2011 Update to *Demystifying Opioid Conversion Calculations: A Guide for Effective Dosing*

Since the publication of this reference in August 2009, time has unsurprisingly marched on! During that time we have seen a new opioid come to market (tapent-adol) as well as several new opioid formulations (refer to Table 1) that may influence our opioid conversion calculations! The purpose of this update is to provide a quick review of these developments for the reader.

New Opioid (Tapentadol)

Tapentadol (Nucynta) is a novel analgesic that is classified as having "opioidergic" and "monoaminergic" mechanisms of action. It acts as a mu-opioid receptor agonist and a norepinephrine reuptake inhibitor. It also weakly inhibits serotonin reuptake but to a clinically insufficient degree to contribute to pain relief.¹ Tapentadol is indicated for the relief of moderate to severe acute pain in patients 18 years of age or older.² At present, there are three immediate-release (IR) tablet formulations on the market in the United States: 50, 75, and 100 mg. While dosing should be individualized to meet specific patient needs, the appropriate dose is 50, 75, or 100 mg every 4 to 6 hours. On the first day of dosing, if the first dose does not adequately relieve the pain, a second dose may be administered as soon as one hour after the first dose. Total daily doses in excess of 700 mg the first day, or 600 mg on subsequent days have not been studied.

Unfortunately, there is no published data that can clearly guide us in converting between tapentadol and other opioids. Tapentadol is less potent than morphine; the prescribing information states it is 18 times less potent than morphine in binding to the human mu-opioid receptor and is 2–3 times less potent in producing analgesia in animal models.² Tapentadol has been shown to be superior to placebo, and has been compared to oxycodone in the management of both orthopedic surgical pain and musculoskeletal pain.¹ When dosed every 4 to 6 hours for orthopedic (bunionectomy) surgical pain, tapentadol 50 and 75 mg dose groups were found to be noninferior to the oxycodone 10 mg dose group. The tapentadol 100 mg dose group, but not the tapentadol 75 mg dose group, was found to be noninferior to the oxycodone 15 mg dose group. In a post-hoc exploratory analysis, the tapentadol 100 mg dose was found to be more effective than oxycodone 10 mg. In the management of moderate to severe pain associated with osteoarthritis of the knee, tapentadol 50 or 75 mg was found to be noninferior to oxycodone 10 mg in a ten-day treatment trial. In a 90-day treatment trial, tapentadol 50 or 100 mg and oxycodone 10 or 15 mg demonstrated similar analgesic effectiveness.¹

It is important to recognize that demonstrating "noninferiority" does not constitute proof of equianalgesic dosing. A noninferiority clinical trial is somewhat onesided by design: the purpose is to show that the new intervention (e.g., in this case, tapentadol) is "no worse" than a reference intervention (e.g., in this case, oxycodone) within a pre-specified noninferiority interval (in other words, the clinical response is

Table 1. Opioid Formulations

Opioid	Oral Tablet or Capsule	Extended Release Tablet or Capsule	Oral Solution, Suspension or Elixir	Sublingual Tablet	Rectal Suppository	Injectable	Transdermal	Transmucosal	Intranasal
Buprenorphine				X		×	Х		
Codeine	×		×			×			
Codeine plus non-opioid	×		×						
Fentanyl				×		×	×	×	×
Hydrocodone plus non-opioid	×		×						
Hydromorphone	×	×	×		×	×			
Methadone	×		×			×			
Morphine	X	Х	×		Х	×			
Oxycodone	×	Х	×			X*			
Oxycodone plus Non-opioid	×		×						
Oxymorphone	X	Х				×			
Tramadol	Х	×				*X			
Tapentadol	×								
*Not available in the LL S									

Not available in the U.S.

"close enough for government work" as the expression goes).³ However, a noninferiority trial design is very useful when an untreated control group (such as untreated pain) is not pleasant or even ethical.

Based on these noninferiority trials, however, some healthcare systems have suggested the following therapeutic interchange when tapentadol is prescribed (and is nonformulary):

- tapentadol 50 mg po every 4–6 hours \rightarrow oxycodone 5 mg po every 4–6 hours
- tapentadol 75 mg po every 4–6 hours \rightarrow oxycodone 10 mg po every 4–6 hours

• tapentadol 100 mg po every 4–6 hours \rightarrow oxycodone 15 mg po every 4–6 hours Again, this guideline does not suggest equianalgesia either as shown or in reverse. Further research is necessary to determine more conclusive equianalgesia guidance with tapentadol.

An extended-release (ER) formulation of oral tapentadol is not available at this time in the United States, although a 100 mg 12-hour tablet is available in Europe (Palexia SR 100 mg).⁴ A New Drug Application (NDA) has been filed with the Food and Drug Administration (FDA) for extended-release oral tapentadol, and several clinical trials have been completed demonstrating efficacy in osteoarthritis, chronic low back pain, and diabetic neuropathy.⁵ One clinical trial evaluated the conversion between tapentadol IR and ER for low back pain.⁶ Patients were titrated to an effective level of pain control over a 3-week period using tapentadol IR. On day 22, half the group received their effective total daily dose of tapentadol as the IR formulation plus and ER placebo, and the other half received this dose of tapentadol as the ER formulation plus an IR placebo. The same exact dose was given whether the active treatment was given as tapentadol IR or ER (basically a 1:1 conversion). This continued for two weeks, and then the groups switched to the alternate strategy for an additional two weeks. Tapentadol ER was available as a 100, 150, 200, or 250 mg tablet, and dosed twice daily. Their conclusion was that approximately equivalent total daily doses of tapentadol IR and ER provided equivalent analgesia for the relief of moderate to severe chronic low back pain. It seems likely that the tapentadol ER product will become FDA approved at some point, so with this little update under your belt, you'll be ready to rock and roll!

New Opioid Delivery Systems

Transdermal Buprenorphine (Butrans)

Buprenorphine is a mu-opioid partial agonist used by the parenteral route of administration for moderate to severe acute pain and the oral route of administration to treat opioid addiction. It is now available in the United States as a new delivery system: transdermal buprenorphine (Butrans). Butrans is indicated for the management of moderate to severe chronic pain in patients requiring a continuous, around-the-clock opioid for an extended period of time.⁷ Transdermal buprenorphine has been shown to be effective in treating a wide variety of moderately to severely painful conditions including chronic cancer and non-cancer pain, ischemic pain, osteoarthritis pain, and neuropathic pain.⁸ Butrans is meant to be worn for 7 days, after which time a new transdermal patch should be applied to a different location (wait a minimum of 3 weeks before reapplying to the same site). Recommended application sites include the upper outer arm, upper chest, upper back or the side of the chest (eight possible application sites). This opioid delivery system is available in three strengths: 5 mcg/hour, 10 mcg/hour and 20 mcg/hour.

Butrans therapy may be initiated in opioid-naive patients with the 5 mcg/hour system. Because it takes three days to achieve steady-state serum levels of buprenorphine with the transdermal system, the dosage should not be increased for at least 72 hours, although many practitioners will wait a full week. The decision to move to the next higher Butrans strength should be based on the patient's need for supplemental short-acting opioid use and their level of pain control. The maximum dose of Butrans is 20 mcg/hour; higher doses (e.g., 40 mcg/hour) have resulted in prolongation of the QTc interval.

So what guidance do we have for switching an opioid-tolerant patient from their current opioid to Butrans? The manufacturer's guideline is as follows⁷:

- Oral morphine equivalent $< 30 \text{ mg a day} \rightarrow \text{Butrans 5 mcg/hour}$
- Oral morphine equivalent 30–80 mg a day → Butrans 10 mcg/hour

The prescribing information advises that there is a potential for buprenorphine to precipitate withdrawal in patients who are already on opioids. The manufacturer recommends tapering the patient's current around-the-clock opioid, for up to 7 days, to no more than the equivalent of 30 mg of oral morphine before switching to Butrans. It is unclear if the rationale is concern that buprenorphine theoretically has a greater affinity for mu-opioid receptors than other opioids such as morphine, or acknowledgement that the recommended conversion ratio is low. The prescribing information further recommends using caution when prescribing Butrans to opioid-tolerant patients receiving > 80 mg/day of morphine or its equivalent. The concern is that Butrans 20 mcg/hour may not provide adequate analgesia for patients receiving > 80 mg/day of oral morphine or an equivalent.

An equipotency ratio of oral morphine to transdermal buprenorphine of 1:75 has been proposed, however, in recent years some data have suggested the ratio may range from 1:70 to 1:100.^{8:10} As a reminder, an equipotency ratio is defined as the ratio of the doses of two opioids required to achieve the same degree of analgesia. As discussed above, the oral morphine transdermal buprenorphine equipotent ratio that has been proposed is 1:75, explained by the following mathematical equation:

mg buprenorphine/day x 75 = mg oral morphine/day

For example, consider the Butrans 10 mcg/hour patch:

 $\frac{\text{(buprenorphine 10 mcg)}}{\text{hr}} \times \frac{\text{(24 hr)}}{\text{day}} \times \frac{\text{(1 mg)}}{1000 \text{ mcg}} = 0.24 \text{ buprenorphine/day}$

0.24 mg buprenorphine/day x 75 = 18 mg oral morphine/day

Sittl and colleagues calculated an equipotency ratio of oral morphine to transdermal buprenorphine by comparing "identical-cohort" groups of patients with cancer and non-cancer pain, using a drug utilization database.¹⁰ Using this methodology, they de-

termined an oral morphine to transdermal buprenorphine ratio of 1:110 or 1:115. However, remember that their methodology was to use retrospective data from "identicalcohort" groups, not a methodology where patients served as their own control.

Mercadente and colleagues evaluated the equianalgesic ratio between oral morphine and transdermal buprenorphine in cancer patients receiving oral morphine ranging from 120 to 240 mg a day.⁹ Patients served as their own control, and were switched from oral morphine (patients had stable doses for at least 6 days) to transdermal buprenorphine using a 1:70 ratio. Pain levels were assessed on days 3 and 6 post-switch. This was a small study (four patients), but all patients maintained good control of their pain and other symptoms, and the only clinical difference in switching to transdermal buprenorphine was an improvement in constipation. Their conclusion was that the proposed conversion ratio from oral morphine to transdermal buprenorphine of 1:70 was appropriate.⁹

If we believe that the oral morphine : transdermal buprenorphine ratio is 1:70 as shown by Mercadente and colleagues, or if we accept Sittl and colleagues' conclusion that the ratio is 1:100 (or more), clearly the conversions recommended by the manufacturer of Butrans are low. Look at the following table:

Buprenorph (using 1:70 r	ine TD Dose atio)	Equipotent Oral Morphine Dose (mg)	Buprenorphine TD Dose (using 1:100 ratio)		Butrans Recommended Conversion
mcg/hour	mg/day		mcg/hour	mg/day	(mcg/hour)
17.9	0.43	30 mg	12.5	0.3	5
47.6	1.14	80 mg	33.3	0.8	10

For example, if a patient was receiving 30 mg/day of oral morphine, using the 1:70 ratio, it calculates to a hypothetical equivalent potency of 17.9 mcg/hour transdermal buprenorphine. Using the 1:100 ratio, it would be 12.5 mcg/hour transdermal buprenorphine. However, the manufacturer of Butrans, in this example, would recommend starting with the 5 mcg/hour transdermal system. Similarly, for total daily oral morphine doses up to 80 mg a day, the manufacturer of Butrans recommends starting with a 10 mcg/hour patch. However, the data that support a 1:70 ratio would suggest a 47.6 mcg/hour patch and the 1:100 ratio would suggest a 33.3 mcg/hour patch. The bottom line from all this is that we should follow the prescribing guidelines, but know that the recommended Butrans dosage conversion is very conservative, and an analgesic for breakthrough pain should also be prescribed simultaneously.

Mercadente also considered the conversion of patients receiving transdermal fentanyl (TDF) 50 to 100 mcg/hour to transdermal buprenorphine (TDB), using a transdermal fentanyl : transdermal buprenorphine ratio of 0.6 : 0.8.⁹ Six patients receiving TDF for 6 or more days with stable pain control were switched to TDB as follows:

- TDF 50 mcg/hour \rightarrow TDB 70 mcg/hour
- TDF 75 mcg/hour \rightarrow TDB 105 mcg/hour
- TDF 100 mcg/hour \rightarrow TDB 140 mcg/hour

Pain and other symptoms were evaluated at days 3 and 6, and no significant changes were noted (except improvement in reported constipation with TDB). These findings are again considerably more aggressive that those from the manufacturer of Butrans.

The only other issue to consider is that of QTc prolongation associated with use of Butrans in excess of 20 mcg/hour. The risk associated with QTc prolongation is the development of torsades de pointes, a potentially fatal ventricular arrhythmia. According to the prescribing information, a Butrans dose of 40 mcg/hour (given as two 20 mcg/ hour Butrans Transdermal Systems) prolonged the mean QTc by up to 9.2 ms across 13 assessment time points. For this reason, in the United States, Butrans is only approved for dosages up to 20 mcg/hour. However, higher concentration buprenorphine patches have been available in Europe for almost ten years (Transtec 35 mcg/hour, Transtec 52.5 mcg/hour and Transtec 70 mcg/hour).¹¹ According to the FDA document "Guidance for Industry: E14: Clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs" the threshold level for regulatory concern "is around 5 ms as evidenced by an upper bound of the 95% confidence interval around the mean effect on QTc of 10 ms."¹² Prescribers should be mindful of the other risk factors for the development of torsades or prolongation of the QTc when using Butrans in their patients.

Transdermal Fentanyl (TDF) Formulations and Contemporary Issues

As discussed on page 84 of this book, TDF patches were designed to provide longlasting opioid therapy to control stable, chronic pain of moderate to severe intensity. The majority of patients achieve pain relief for 72 hours after TDF patch application, while a small number of patients seem to require changing to a new patch(es) after 48 hours. Notwithstanding, practitioners continue to inappropriately use TDF in practice. The most common errors are use of TDF for acute pain management, or for intermittent or mild pain. Probably even more common (and inappropriate) is the use of TDF for patients who are not considered to be "opioid tolerant." This is defined as a patient who has been taking, for a week or longer, at least 60 mg of oral morphine, 30 mg of oral oxycodone, 8 mg of oral hydromorphone, or an equianalgesic dose of another opioid. It is imperative that prescribers follow these guidelines to avoid patient or prescriber harm (e.g., avoiding a lawsuit!).

As shown on page 85, the first TDF product on the market (Duragesic) was a gelcontaining reservoir. There are now many generic formulations of TDF on the market, many of which use a different formulation known as the drug-in adhesive matrix layer formulation. The following is a depiction of a drug-in-matrix formulation of fentanyl¹³:



IMPERMEABLE BACKING FENTANYL IN POLYISOBUTENE ADHESIVE MATRIX REI FASE LINER

As you can see, the patch has three layers: a release liner, an adhesive drug formulation, and a backing film. This is the most common design for transdermal drug delivery and is often used with drugs that are relatively easy to deliver transdermally, such as fentanyl.¹⁴ The reservoir and matrix transdermal fentanyl products are bioequivalent (i.e., interchangeable) and produce similar therapeutic outcomes.¹⁵

Rapid-Acting Fentanyl Products

In Chapter 4 of this book, you will learn about the management of breakthrough pain, which is defined as a transitory flare of pain that occurs against a background of other-

wise controlled pain.¹⁶ Breakthrough pain can further be characterized as spontaneous (no precipitating stimulus identified), volitional incident pain (an identified cause that is under the patient's control), nonvolitional incident pain (an identified cause that the patient cannot control), and end-of-dose failure from a long-acting opioid. For breakthrough pain that is fairly slow in evolution (e.g., 30 minutes from start to peak), or volitional incident pain, we can use traditional opioids as oral solution (e.g., oral morphine or oxycodone solution) or oral tablets. However, for idiopathic or quickly evolving breakthrough pain, or nonvolitional incident pain, we may need to consider a more rapid-acting opioid. In Chapter 4, we discuss two oral transmucosal fentanyl products that were available at the time of the original writing: oral transmucosal fentanyl citrate lozenge (OTFC, ACTIQ, generic) and fentanyl buccal tablet (Fentora). Since the original writing, three new rapid-acting fentanyl products have been approved by the FDA: Onsolis (fentanyl buccal soluble film), Abstral (fentanyl sublingual tablet), and Lazanda (fentanyl nasal spray). Just like the OTFC and buccal tablet, all three of the newer products are ONLY approved to treat breakthrough pain in patients with cancer who are 18 years and older and who are opioid tolerant. Opioid tolerance for all three products is defined as a patient taking at least one of the following for a week or longer:

- 60 mg of oral morphine per day
- 25 mcg/hr of TDF
- 30 mg of oral oxycodone per day
- 8 mg of oral hydromorphone per day
- 25 mg of oral oxymorphone per day
- or an equianalgesic dose of another opioid

These three products (like the previously approved other two) are not approved for acute or postoperative pain. Also, similar to the first two products, there is no approved dosing strategy for converting to these three new products from other opioids; practitioners must start with the lowest dose and follow the approved titration schedule. Let's take a closer look at the particulars for these three delivery systems.

Fentanyl Buccal Soluble Film (Onsolis)¹⁷

Initial dose and titration instructions	For opioid-tolerant patients ONLY (patients taking at least 60 mg of oral morphine/day, 25 mcg/hr of TDF, 30 mg of oral oxycodone daily, 8 mg of oral hydromorphone daily, 25 mg oral oxymorphone per day, or an equianalgesic dose of another opioid for a week or longer).
	Initial dose of Onsolis is 200 mcg in all patients (even when switching from a different transmucosal fentanyl product).
	Use the tongue to wet the inside of the cheek or rinse the mouth with water. Using a dry finger with the pink side facing up, place the pink side of the Onsolis film against the inside of the cheek, press and hold in place for 5 seconds.
	Single doses should be separated by at least two hours; Onsolis can only be used once per episode of breakthrough cancer pain. Onsolis cannot be re-dosed within an episode of breakthrough pain.

Fentanyl Buccal Soluble Film (Onsolis)¹⁷ (contd.)

Initial dose and titration instructions	If adequate pain relief is not achieved after one 200 mcg Onsolis film, titrate using multiples of the 200 mcg Onsolis film (for doses of 400, 600, or 800 mcg) in subsequent breakthrough pain episodes.
	When multiple 200 mcg films are used, do not place them on top of each other; they may be placed on both sides of the mouth.
	If adequate pain relief is not achieved after 800 mcg Onsolis (four of the 200 mcg Onsolis films simultaneously), treat the next episode of breakthrough pain with one 1200 mcg Onsolis film. Doses above 1200 mcg have not been evaluated.
	Once adequate pain relief is achieved with a dose between 200 and 800 mcg Onsolis, the patient should receive the appropriate dose using ONE Onsolis film (e.g., 200, 400, 600, 800, or 1200 mcg Onsolis film: one per episode).
Maintenance dosing	Once a successful dose of Onsolis has been identified, each episode of breakthrough pain should be treated with a single film.
	During any episode of breakthrough pain, if adequate pain relief is not achieved within 30 minutes, the patient may use a different rescue medication as directed (e.g., a different short-acting opioid).
	 Onsolis should be limited to four or fewer doses per day; if this is insufficient then consider increasing the around-the-clock opioid prescribed.

Fentanyl Sublingual Tablet (Abstral)¹⁸

Initial dose and titration instructions	For opioid-tolerant patients ONLY (patients taking at least 60 mg of oral morphine/day, 25 mcg/hr of TDF, 30 mg of oral oxycodone daily, 8 mg of oral hydromorphone daily, 25 mg oral oxymorphone per day, or an equianalgesic dose of another opioid for a week or longer).
	 Initial dose of Abstral is 100 mcg in all patients (even when switching from a different transmucosal fentanyl product).
	Place the Abstral tablet on the floor of the mouth directly under the tongue immediately after removal from the blister unit. Allow the tablet to completely dissolve in the sublingual cavity. Do not drink or eat anything until the tablet is dissolved.
	If breakthrough pain is not relieved within 30 minutes of the first dose, one additional 100 mcg ABSRAL tablet may be administered.
	No more than two doses of Abstral may be used to treat an episode of breakthrough pain.
	 Patients must wait at least 2 hours before treating another episode of breakthrough pain with Abstral.
	If the 100 mcg dose was insufficient to treat the episode of breakthrough pain, increase the dose by 100 mcg multiples up to 400 mcg as needed. If adequate analgesia is not achieved with a 400 mcg dose, the next titration step is 600 mcg, then 800 mcg. Doses above 800 mcg have not been evaluated.
	No more than two doses of Abstral may be used to treat an episode of breakthrough pain.

Fentanyl Sublingual Tablet (Abstral)¹⁸ (contd.)

Maintenance dosing	•	Once an appropriate dose for treating an episode of breakthrough pain has been established, instruct patients to use only one Abstral tablet of the appropriate strength.
	•	No more than two doses of Abstral may be used to treat an episode of breakthrough pain.
	•	If more than four episodes of breakthrough pain are experienced per day then consider increasing the around-the-clock opioid prescribed.
		Limit the use of Abstral to treat four or fewer episodes of breakthrough pain per day.

Fentanyl Nasal Spray (Lazanda)¹⁹

Initial dose and titration instructions A For opioid-tolerant patients ONLY (patients taking at least 60 mg of oral morphine/day, 25 mcg/hr of TDF, 30 mg of oral oxycodone daily, 8 mg of oral hydromorphone daily, 25 mg oral oxymorphone per day, or an equianalgesic dose of another opioid for a week or longer).

- Initial dose of Lazanda is a 100 mcg spray in all patients (even when switching from a different transmucosal fentanyl product). This refers to one spray in one nostril.
- Instruct the patient to prime the device before use by spraying into the included carbon-lined pouch (4 sprays in total). Patients should insert the nozzle of the Lazanda bottle a short distance (1/2-1 cm) into the nose and point towards the bridge of the nose, tilting the bottle slightly. They then press down firmly on the finger grips until patient hears a "click" and the number in the counting window advances by one.
- Single doses should be separated by at least two hours; Lazanda can only be used once per episode of breakthrough cancer pain. Lazanda cannot be re-dosed within an episode of breakthrough pain.
- If adequate analgesia is not achieved with the first 100 mcg dose, dose escalate in a step-wise manner over consecutive episodes of breakthrough pain until adequate analgesia is achieved as follows:
 - Lazanda 100 mcg (1 x 100 mcg spray)
 - Lazanda 200 mcg (2 x 100 mcg sprays; 1 in each nostril)
 - Lazanda 400 mg (1 x 400 mcg spray)
 - Lazanda 800 mcg (2 x 400 mcg sprays; 1 in each nostril)
 - Doses higher than 800 mcg have not been evaluated.

Maintenance Once an appropriate dose for treating an episode of breakthrough pain has been established, instruct patients to use that dose for subsequent breakthrough cancer pain episodes.

Fentanyl Nasal Spray (Lazanda)¹⁹ (contd.)

Maintenance dosing	•	During any episode of breakthrough pain, if adequate pain relief is not achieved within 30 minutes following Lazanda dosing or if a separate episode of breakthrough cancer pain occurs before the next dose of Lazanda is permitted (e.g., within 2 hours), the patient may use a different rescue medication as directed (e.g., a different short-acting opioid).
	•	Limit the use of Lazanda to treat four or fewer episodes of breakthrough pain per day.
	•	If more than four episodes of breakthrough pain are experienced per day, re- evaluate the dose of the long-acting opioid used for persistent underlying cancer pain.

Extended-Release (ER) Hydromorphone (Exalgo)

Exalgo is a once-daily, ER oral tablet available as 8, 12, or 16 mg. It is indicated for the management of moderate to severe pain in opioid tolerant patients who require continuous, around-the clock analgesia for an extended time period.²⁰ A similar definition of "opioid tolerance" is described in the prescribing information for Exalgo: a patient taking 60 mg oral morphine/day, 25 mcg/hr TDF, 30 mg oral oxycodone/day, 8 mg oral hydromorphone/day, 25 mg oral oxymorphone/day, or an equianalgesic dose of another opioid, for a week or longer. This opioid formulation has been shown to be efficacious in a variety of cancer and non-cancer pain states, including osteoarthritis and low back pain, and comparable to ER oxycodone in treating osteoarthritis pain.²¹ Exalgo is not approved for the management of acute or postoperative pain, intermittent pain, or for "as needed" use (i.e., breakthrough pain).

When converting from unmodified IR hydromorphone to Exalgo, determine the total daily dose of the IR hydromorphone and switch to an equivalent total daily dose of Exalgo (as described in Chapter 2). The absolute bioavailability of IR hydromorphone and Exalgo (compared to IV hydromorphone) is $19\% \pm 5\%$, and $24\% \pm 6\%$, respectively.²¹ With multiple doses of Exalgo, the Tmax is about 12 hours (ranges from 12 to 16 hours) and the half-life is approximately 11 hours (range from 8 to 15 hours).²⁰ Steadystate plasma concentrations are reached after 3 to 4 days of once-daily dosing with Exalgo. Therefore, when switching to Exalgo, the dose should not be adjusted before 3 days of continuous therapy. It would be reasonable to provide IR hydromorphone for breakthrough pain, dosed as 10% to 15% of the total daily long-acting hydromorphone (Exalgo).

Converting from other opioids to Exalgo is just as described in Chapter 3. Data evaluating the conversion of patients from oral morphine to Exalgo confirm the conversion ratio shown in the Equianalgesic Opioid Dosing table provided with this book (and shown below in Table 2). In a study by Wallace et al., 336 patients were enrolled in a conversion trial, using an oral morphine : hydromorphone (Exalgo) ratio of 5:1.²² Two hundred twenty two patients completed the trial, and the investigators did not reduce the calculated dose of hydromorphone to allow for cross tolerance. Dosage adjustments (titrating up to achieve maximal pain relief) were allowed, and 87% of patients required two or fewer dosage increases. The conclusion was the 5:1 ratio was safe and effective when converting from morphine to Exalgo. This is further consis-

tent with the footnote of the Equianalgesic Opioid Dosing table in this book that states the morphine : hydromorphone conversion is not bidirectional; when switching from morphine to hydromorphone the ratio is 5:1 (M:HM), whereas the conversion from hydromorphone to morphine is 3.7:1 (HM:M). Wallace et al. did not evaluate converting patients back from Exalgo to oral morphine.²²

Wallace et al. also evaluated patients being switched from TDF to Exalgo.²² They used a ratio of TDF 25 mcg/hr to Exalgo 8 mg orally daily. This is consistent with our discussion of converting to/from TDF in Chapter 5, where we see "every 2 mg oral morphine per day is approximately 1 mcg/hr TDF" (e.g., 50 mg per day oral morphine is approximately 25 mcg/hr TDF). We can use this approximation in the other direction as well, so TDF 25 mcg/hr is roughly equivalent to 50 mg oral morphine/day. Using the M:HM ratio of 5:1, this would be approximately 10 mg oral hydromorphone/day. It would be entirely reasonable to reduce the hydromorphone dose to 8 mg per day (and Exalgo is available as an 8 mg tablet). Patients in this group fared equally as well. The manufacturer's guidelines recommend starting Exalgo 18 hours after removal of the TDF.²⁰ This makes sense because 17 hours after removal of TDF, 50% of the fentanyl is eliminated from the body. If you begin Exalgo at that time, it takes about 12 hours to the maximum hydromorphone serum concentration, at which point 75% of the fentanyl has been eliminated from the body (see page 96). When switching from Exalgo to TDF, it would make sense to apply the TDF approximately 12 hours after the last dose of Exalgo. The terminal half-life of Exalgo is about 11 to 12 hours; at the 12 hour mark, about 50% of the hydromorphone has been eliminated, and 75% has been eliminated by 24 hours after the last dose. It takes about 12 to 16 hours to achieve therapeutic fentanyl serum concentrations, with near steady-state achieved at 24 hours. By applying the TDF 12 hours after the last Exalgo dose, over the next 12 hours the hydromorphone serum concentration will decline from 50% to 25% of the steady-state concentration and, during the same 12-hour period, fentanyl serum concentration will approach a therapeutic range. Of course it would be prudent to supply an IR opioid for breakthrough pain.

Abuse-Deterrent Opioid Formulations

In the United States, the abuse and misuse of opioids is as critical an issue as unresolved pain. One new tool to help limit the former while fighting the latter is the development of abuse-deterrent opioid formulations. Of course, it is impossible to guarantee that a tablet or capsule is "abuse proof," but even small steps in the right direction are welcomed. There are several examples of opioids that have been reformulated or newly formulated for this purpose. By and large, these pharmaceutical changes do not influence our opioid conversion calculations. A few examples are as follows:

- OxyContin (ER oxycodone tablet) has been reformulated with the intent to prevent the tablets being cut, broken, chewed, crushed or dissolved in an attempt to release the opioid all at one time (as opposed to the intended 8-12 hour release time).²³
- The long-acting capsule of Kadian (ER beads containing morphine in a capsule) have been reformulated as Embeda. With Embeda, the core of each bead contains naltrexone, an opioid antagonist. If the capsule or the beads are swallowed whole, the naltrexone has no pharmacologic effect. However, if the capsules or beads are crushed, cut or chewed, the naltrexone negates the effect of the morphine, both euphoric and analgesic. There are six strengths of this combination (20 mg/0.8 mg,

Table 2. Equianalgesic Opioid Dosing

Drug	Equianalgesic Doses (mg)		_ Formulation Comments	
	Parenteral	Oral		
Morphine ^a	10	30	Available as short-acting tablets and capsules, and oral solution (including oral concentrate Roxa- nol, 100 mg/5 mL).	
			Available as oral long-tablet tablets and capsules (MS Contin, Oramorph SR, Kadian, Embeda, Avinza, generic).	
			Available as rectal suppositories (equivalent dos- ing to oral).	
Buprenorphine ^ь	0.3	0.4 (sl)	Available as sublingual (sl) tablets and injection.	
			Transdermal 4- and 7-day patches available in Europe. Butrans 7-day patch available in the United States.	
Codeine	100	200	Codeine is a prodrug, metabolized to morphine by the liver.	
			Available as injectable, tablets and oral solution; most commonly administered in combination with acetaminophen (e.g., Tylenol #3).	
Fentanyl ^c	0.1	NA	Available as injection, transmucosal, intranasal and transdermal. Refer to chapters 4 and 5 for further discussion of transmucosal/intranasal and transdermal dosing of fentanyl, respectively.	
Hydrocodone ^d	NA	30	Only available as a combination product (e.g., hydrocodone plus acetaminophen or ibuprofen). Oral solution (Hycodan) contains hydrocodone and homatropine.	
			Most commonly given in combination with acet- aminophen (Lorcet, Lortab, Vicodin, others).	
Hydromorphone®	1.5	7.5	Available as oral tablets, long-acting tablet (Ex- algo), solution, injection and rectal suppository.	
Meperidine	100	300	Available as tablets, syrup, oral solution and injec- tion.	
			Not recommended for routine clinical use.	
Methadone ^f	See methado	ne chapter	Available as oral tablets and oral solution (includ- ing oral concentrate, 20 mg/1 mL).	
			Dispersible tablet (40 mg) not used for chronic pain management (only for opioid treatment programs).	

Table 2. (contd.) Equianalgesic Opioid Dosing

Drug	Equianalgesi	c Doses (mg)	Formulation Comments
	Parenteral	Oral	
Oxymorphone ^h	1	10	Available as a short-acting tablet, oral long-acting tablet, and parenteral formulation.
Tramadol ⁱ	100	120	Available as a short-acting tablet, extended- release oral tablet, and injectable.
			Parenteral formulation is not available in the United States.

Note: Equianalgesic data presented in this table is that which is most commonly used by health care practitioners, but it is *approximate*. The clinician is urged to read the following caveats, along with the text, and use good clinical judgment at all times.

Data adapted from:

Carr DB, Jacox AK, Chapman CR, et al. Acute Pain Management: Operative or Medical Procedures and Trauma. Clinical Practice Guideline No. 1. AHCPR Pub. No. 92-0032. Rockville, MD: Agency for Health Care Policy and Research, Public Health Service, U.S. Department of Health and Human Services. Feb. 1992.

Jacox A, Carr DB, Payne R, et al. Management of Cancer Pain. Clinical Practice Guideline No. 9. AHCPR Publication No. 94-0592. Rockville, MD. Agency for Health Care Policy and Research, U.S. Department of Health and Human Services, Public Health Service, March 1994.

^aWith chronic morphine dosing, the average relative potency of intravenous (IV) or subcutaneous (SC) morphine to oral morphine is between 1:2 and 1:3 (e.g., 20-30 mg of morphine orally or sublingually is equianalgesic to 10 mg IV or SC). (Kalso E, Vainio A. Morphine and oxycodone hydrochloride in the management of cancer pain. Clin Pharmacol Ther. 1990;47:639-646.)

Oral:rectal bioavailability is considered to be approximately equivalent. (Westerling D, et al. Absorption and bioavailability of rectally administered morphine in women. Eur J Clin Pharm. 1982;23(1):59-64. Brook-Williams P. Morphine suppositories for intractable pain. CMA J. 1982;126:14.)

^bSublingual buprenorphine 0.4 mg has been shown to be equivalent to 0.3 mg buprenorphine given parenterally. (Bullingham RES, et al. Sublingual buprenorphine used postoperatively: clinical observations and preliminary pharmacokinetic analysis. Br J Clin Pharma. 1981;12:117-122.)

Buprenorphine 0.3 mg given intramuscularly (IM) has been shown to be equivalent to morphine 10 mg IM. (*Kjaer M, et al. A comparative study of intramuscular buprenorphine and morphine in the treatment of chronic pain of malignant origin. Br J Clin Pharmacol.* 1982;13:487-492.) Similar findings have been seen with IV doses of both opioids. (*Zacny J, et al. Comparing the subjective, psychomotor and physiological effects of intravenous buprenorphine and morphine in healthy volunteers. J Pharm and Exper Ther.* 1997;282:1187-1197.)

Buprenorphine is available as a 4- and 7-day transdermal patch in Europe. Butrans (a 7-day patch) is available in the United States. Both brands (Butrans and Transtec) recommend starting with the lowest strength patch (e.g., 5 mcg/hr in the United States) when switching to transdermal buprenorphine. In the reference *Palliative Drugs*, a conversion of 100:1 (morphine:buprenorphine) is suggested. Example: multiply 24-hour oral morphine dose in mg by 10 to obtain 24-hour buprenorphine dose in micrograms; divide answer by 24 to obtain mcg/hr patch strength; round down to closest patch strength. *(Palliative Drugs; www.palliativedrugs.com/opioid-dose-conversion-ratios.html, Accessed January 9, 2009)*. The U.S. manufacturer of Butrans has a more conservative recommendation when switching to transdermal buprenorphine (see text).

^cAlthough parenteral MS:fentanyl is shown as 10:0.1 mg (which is a 100:1 ratio) based on a mg-to-mg ratio, in clinical practice the ratio is described as 15-112.5:1; many clinicians use an equivalency of 4 mg/hr IV morphine equivalent to 100 mcg/ hr parenteral or transdermal fentanyl. (*Indelicato RA, Portenoy RK. Opioid rotation in the management of refractory cancer pain. JCO 2003;21:87s-91s. Patanwala AE, Duby J, Waters D et al. Opioid conversions in acute care. Ann Pharmacother. 2007;41:255-67. Lawlor P, Pereira J, Bruera E. Dose ratios among different opioids: underlying issues and an update on the use of equianalgesic table. In: Bruera E, Portenoy RK, eds. Topics in Palliative Care, Volume 5. Oxford University Press, 2001. New York.*)

Transdermal fentanyl (TDF) patch (used for chronic pain) dosed in mcg, is roughly equivalent to 50% of the total daily dose of oral morphine in mg (e.g., TDF 25 mcg/hr patch is roughly equal to 50 oral morphine/day). Refer to Chapter 5 for additional information on dosing transdermal fentanyl. (*Breitbart W, Chandler S, Eagel B, et al. An alternative algorithm for dosing transdermal fentanyl for cancer-related pain. Oncology. 2000;14:*695-705.)

^dEquivalence to oral morphine not clearly defined; generally thought to be equal to or less potent than oxycodone. (Hallenbeck JL. Palliative Care Perspectives. New York: Oxford University Press; 2003:71).

^eOral bioavailability may be as high as 60%, particularly with chronic dosing; ranges from 29% to 95%. (Vallner JJ, et al. Pharmacokinetics and bioavailability of hydromorphone following intravenous and oral administration to human subjects. J Clin Pharmcol. 1981;21:152-156. Ritschel WA, et al. Absolute bioavailability of hydromorphone after peroral and rectal admini-

Table 2. (contd.) Equianalgesic Opioid Dosing

istration in humans: saliva/plasma ratio and clinical effects. J Clin Pharmacol 1987;27:647-653. Parab PV, et al. Pharmacokinetics of hydromorphone after intravenous, peroral and rectal administration to human subjects. Biopharm Drug Dispos. 1988;9:187-199).

Research has shown a lower dose ratio and a directional influence seen when converting between morphine and hydromorphone. It is suggested that when switching from morphine (M) to hydromorphone (HM) (using the same route of administration; e.g., SC to SC or oral to oral), a conversion ratio of 5:1 (M:HM) for morphine to hydromorphone and a dose ratio of 3.7:1 (M:HM) when switching from morphine to hydromorphone (again, using the same route of administration). (*Lawlor P, et al. Dose ratio between morphine and hydromorphone in patients with cancer pain: a retrospective study. Pain 1997;72:79-85. Anderson R, et al. Accuracy in equianalgesic dosing: conversion dilemmas. J Pain Symptom Manage 2001;21:397-406).*

Oral:rectal bioavailability approximately equal; the FDA-approved dosing interval for rectal hydromorphone is every 6 hours.

¹Methadone dosing is highly variable, and conversion to/from other opioids is NOT linear. Refer to Chapter 6 for additional information on methadone dosing.

^oBecause of the variations in bioavailability between morphine (15% to 64%) and oxycodone (60% or more), the equianalgesic ratio for oral morphine:oxycodone ranges from 1:1 to 2:1, partially dependent on the patient's ability to absorb the opioid. A ratio of 1:1.5 is used clinically as a compromise. (Anderson R, et al. Accuracy in equianalgesic dosing: conversion dilemmas. J Pain Symptom Manage. 2001;21:397-406).

Parenteral oxycodone is not available in the United States. According to manufacturer's information (Mundipharma New Zealand Limited, Distributed by Pharmaco (N.Z.) Ltd,) 2 mg of oral oxycodone is approximately equivalent to 1 mg parenteral oxycodone. (*Medsafe: Information for Health Professionals, Oxynorm Injection. Available at: http://www.medsafe.govt.nz/* profs/Datasheet/o/OxyNorminj.htm). Accessed January 8, 2009. This ratio may be somewhat conservative because the oral bioavailability of oxycodone has been shown to be 60% or greater. (*Poyhia R, et al. The pharmacokinetics and metabolism of oxycodone after intramuscular and oral administration to healthy subjects. Br J Clin Pharmacol.* 1992;33:617-621.).

^hConversion from oral morphine or oral oxycodone to oxymorphone is shown as 30:10 and 20:10, respectively per package labeling. Some data suggests the conversion ratio when switching to oxymorphone is closer to 18:10 for morphine, and 12:10 for oxycodone, especially once at steady state. (*Sloan P, et al. Effectiveness and safety or oral extended-release oxymorphone for the treatment of cancer pain: a pilot study. Support Care Cancer. 2005;13:57-65.).*

Parenteral tramadol has been shown to be approximately equipotent to parenteral morphine in a 10:1 (tramadol:morphine) ratio. (Wilder-Smith C, et al. Effects of morphine and tramadol on somatic and visceral sensory function and gastrointestinal motility after abdominal surgery. Anesthesiology 1999;91:639-647). With chronic dosing, oral tramadol achieves between 90% and 100% bioavailability. (Grond S, et al. Clinical pharmacology of tramadol. Clin Pharmacokinet 2004;31:879-923.) Despite bioavailability data, equipotent use of oral morphine and oral tramadol ranges from 1:4 to 1:10 (morphine:tramadol). Therefore, using an equivalence of 120 mg oral tramadol may be very conservative. (Grond S, et al. High-dose tramadol in comparison to low-dose morphine for cancer pain relief. J Pain Symptom Manage 1999;18:174-179).

 $30 \text{ mg}/1.2 \text{ mg}, 50 \text{ mg}/2 \text{ mg}, 60 \text{ mg}/2.4 \text{ mg}, 80 \text{ mg}/3.2 \text{ mg}, and 100 \text{ mg}/4 \text{ mg}, morphine sulfate/naltrexone hydrochloride}; however, as of this writing, EMBEDA is not available in the United States. It is anticipated that this is a temporary situation and it will be back on the market.²⁴$

- The FDA recently approved an IR oxycodone tablet (Oxecta), which is indicated for the management of acute and chronic pain of moderate to severe intensity. Oxecta uses technology designed to discourage common methods of medication tampering. An added ingredient causes the oxycodone to gel, thus preventing injection, or to irritate the nasal passages to discourage inhalation.²⁵
- Several other abuse-deterrent opioid formulations are in various stages of development and approval.

Lagniappe (A Small Gift or Unexpected Benefit)²⁶

I frequently get calls from hospice and palliative care providers about patients with very difficult-to-control pain problems. In these cases, we occasionally use ketamine parenterally (either intravenous [IV] or subcutaneous [SC]), or the parenteral formulation of ketamine mixed in orange juice and given orally) to reduce hyperalgesia

or opioid-induced neurotoxicity, usually with very good effect. Benitez-Rosario and colleagues evaluated a 1:1 conversion from to oral ketamine in cancer patients.²⁶ In a cohort of 29 cancer pain patients, after establishing good pain control with a continuous SC infusion of ketamine, the investigators calculated the total dose of ketamine administered subcutaneously. This total daily dose was divided into thirds and administered orally every 8 hours, using the parenteral formula mixed with fruit juice. The first oral ketamine dose was given 4 to 8 hours after the SC infusion was discontinued. After switching to oral ketamine, 27 of the 29 patients maintained good pain control; 2 patients required a dose increase (to a ratio of 1:1.3 and 1:1.5) to maintain analgesia. There were no additional adverse effects and, in fact fewer adverse effects where experienced when the patients were switched to oral ketamine.

While it is exciting that we are beginning to see data accumulate on the effective use of ketamine for difficult pain cases, it is still early days. Ketamine should not be used by the uninitiated or the faint of heart due to the need for close attention to detail in dosing, and monitoring. It is important to also point out that ketamine would likely only be initiated in an inpatient facility. But this piece of research is a welcomed addition, as we continue to explore the analgesic properties of ketamine.

Conclusion

Given the magnitude of the pain problem in the United States and worldwide, and the competing problem of opioid misuse and abuse, it is not unexpected that new analgesics and dosage formulations will continue to be introduced to the market. Well-designed clinical trials that help practitioners calculate safe and effective opioid doses when converting between drugs, routes of administration, and formulations is always welcomed.

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