in between the recommendation, which is really unique.

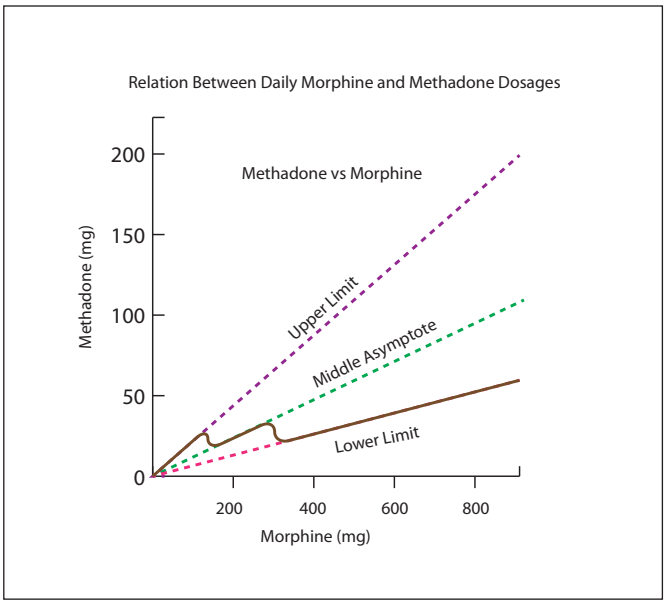

Figure 1. Graph representing conversion calculations based on Ripamonti et al formula. The graph shows clear dips when the dose of morphine hits 91 mg and 301 mg.

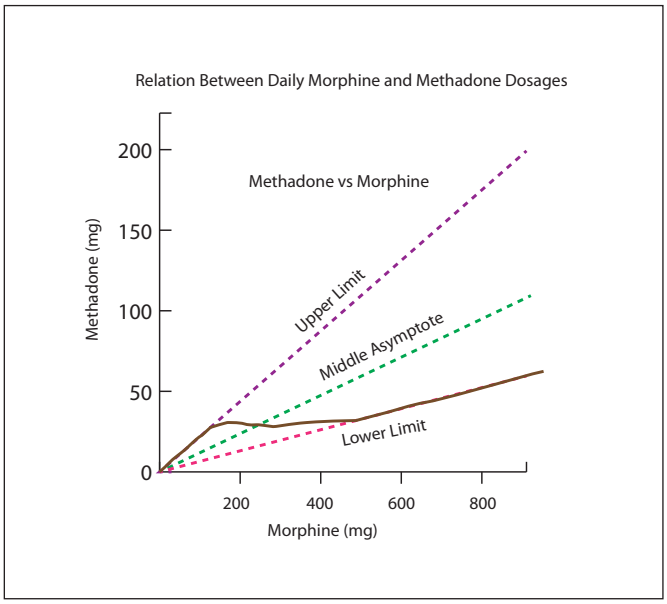

Figure 2. Graph representing conversion calculations based on the Methadone Fudin Factor.

Methadone mg =
$X/21\ \{5.7 - 3*\sin[90/((110/x)^5 + 1)] - \sin[90/((320/x)^7 + 1)]\}$

Figure 3. The Methadone Fudin Factor. The sine function above assumes the variable is in degress, no radians.

Developed by Jeffrey Fudin, BS, PharmD, FCCP, and Jason Andrew Fudin, BA, MS.

PPM **I noticed that the calculator will provide a warning statement if a requested dosage is too high.**

Dr. Perkins: Correct. There are some opioids with maximum doses, like codeine, because they are not pure agonists like morphine. With codeine, for example, there is no increased efficacy above a certain point, and patients experience more side effects, so we have cut the calculator off at that maximum dose. Another example is hydrocodone, which is almost always combined with acetaminophen (Tylenol). So, what we did is cut it off so that you can't exceed the FDA-recommended daily allowance of Tylenol. The calculator will alert you that this is the maximum dose and to supplement with another opioid.

PPM **What other unique features were included in the calculator?**

Dr. Perkins: I think the fact that every result includes not only the conversion result, but also a vast amount of other data, such as starting dose, maximum daily dose, dosage intervals, peak, onset, pharmacokinetic data, pharmacodynamic data, etc. This is very different from any other calculator, and it is extremely easy to use.

Dr. Fudin: I agree. It's extremely easy to use and straightforward, unlike some of the other calculators that just provide a morphine equivalent, but don't convert it to something else. For example, if you convert an opioid to transdermal fentanyl, the *PPM* calculator will tell you in red text, "This is the 24-hour dose. You need to divide by 24 hours to get micrograms per hour."

Another unique feature is that you can add up to three opioids into the calculator, and it really doesn't matter whether they're long acting or short acting because everything is done in 24-hour increments. For example, take a patient who is currently on the equivalent of 60 mg of morphine every eight hours, extended release (180 mg/day). The calculator allows you to put in the morphine dose, the fentanyl dose, and the oxycodone dose. Let's say you want to change to something completely different. You want to change to methadone or you want to change to fentanyl, because you don't want the patient on three separate drugs. You select the drug you want

Highlights of the New Calculator[a] Include:
1. Easy-to-use design and functionality
2. Calculator includes all types of opioids. Calculations include IV, IM, SQ, TD, and oral doses
3. Capable of multiple opioid conversions at one time. If a patient is on up to 3 opioids, the calculator can calculate the conversion of the 3 opioids into a single opioid, and vice versa
4. Tips and warnings. Every calculation result is accompanied by tips and warnings about converting from the original opioid to the new opioid. This has been custom written by the 3 authors
5. Vast amount of data. Every result includes not only the conversion result, but also a vast amount of other data, including starting dose, maximum daily dose, dosage intervals, peak, onset, pharmacokinetic data, pharmacodynamic data, etc
6. Safety. If a calculation result exceeds the maximum daily dose allowed (eg, for hydrocodone), a warning is presented directing the user to try a conversion to other opioids
7. Starting dose information is provided for all opioids
8. Tolerance. All calculations can be adjusted for incomplete tolerance
9. Weight differences. Starting doses are calculated for patients above or below 50 kg

[a]*PPM* Opioid Conversion Calculator now available at PracticalPainManagement.com.

to convert them to, and the calculator will give you the dosage calculation, or what it will allow you to reduce the dose for cross-tolerance. Since many people believe it is appropriate to decrease the dose by 25% to 50% when switching agents, they are afforded this option. If you want to reduce the dosage, you can select a percentage, and the calculator will give you the equivalent dose at, say, a 25% reduction. Or, if you just want see the real number, you can choose "No Dose Reduction," and it will give you the medical equivalent of all those drugs into the single drug you want to convert it to. Then you can go back and give any percentage you want. All these features are unique to the *PPM* opioid calculator.

PPM **The calculator launched a few weeks ago. How's the response been so far?**

Dr. Fudin: Fantastic. I've received calls and e-mails from colleagues across the country who are finding it to be extremely helpful. They comment about the ease with which they can now make calculations; they appreciate the warnings, tips, and the abundance of other data that is presented; and they like the calculator's flexibility, such as it can reduce doses for tolerance, and modify starting doses based on the patient's weight. They are also happy about our last-minute decision to include transdermal buprenorphine; that presented quite a challenge because of its "partial agonist" activity and kappa antagonist properties. The science is such that we needed to set different parameters for convert "to" versus converting "from" buprenorphine and we needed to add a number of warnings, some of which pop up in red.■

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Dr. Brennan is interested in the management of pain as well as in the disability of patients suffering from the acute and long-term effects of musculoskeletal diseases, neurological disorders, cancer, and various cancer treatments. He has published widely on the treatment of cancer-related disabilities, including lymphedema and cancer pain, as well as various aspects of chronic noncancer pain (including assessment and management), breakthrough pain, and the impact of pain on sleep. Dr. Brennan is on the Editorial Board of Practical Pain Management.

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Dr. Brennan has disclosed that he is a consultant for Endo Pharmaceuticals; Cephalon, Inc.; Eli Lilly and Company; Pfizer Inc.; ProStrakan; Purdue Pharma L.P.; and Covidien. He is on the speakers' bureau of Endo Pharmaceuticals; Cephalon, Inc.; Eli Lilly and Company; Pfizer Inc.; ProStrakan; Purdue Pharma L.P.; Covidien; and Ortho/Johnson & Johnson Pharmaceutical Research & Development, L.L.C.

Dr. Fudin has disclosed that he is on the speakers' bureau of Cadence Pharmaceuticals, Cumberland Pharmaceuticals, Janssen Pharmaceuticals, and Purdue Pharma L.P. Dr. Fudin wishes to disclose that his commentary represents his opinion alone, and does not reflect the opinion of, nor was it reviewed by, any government agency or companies for which he participates as a speaker. Also, it was not prepared as a part of Dr. Fudin's official government duty as a clinical pharmacy specialist.

Dr. Perkins has no financial information to disclose.

Methadone should only be prescribed by a physician who is thoroughly trained in its use.

Reference

1. Ripamonti C, Groff L, Brunelli C, Polastri D, Stavrakis A, De Conno F. Switching from morphine to oral methadone in treating cancer pain: what is the equianalgesic dose ratio? *J Clin Oncol.* 1998;16(10):3216-3221.