Topics in
PAIN MANAGEMENT

Vol. 27, No. 10 | Current Concepts and Treatment Strategies | May 2012

CME ARTICLE

Opioid Rotation: Methods and Cautions

Clifford Gevirtz, MD, MPH

Learning Objectives: After participating in this activity, the physician should be better able to:

1. Apply the process for performing opioid rotation.
2. Assess the dangers in rotating to methadone.
3. Evaluate the dangers of rotating to and from various oral forms of fentanyl.

In a landmark article, Knotkova et al[1] first explored the limitations of our knowledge of opioid rotation (OR). They defined OR as the process of switching from one opioid to another in an effort to improve the response to analgesic therapy or to reduce adverse effects. Rotation is used to address the problem of a patient's poor responsiveness to a particular opioid despite optimal dose titration.

Guidelines for OR are empirical rather than based purely on pharmacology. It starts with the selection of a safe and reasonably effective initial dose of the new opioid, followed by careful dose titration to optimize the balance between analgesia and adverse effects with an awareness of the dangers of rotating to the opioid.

The selection of a starting dose must be based on an estimate of the relative potency of the existing opioid compared with the new one. *Potency*, which is defined as the dose required to produce a given effect, differs widely among opioids and also among individuals under varying clinical conditions. To rotate effectively from one opioid to another, the new opioid must be started at a dose that will cause neither toxicity nor the abstinence syndrome, and that will be sufficiently efficacious in that the pain is no worse than before the change. The estimate of relative potency used in calculating this starting dose has been codified with "equianalgesic dose tables," which historically have been based on the best science available and have been used with little modification for more than 40 years. These tables, and the clinical protocols used to apply them to OR, may need revision, however, as the detailed pharmacology underlying relative potency evolves.

Indications

OR is considered a therapeutic option in the following situations:

- Opioid dose escalation has yielded intolerable and unmanageable adverse effects, such as somnolence or mental clouding;

In This Issue

Dr. Gevirtz is Associate Professor of Anesthesiology, Louisiana State University Health Center, New Orleans, and Medical Director, Somnia Pain Management, 627 W St, Harrison, NY 10528; E-mail: cliffgevirtzmd@yahoo.com.

All faculty and staff in a position to control the content of this CME activity and their spouses/life partners (if any) have disclosed that they have no financial relationships with, or financial interests in, any commercial companies pertaining to this educational activity.

Dr. Gevirtz has disclosed that the U.S. Food and Drug Administration has not approved the use of buccal and oral fentanyl as discussed in this article. Please consult the product labeling for approved information.

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- The patient has severe pain (often accompanied with intolerable adverse effects) that continues despite repeated dose escalations;
- The patient may benefit from a switch to a different route of administration (eg, transdermal or buccal rather than oral) or formulation (eg, a formulation with an extended release pattern);
- There is a change in clinical status, suggesting need for an opioid with different pharmacokinetic properties (eg, a drug without active metabolites in the setting of progressive renal insufficiency);
- There are cost considerations, as in a change in formulary coverage with a lower copayment, mandating a change in therapy.

The strategy of rotation derives from the expectation that a switch to a new drug is likely to yield equivalent or better analgesia and fewer adverse effects. From an evidence-based approach, this hypothesis is supported by a small number of short-term observational studies,[2,3] and with substantial anecdotal clinical experience that has accumulated over many decades and millions of patients.

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Although no one knows the specific mechanisms by which OR improves the overall response to therapy, the theoretical basis is the large individual variation that characterizes the responses to different mu-agonist opioids, the variation among the binding coefficients

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Topics in Pain Management (ISSN 0882-5646) is published monthly by Lippincott Williams & Wilkins, 16522 Hunters Green Parkway, Hagerstown, MD 21740-2116. **Customer Service: Phone (800) 638-3030, Fax (301) 223-2400, or Email customerservice@lww.com**. Visit our website at **lww.com.**

 Priority postage paid at Hagerstown, MD, and at additional mailing offices. GST registration number: 895524239. POSTMASTER: Send address changes to ***Topics in Pain Management***, Subscription Dept., Lippincott Williams & Wilkins, P.O. Box 1600, 16522 Hunters Green Parkway, Hagerstown, MD 21740-2116.

Publisher: Randi Davis

Subscription rates: *Individual:* US $274, international: $381. *Institutional:* US $538, international $640. *In-training:* US $123 with no CME, international $154. *Single copies:* $49. Send bulk pricing requests to Publisher.

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Topics in Pain Management is indexed by SIIC (Sociedad Iberoamericana de Información Científica).

of the mu-receptor subtypes by drug, and, more specifically, to the phenomenon of incomplete crosstolerance to both analgesic and nonanalgesic opioid effects.[4] If crosstolerance to the analgesic response produced by the first drug is less complete than crosstolerance to treatment-limiting adverse effects, the switch will yield a more favorable overall response to therapy. The mechanism of individual variation and cross-tolerance remains poorly understood.

Methodology of OR

The process of OR is started by calculating an approximate equianalgesic dose between the current opioid and the proposed new opioid. It is important that the calculated starting dose be safe, neither high enough to cause opioid toxicity nor low enough to cause the withdrawal syndrome, but also sufficiently efficacious to produce no worsening of the pain. Generally, it is set at 75% of the original equal potency, with additional analgesic coverage by short-acting opioids in breakthrough dosing to prevent any shortfall. The dose of the new drug usually must be titrated from this starting dose, producing better analgesia and fewer adverse effects. This approach has proven very safe with few reports of complications when changing between oral opioids, aside from fentanyl, and methadone, where major complications have been reported.

The mechanism of individual variation and crosstolerance remains poorly understood.

The calculation of an approximate equianalgesic dose is necessary because the analgesic potency of the various opioid drugs varies greatly among patients. Potency refers to the dose required to produce a given effect. Among the various opioids available for clinical use, potency varies by orders of magnitude (ie, from micrograms to milligrams). For example, a typical patient with relatively little previous opioid exposure is likely to experience comparable analgesic effects from parenteral administration of a single 100-mcg dose of fentanyl and a single 10-mg dose of morphine. Clearly, there could be no way to switch among drugs safely and effectively unless the relative potencies among them were known. It is important to recognize that this relationship does *not* necessarily carry over to the situation of chronic administration.

Relative potency, which may be defined as the ratio of opioid doses necessary to obtain roughly equivalent effects, can be determined through controlled clinical trials that compare different drugs or routes of administration. The relative potency can be calculated for analgesia or any measurable nonanalgesic effect. Relative analgesic potency can be converted into equianalgesic doses by applying the dose ratio to a standard. Historically, 10 mg of intramuscular morphine has been considered the gold standard for this determination, and doses equianalgesic to this have been calculated by using the empirically derived relative potency estimates (Table 1).[4,5]

The first equianalgesic dose table was published more than 40 years ago[6,7] and codified the results of numerous relative potency studies. Although many versions of the table have been published and placed online[8] since then, the potency estimates represented by the values in the table have undergone little modification (Table 2).

The original relative potency assays were designed as controlled 4-point, single-dose studies. A low dose and a high dose of a study drug were compared with a low dose and high dose of a standard analgesic, usually parenteral morphine. Using double-blind technique and random treatment assignment, each patient received 1 or more of the study doses. Most studies used a partial crossover design so that each patient received more than 1 of the study doses, but not all of them.

The subjects chosen for these studies either had acute postoperative pain or chronic cancer pain. Postoperative patients were

Table 1. Dose Conversion Guideline

- Calculate the equianalgesic dose of the new opioid based on the equianalgesic table.
- If switching to any opioid other than methadone or fentanyl, decrease the equianalgesic dose by 25% to 50%.
- If switching to methadone, reduce the dose by 75% to 90%.
- If switching to transdermal fentanyl, do not reduce the equianalgesic dose.
- Consider further changes in the adjusted equianalgesic dose based on medical condition and pain.
- If the patient is elderly or has significant cardiopulmonary, hepatic, or renal disease, consider further dose reduction.
- If the patient has severe uncontrolled pain, consider a lesser dose reduction.
- Calculate a rescue dose as 5% to 15% of the total daily opioid dose and administer at an appropriate interval.
- Frequently reassess and titrate the new opioid as needed.

Table 2. The Original Equianalgesic Dose Table—Unidirectional From Morphine to the Alternate Drug

Drug	Equianalgesic Doses
Morphine	10 mg IM/IV/SC 60 mg PO
Hydromorphone	1.5 mg IM/IV/SC 7.5 mg PO
Oxycodone	20–30 mg PO
Oxymorphone	1 mg IM/IV/SC 10 mg PR 15 mg PO
Methadone	10 mg IM/IV/SC 20 mg PO
Fentanyl	50–100 mcg IV/SC

Modified from *J Pain Symptom Manage*, 2009; 38(3):426–439.[1]

studied on the first day after surgery and typically had minimal opioid exposure. Studies of patients with chronic pain typically limited the population to those who had been receiving no more than a relatively low dose of opioid before the study.

Newer data suggest that these ratios differ depending on the direction of a switch from one drug to another.

The study of each opioid was conducted by repeatedly administering the drug and then measuring analgesia and other effects over a period of hours using simple visual analog scales. The multiple pain measurements were then used to calculate the total amount of pain reduction after a dose of study medication.

Bidirectional Differences

More recent data have complicated the interpretation of these relative potency ratios. The newer data suggest that these ratios differ depending on the direction of a switch from one drug to another. In one retrospective study, for example, the morphine:hydromorphone ratio for patients who switched from morphine to hydromorphone was 5.33:1. However, the ratio for patients who switched from hydromorphone to morphine was 3.8:1.12.

These studies indicate that a bidirectional difference in potency between morphine and hydromorphone may apply to both oral and parenteral dosing, and may be independent of previous opioid exposure. On the basis of these findings, Bruera et al[9] recommend a dose ratio of 5:1 for rotation from morphine to hydromorphone and a dose ratio of 3.7:1 for a switch in the opposite direction. The 5:1 ratio was used safely and effectively in a large survey of patients who were switched from oral morphine to a modified-release, once-daily oral formulation of hydromorphone.

The Methadone Puzzle

The use of methadone (please also see *Topics in Pain Management* vol. 23, no. 5, December 2007) in OR has received a great deal of attention in recent years. Initial enthusiasm for a switch to methadone based on anecdotal observations suggesting that the potency of this drug is much greater than anticipated has been tempered by recent concerns about serious adverse events related to unanticipated toxicity, inappropriate prescribing, and the newly appreciated potential to prolong the QTc interval (rate-corrected electrocardiographic QT interval). Although methadone may be very useful in OR, there is a call for greater caution in the prescribing of this drug, especially by inexperienced clinicians, and in directions to patients.

The potency of methadone when patients are switched from another mu-agonist is greater than would be anticipated from the early studies.

In early single-dose relative potency assays, the equianalgesic dose ratio for parenteral morphine:methadone was 1:1, and the ratio between parenteral methadone and oral methadone was 1:2.

More recent studies,[10,11] however, have confirmed that the potency of methadone when patients are switched from another mu-agonist is greater than would be anticipated from the early studies. For example, Ripamonti et al[12] reported a dose ratio for oral morphine:oral methadone of 7.75:1 (range, between 14.1 and 2.5:1). A dose ratio of subcutaneous morphine to oral methadone was reported to range between 5:1 and 7:1.

Dose Can Affect Relative Potency

Several studies have demonstrated a significant relationship between the relative potency of methadone and the dose of the opioid taken at the time that methadone is administered. One study[13] noted that the oral morphine:methadone ratio for patients receiving less than 1165 mg/d was 5.42:1, whereas the ratio for those receiving more than 1165 mg/d was 16.8:1.

Another study determined the morphine:methadone ratios as 3.71:1 if the dose of morphine before the switch was 30 to 90 mg/d, but that it would be 7.75:1 if the morphine dose before the switch was 90 to 300 mg/d, and 12.25:1 if the previous morphine dose was less than 300 mg/d.

Yet another study noted a bidirectional difference in the oral morphine:methadone ratio, reporting that the ratio was 8.25:1 when switching from methadone to morphine, and 11.36:1 when switching from morphine to methadone. In contrast, Walker et al[14] reported the mean dose ratio for switching from oral methadone to oral morphine to be 1:4.7, and IV methadone:oral morphine to be 1:13.5. However, the study did not find a significant relationship between the relative potency of methadone and the dose of methadone taken by the patient at the time of the switch.

The Fentanyl Dilemma

Transdermal, sublingual, and buccal formulations of fentanyl are now widely used, off label, in populations with chronic pain.[15] On the basis of accumulated evidence from controlled trials, the manufacturer of the transdermal fentanyl citrate delivery system provided a conversion tool that presented dose ratios in broad ranges.

The decision to apply a narrower range at the higher dose of fentanyl was based on very limited data, yet tens of thousands of patients have been managed on this small data set.

For example, the transdermal fentanyl patch delivering 25 μg/hour was supposedly equianalgesic to oral morphine sulfate at 60 to 134 mg/d, whereas transdermal fentanyl at 300 mcg/hour was described as equianalgesic to oral morphine at a dose between 1035 and 1124 mg. The decision to apply a narrower range at the

higher dose of fentanyl was based on very limited data, yet tens of thousands of patients have been managed on this small data set.

In a prospective study of cancer patients receiving extended-release morphine who were converted to chronic dosing with transdermal fentanyl, the mean ratio of morphine:fentanyl was 70:1, whereas another study yielded a ratio of 96.6:1. In a small survey of 11 patients switched from morphine or codeine to a subcutaneous fentanyl infusion, the mean relative potency of morphine:fentanyl was 68:1, and the range was 15:1 to 100:1, which is a very startling result.

A study comparing oral morphine and subcutaneous fentanyl demonstrated the dose ratio to be 84.5:1. A study comparing subcutaneous morphine and subcutaneous fentanyl suggested a ratio of 70:1.

These studies demonstrate the marked variability in conversion ratios, both within and across studies, and emphasize the need for caution in applying ratios during OR.

Caution About Transmucosal and Buccal Formulations

It is extremely important to note the following: studies of oral transmucosal and buccal fentanyl formulations for breakthrough pain demonstrate no relationship between the dose of the drug and the dose of the baseline regimen. This finding would be unexpected if the potency of the fentanyl were strongly influenced by analgesic tolerance, and it further reinforces the conclusion that relative potency may be influenced by a variety of factors, such as rapidity of transit across the blood-brain barrier for a highly lipophilic drug, such as fentanyl, or avidity for receptor sites.

A study that formally evaluated the relative potency of oral transmucosal fentanyl (OTFC) and IV morphine in postoperative patients demonstrated that the best equianalgesic ratio of IV morphine:OTFC was 80:1, that is, in this study, 800 mcg of the fentanyl produced analgesia roughly comparable to 10 mg morphine. Again, this is dramatically different than the tabular value of 100 mcg equal to 10 mg of morphine.

Clinical Issues That Impact the Use of Relative Potency

Relative potency estimates may be affected by numerous factors that are minimized in the clinical trial setting and similarly affect the validity of the data. When switching to a new opioid, these potential sources of variation also must be considered.

Major Organ Dysfunction

Physiologic changes may change the pharmacokinetics of the opioid or its active metabolites. Similarly, these changes may alter the pharmacodynamics. Although these changes may shift relative analgesic potency among opioids in ways that are predictable, studies that would delineate these changes have not been performed.

Renal insufficiency is likely to change the potency of some drugs that depend on renal clearance of the parent compound and its active metabolites. Although information about these renal effects on opioid metabolism is incomplete, patients with renal insufficiency who undergo OR generally need relatively lower starting doses and more cautious dose escalation because of pharmacodynamic changes leading to increased risk of adverse effects, and the potential for risk of accumulation of the parent compound or its metabolites. The classic example of this is meperidine, where doses more than 600 mg/d caused seizures in patients with chronic renal insufficiency.

Patients with adrenal insufficiency and hypothyroidism may show a prolonged and increased responsiveness to opioids. Abnormal levels of plasma proteins may change the relationship between protein-bound and protein-free drugs, and thereby influence opioid effects. These changes also may influence relative potency estimates when converting from 1 drug to another, but again, the details are not known.

Demographic Issues

Race, Age, and Sex Can Affect the Potency of Opioids

Although the impact of these characteristics on relative potency estimates between pairs of drugs is unknown, data are continuing to emerge. It is possible that future studies will demonstrate how to apply this information systematically to guidelines for OR.

Race-Related Differences

Recent data have illustrated the importance of genetically determined racial differences in the response to opioids. A clear example of this genetic variation is the number of alleles with differing activity of the CYP2D6 isoenzyme of the hepatic P450 system, and its encoding gene. It is the only one of the drug-metabolizing CYPs that is not inducible, and as a consequence, genetic variation contributes largely to the individual variation in the enzyme's metabolic activity.

It is prudent to exercise caution when calculating dose conversion from the equianalgesic dose table in patients who are not white.

Different *CYP2D6* alleles result in enzyme variants associated with abolished, decreased, normal, or ultrarapid enzyme activity. Clinically, they allow grouping of patients into ultra-rapid metabolizers, extensive metabolizers, intermediate metabolizers, and poor metabolizers. For example, in Japanese patients, there is often a large number of poor metabolizers, whereas Western European whites have more extensive and ultra-rapid metabolizers.

In the absence of a more robust scientific understanding of the impact of race on relative potency estimates, it is prudent to exercise caution when calculating dose conversion from the equianalgesic dose table in patients who are not white, the population studied in most relative-potency assays.

Age-Related Differences

Like racial differences, age also may affect the apparent potency of opioid drugs. Opioid potency may be altered in infants less than 6 months old and in geriatric patients, because

of pharmacokinetic differences and changes in pharmacodynamic sensitivities compared with older children, and young and middle-aged adults. These shifts tend to increase the potency of these drugs above those that characterize the adult populations included in relative-potency assays and would explain, in part, the relatively lower opioid dose requirement for older, compared with younger, cancer patients with chronic pain. Although the different effects of age on relative potencies among various opioids are not known, the concern about excessive toxicity suggests that dose conversion based on the equianalgesic dose table should be undertaken with much caution in the very young and in the geriatric age group.

Sex-Related Differences

Recent animal and human studies also have indicated sex-related differences in the analgesic effects of opioids. However, the factors that determine the magnitude and direction of sex differences have not been fully elucidated but tend to focus on variations during menstrual cycle, and the impact on relative potency remains speculative. A study in normal volunteers suggested that morphine may have greater potency but slower speed of onset and offset in women. Overall, the data suggest that there is likely to be an influence of sex on the potency ratios between drugs, but the data are not sufficient to predict the direction or extent of this influence.

These data demonstrate the existence of various factors that may influence opioid potency. Like the methodologic strategies that may reduce generalizability, they justify the conclusion that the ratios in the equianalgesic tables are best viewed as broad indicators of relative analgesic potency, and cannot be applied to OR without significant adjustment.

Conclusion

OR is more of an art than an empirical science, so there is a need for clinical caution when performing OR. The popular media is replete with stories of celebrities found dead with unexpected overdoses. It behooves practitioners not to join the cast of characters parading before various boards of inquiry: a slow and measured approach with careful titration is the path of safety; rapid dose escalations and careless computation mark the path to notoriety. ■

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Coming Soon:

- My Pain Patient Needs Anesthesia....Which Tests Should I Order?
- Pain Education in Medical Schools Lacking, According to Study

Conversation: Alex Cahana, MD, on the Impact of the Washington State Pain Care Law's First Year

The controversy that swirled around the Washington State pain care act before it took effect on July 1, 2011, continues, but data already show a decrease in opioid-related deaths and other positive signs, said one of the act's biggest advocates, Alex Cahana, MD.

In particular, Cahana cited a study published by Gary Franklin, MD, MPH, et al showing that the introduction in Washington of an opioid-dosing guideline in the Workers' Compensation population in the state, even before the guideline was adopted as law statewide, seems to be associated temporally with a decline in the mean dose for long-acting opioids, a decline in the percentage of Workers' Compensation claimants receiving opioid doses of 120 mg or more morphine-equivalent per day, and decline in the number of opioid-related deaths among injured workers.[1]

And here are the data that Cahana is most excited about: From 2009 to 2010, Franklin et al[1] determined there was a 50% decrease in deaths related to opioids.

Cahana is professor and chief of the Division of Pain Medicine in the Department of Anesthesiology and Pain Medicine, University of Washington. His involvement in drafting this legislation came after the initial attempt by Rep Jim Moeller, a Washington State legislator and chemical dependency counselor for Kaiser Permanente, to draft a bill setting certain continuing medical education (CME) credits for physicians to prescribe opioids for pain management.

Instead, with Cahana's involvement, he drafted a more comprehensive law that is the first of its kind in the country. One of the unique provisions is one requiring prescribers to be familiar with best practices when treating patients with opioids for chronic noncancer pain and to consult with a pain specialist when a patient who has shown no improvement in pain, mood, or function reaches a threshold daily dose of 120 mg morphine equivalent and the provider is considering escalating the dose of opioids. To facilitate access to specialty care, the University of Washington School of Medicine pain specialists provide a resource called TelePain/ECHO to increase access, especially to pain care in rural and underserved populations.

Developed in partnership with the University of New Mexico's ECHO Program, the TelePain/ECHO service is used by primary care providers in the greater Washington, Wyoming, Alaska, Montana, and Idaho regions. Providers are organized into learning networks that meet weekly by videoconferencing to present cases, obtain consultation, and track patients with complex pain, using a team of multidisciplinary specialists in anesthesiology, rehabilitation medicine, internal and integrative medicine, behavioral health, and addiction medicine.

Several pain advocates, including members of the American Pain Foundation, had lobbied against the new law and warned that it would lead physicians to abandon patients rather than follow the law's requirements for consulting with specialists, who are in short supply.

Alex Cahana, MD

Other objections were that the act did not adequately address methadone, which was involved in most of the opioid-related deaths.

Cahana gave an interview to *Topics in Pain Management* (*TPM*) to address these allegations.

***TPM:* A series of articles in the *Seattle Times* this winter highlighted cases where patients in chronic pain have been told by their primary care providers that they could no longer prescribe pain medicine to them—even in cases where the patients were not at the threshold dose for requiring consultation with a specialist. Is there any figure for how many patients have experienced this?**

Cahana: There were a couple of surveys done by the American Pain Foundation, and they went to the Washington State Medical Association. But they never contacted us for help in the scientific structure of the survey, so it was more like a poll than a true scientific survey. Obviously the concerns are that it wasn't a very rigorous tool. I just hope that [as] time moves on, people really see that we've had phenomenal results.

***TPM:* Are you doing a more valid method to capture data about patient abandonment? Is there a survey that is more scientific?**

Cahana: The answer is no, because we don't think that's an important scientific question. The hypothesis that the bill is a reason for patient abandonment is not a scientific question. It's like, do you want to do a study to show that last year was chilly so there's no global warming? There's no scientific hypothesis behind it to work on.

***TPM*: Is there something you can come up with to have a valid objective measure of whether patients are well served?**

Cahana: Absolutely. The measurements are, what do we want? We want decreased mortality from opioids, we want decreased utilization of emergency rooms for health care, and we want better patient outcomes, and that doctors have an accrued sense of knowledge.

We're looking at what are the death rates, what are the amount of opioids dispensed in emergency departments, how many kids are going into rehab, how many burglaries there are in pharmacies, nonfatal hospitalizations, falls among elderly people. Those are the kinds of scientific questions that we need to ask, and not someone saying, "Well, I think this is bad because we don't want to see patients lose care." But that's just a hunch, and it's a poll.

***TPM:* Has there been any kind of documentation about patients who have been abandoned by their physicians and told that it's because of this law? Has there been any kind of quantification of that?**

Cahana: Listen, patient abandonment is not something new. I came to Washington in 2008. And for 2 out of 3 patients who were sent to our clinic, it was because of transfer of care, which is the codeword for patient abandonment. So that's not new. They're patients, they're nice patients, with difficult situations, presenting themselves to primary care physicians who are working under pressure and who have no incentive to take care of them.

Now, if there are those who want to use the law as an excuse, then that has to do with their work ethic.

It's a list of shame, and no doctor wants to be on that list.

***TPM*: Is there any movement to address physician abandonment?**

Cahana: Absolutely. Our Medical Quality Assurance Commission is the commission that keeps licensure on the 27,000 licensed physicians in the state of Washington. They said that they would print in their monthly newsletter, a statement that it is against the law to abandon or to drop patients under the pretext of the law. They will reiterate that. Any complaint that they will receive from doctors—not doctors who don't prescribe opioids because they don't think they're helpful, not doctors who give patients treatment and patients don't comply because they want something else. Doctors who refuse to see patients simply because they say that there's a law out there, their name will be published in that newsletter.

It's a list of shame, and no doctor wants to be on that list.

***TPM*: It's peer pressure, to change practice, rather than enforcement?**

Cahana: That's right.

***TPM*: Is there any plan to link physician abandonment to physician's licenses?**

Cahana: No. Despite how people might try to depict us, we're not a police state. We are doing this, we are putting in place evidence-based solutions to take care of a health-care emergency.

And we are showing, in a very short time, very encouraging results. We believe that the average provider will want to do this, because they see the utility, and the logic behind it.

Now, it is unfortunate that we are in a system that doesn't incent us to do the right thing. That's why, from the beginning, we were stuck with this problem. Because if from the beginning, you were to send patients to better nutrition, smoking cessation, alternative healing, et cetera, instead of inundating them with pills, and devices, and injections and unnecessary surgery, then we wouldn't be in this mess from the beginning.

***TPM*: Can you recap for our readers what the new law's provisions are?**

Cahana: The bill has 4 provisions in it. The first provision is state guidelines, which help the provider know what to do with patients that he or she wants to start to initiate in opioid therapy for chronic non-cancer pain, or for patients who already are on high doses of chronic opioid treatment, which are defined as over 120 mg of morphine equivalent a day. That threshold was chosen based on current publications that speak about a 9-fold increased risk of death at that level, due to respiratory arrest or cardiac arrhythmia. So we guide physicians about what to do with a patient who is on these high doses, but who is not shown as doing better, yet who also wants to escalate those doses.

All of these guidelines are in the Agency Medical Directors' Group (AMDG) Opioid Dosing Guidelines, 2010 version.

Because in the first provision it says that at that threshold you need to consult with a specialist if the patient is at that dose, and there's a paucity of specialists, the second provision in the new law is for TeleHealth Services offered by University of Washington pain specialists as a continuing medical education activity.

The third provision is the use of a prescription monitoring program (PMP), and what we call the Emergency Department Information Exchange program, or EDIE. The EDIE is a real-time program where the emergency departments are all connected on a network. If a patient is doctor-shopping, then their name pops up and we can identify that the patient has been moving from one emergency room to another to ask for treatment. The EDIE then links them back to their primary care doctor, or if [they don't have one], assigns them a primary care doctor for follow-up.

The fourth provision is where we measure pain, mood, and function in every clinical encounter.

And the fourth provision, which is my baby, is where we measure pain, mood, and function in every clinical encounter. So, we ask and record what is the patient-reported outcome tool that is used in every encounter.

This provision was the game changer. Because there are studies that show that education alone will increase providers' confidence, but will not change prescribing habits. So the only way to change prescription habits is for you to get a report of how your patients are doing.

The AMDG provision alone has shown impressive results. These opioid dosing guidelines developed by AMDG were initially developed in the Workers' Compensation population. Gary Franklin published last year in the *American Journal of Industrial Medicine*, data showing a decrease in deaths from opioids of 50% because of utilization of these guidelines.

Fifty percent fewer people died after the systematic utilization of these guidelines.

I didn't hear you say "Wow!"

***TPM*: OK—wow! Why did the number of deaths go down by 50%?**

Cahana: You tell me.

***TPM*: Because by using these guidelines, the physicians' prescribing patterns changed?**

Cahana: Exactly. The point is this is just amazing.

***TPM*: One physician in Washington who opposed this law said these guidelines were more of a cost-saving approach, rather than focused on patient pain relief. Can you address that?**

Cahana: Before we start to talk about conjecture and opinion, I'm first of all talking about data.

***TPM*: Would you say this reduction in the number of deaths answers that question?**

Cahana: Of course. The bill is to give Washingtonians better care. It doesn't matter that there are doctors who are saying the bill is to give less care or cheaper care, or poorer care. The point is that we construed those four provisions to give better care. And the data, already after a year, show phenomenal results. So the first provision is we systematically applied those guidelines, and already, from that provision alone, we see a 50% reduction in deaths.

Now the second provision is TelePain, our specialty service. We have shown that in counties that received a more aggressive intervention because they sought out the TelePain consulting service from University of Washington, we saw even more decreases in deaths and prescriptions—up to 65%.

Providers who dialed in to TelePain received guidance from the specialty care and enjoyed even better outcomes for their patients.

***TPM*: Can you tell us more about TelePain and TeleHealth?**

Cahana: It's University of Washington [pain specialists] talking to providers. And in one year, we were able to reach out to 2100 providers, and provided them more than 10,000 hours of continuing medical education.

***TPM*: One-on-one consultations and education?**

Cahana: No! In groups, of course. Not enough hours in the day to do one-on-one. But that's the whole idea—to create a knowledge network.

***TPM*: Does the provider call in for an education session, or for a consultation on a specific and actual patient?**

Cahana: Both, actually. The providers call in and can discuss patients in an anonymous way. Multiple providers can dial in—we have up to 50 dial-ins at a time—and people listen to each other, so there's a multiplier effect. People say, "Oh, so that's how you do it." The physicians who participate in that have an accrued sense of knowledge and an accrued sense of competence. And their patients are doing better.

***TPM*: Are the physicians who dial in pain specialists?**

Cahana: They're all nonspecialists who dial in, so the provision of saying over a certain threshold you need to call a specialist, and the people who keep saying there are not enough specialists—which is true—we've created that solution, which again has shown not only to have a positive effect on providers, but also on their patients.

***TPM:* Who are the pain experts who staff TeleHealth?**

Cahana: The University of Washington pain specialists. The staff we have is about 6 to 10 specialists from various domains: anesthesia, psychiatry, rehab, surgery, primary care. It's a 90-minute session during lunchtime, so it won't be intrusive. It starts with a 60-minute presentation. We move quickly. We use outcome measures. It's very structured. We talk about 4 to 6 patients, then 30 minutes of some didactics, so they also get their CME.

The third provision, the prescription monitoring program, we just started early this year. And we're also using EDIE. We have decreased the amount of nonurgent visits to the emergency room by 56%. So if 250 patients generated over 11,000 visits, after using this system, [that number went down to] less than 5,000.

If we let the doctor know that his or her patient was asking for drugs at more than one emergency department, we reduce the doctor-shopping.

***TPM:* Why did the emergency room visits go down?**

Cahana: They stopped doctor shopping. If I were to go from north to south and hit every emergency room to ask for methadone or Percocet, the emergency physicians would be able to enter my name in the system and say, "Wait a minute, Mr. Cahana, what's going on?" And I would be linked to my primary care provider.

If we let the doctor know that his or her patient was walking around and asking for drugs at more than one emergency department, we reduce the doctor-shopping.

***TPM:* How do you know it is not keeping patients who really need pain relief from getting it?**

Cahana: If you go in less than 24 hours to find different emergency rooms to say you need methadone pills because you ran out of them, something's wrong. It's about creating an information exchange.

***TPM:* Is the PMP going to be real-time as well?**

Cahana: Yes. It will be as good as all the other PMPs. In order to make it real time, it's not the technological capacity; It's making sure that the people who are using it immediately enter the information.

***TPM:* Are you saying the success of the PMP will depend on compliance?**

Cahana: Yes, but if there's a law, there's compliance. That's why there's a law. I know that people hate it because they don't like to be told what to do. I get it! But the problem is not because of the law. The law is the response to the problem.

If we were to have a good or proper hygiene in our treatment and our standard of care, we wouldn't need to do this. But before

the law was in place, people would read the guidelines and think, "If I feel like it, I'll do it, and if I don't feel like it, I won't do it."

But now, there's a law. And you have to do 4 hours CME to prove that you did it. And afterwards if you have a patient who dies and [regulators and investigators] go back and check for that, that's very different.

***TPM:* What if they ignore the law? How is it being enforced?**

Cahana: There's a law that you can't drive more than 60 miles per hour. Are there people who drive more than 60? Yes. What's the incentive to drive less than 60? It's the law. If you drive more than 60 and you kill someone, you'll have to explain.

The world is then divided into two: Those who don't speed because they understand that when you speed, you can kill someone, and then those who say, listen, I'll never kill anyone.

But before this law, there was a law that said that no doctor can ever be pursued legally regardless of the amount or dose they're giving patients. So you could open a pill mill, and give people grams of opioids, and you were untouchable.

The problem is not because of the law. The law is the response to the problem.

***TPM:* Getting back to the law's main components, you mentioned the fourth provision is the one you are most engaged in.**

Cahana: Yes. The fourth provision is the measurement-based care. We have shown that our physician population, working together with primary care—where we measure outcomes with patients who are well engaged and who receive coordinated care according to the guidelines—we see less pain, less anxiety, less depression, improved sense of wellbeing, and over 56% decrease in the opioid prescriptions.

Now, those patients who are not engaged, they are the same. What they have to do is the other kinds of treatment. But those who are engaged and seek to do better, will do better with this kind of care. The bill seeks only to codify "Best Care."

If the physician has to use a tool that measures pain outcomes at regular intervals—and it's a law—then they will do it.

***TPM:* Do they have to use the tool?**

Cahana: They have to use it. It's like hemoglobin A_{1c} when you have diabetes.

***TPM:* Are all doctors using the tool?**

Cahana: I couldn't tell you [about all doctors]. In our practice, it is used. We have a very large system with 9 primary care clinics that are part of the University of Washington neighborhood clinics. I have no say in what goes on in other health care systems in the state.

Just as there are doctors who say, "I don't want to do this," there are patients who say, "I don't want to do this."

***TPM:* So you're comparing the outcomes of the patients who are cooperating with this tool, with the outcomes of the patients who are not?**

Cahana: Exactly.

***TPM*: And these measurements are within your system, not across the state, right?**

Cahana: Yes. I think that there's another portion that hopefully will change. The patient advocacy groups who have a very strong platform are reaching out to physicians and misleading them, and telling them, "Did you hear about the bad [law]? Did you know you're not able to do this or that?" Now, obviously they haven't called me. I just have feedback from providers who told me that, when we gave our talk to them, they were surprised, because they had received other information.

So what I hope, is that now that the American Pain Foundation has new leadership, they will reach out to me and say, "Alex, we are very impressed, because initial data implicates that the implementation of your law resulted in patients who have better function, improved mood, decreased opioid prescription, decreased death, decreased visits to the ER and improved provider satisfaction."

And any concern that we have regarding access has been addressed by increasing capacity, implementing TeleHealth solutions, and increasing immensely the continuing education activity. Those are the facts.

***TPM:* The last time *TPM* interviewed you, you mentioned informally talking with some leaders in the American Academy of Pain Medicine. Did they ever formally support this initiative?**

Cahana: No. I was hoping that they were very serious in moving forward in some way toward a standard of care, but that's not the case. At the end, they said, they're not going to do this. I was in very close contact with the academy, and I was trying to recommend to them to implement our system for the academy members. I was told that it will not happen, and was politely removed from being co-chair of the research committee and then from the committee in general. We were unable to reach agreement on the politics of moving forward with the academy.

***TPM:* There was a great deal of criticism from the beginning, and in the *Seattle Times* series that ran this winter, continuing to say that this bill does not address methadone, and that this drug is responsible for the greatest number of deaths. Is that a fair report?**

Cahana: Again, this argument about methadone is one of these things that people just cling to. There's no good or bad medicine. There are medicines that are prescribed safely or not. The reporter for the *Seattle Times*, by the way, did not want to interview me, and the *Seattle Times* also did not print or publish my op-ed, because they already received enough op-eds, they said.

***TPM:* Can anyone read your op-ed elsewhere?**

Cahana: It's on the site of KCTS-TV, public broadcasting, http://kcts9.org/prescription-for-abuse—there is a documentary called "Prescription for Abuse." You can see that 30-minute documentary followed by a 30-minute panel discussion. I'm also there. And my op-ed about the next steps to improve pain care for Washingtonians.

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Topics in Pain Management CME Quiz

To earn CME credit, you must read the CME article and complete the quiz and evaluation assessment survey on the enclosed form, answering at least 70% of the quiz questions correctly. **Select the best answer and use a blue or black pen to completely fill in the corresponding box on the enclosed answer form.** Please indicate any name and address changes directly on the answer form. If your name and address do not appear on the answer form, please print that information in the blank space at the top left of the page. Make a photocopy of the completed answer form for your own files and mail the original answer form in the enclosed postage-paid business reply envelope. Your answer form must be received by Lippincott CME Institute by **April 30, 2013.** Only two entries will be considered for credit.

Online quiz instructions: To take the quiz online, **log on to your account at http://www.topicsinpainmanagement.com,** and click on the "CME" tab at the top of the page. Then click on "Access the CME activity for this newsletter," which will take you to the log-in page for **CME.lwwnewsletters.com.** Enter your ***username and password for this screen as follows***: Your ***CME username*** will be the letters LWW (case sensitive) followed by the 12-digit account number above your name on the paper answer form mailed with your issue. Your ***CME password*** will be **1234**; this password ***may not*** be changed. Follow the instructions on the site. You may print your official certificate ***immediately***. Please note: Lippincott CME Institute, Inc., ***will not*** mail certificates to online participants. **Online quizzes expire at 11:59 pm Pacific Standard Time on the due date.**

1. **Potency refers to the dose required to produce a given effect.**
   A. True
   B. False

2. **OR is indicated in all of the following situations *except***
   A. Opioid dose escalation has yielded intolerable and unmanageable adverse effects, such as somnolence or mental clouding.
   B. Severe ongoing pain (often accompanied with intolerable adverse effects) that continues despite repeated dose escalations.
   C. The patient requests a different route of administration.
   D. The patient states that he likes "oxys" and "dlaudid."

3. **All of the following are correct steps to calculate the appropriate dose in OR *except***
   A. Calculate the equianalgesic dose of the new opioid based on the equianalgesic table.
   B. If switching to any opioid other than methadone or fentanyl, decrease the equianalgesic dose by 25% to 50%.
   C. If switching to methadone, reduce the dose by 75% to 90%.
   D. If switching to transdermal fentanyl, reduce the equianalgesic dose by 40%.

4. **During OR, the rescue or breakthrough dose is set at between 5% and 15% of the total daily opioid dose, administered at an appropriate interval.**
   A. True
   B. False

5. **At least 1 study noted a bidirectional difference in the oral morphine to methadone ratio, reporting that the ratio was 8.25:1 when switching from methadone to morphine, and 11.36:1 when switching from morphine to methadone.**
   A. True
   B. False

6. **Race, age, and sex can affect the potency of opioids.**
   A. True
   B. False

7. **Oral transmucosal and buccal fentanyl formulations for breakthrough pain demonstrate a pure linear relationship between the dose of the drug and the dose of the baseline regimen.**
   A. True
   B. False

8. **Patients with adrenal insufficiency and hypothyroidism may show a prolonged and increased responsiveness to opioids.**
   A. True
   B. False

9. **Which one of the following statements about alleles that govern CYP2D6 is *false*?**
   A. Various CYP2D6 alleles result in enzyme variants associated with abolished, decreased, normal, or ultrarapid enzyme activity.
   B. In the Japanese patient population, there is often a large number of poor metabolizers.
   C. CYP2D6 is an inducible enzyme.
   D. Western European white populations have more extensive and ultrarapid metabolizers.

10. **Morphine may have greater potency but slower speed of onset and offset in women.**
    A. True
    B. False

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TPM: **What about the rest of the country? Are there any other states that are close to passing a law similar to Washington's?**

Cahana: The short answer is no. The long answer is yes, in the sense that there are a lot of legislative efforts going out, and the American Academy of Pain Management created a portal for legislation. They did a good job creating that as a resource on legislation that has over 200 bills throughout the country. It's in real-time and they're following up on that. It's through their website, www.aapainmanage.org, and under the "Advocacy" heading. ■

Reference

1. Franklin GM, Mai J, Turner J, et al. Bending the prescription opioid dosing and mortality curves: impact of the Washington State opioid dosing guideline [published online ahead of print December 27, 2011]. *Am J Ind Med*. 2011. doi: 10.1002/ajim.21998.

NEWS IN BRIEF

More on the *Seattle Times* Series

The *Seattle Times* published a 3-part series from December 10-12, 2012, with a total of 6 articles on pain-related issues in the state, in particular on methadone-related deaths occurring disproportionately among the low-income residens in Washington; the impact of the new Washington State pain care act, alleging that many primary care physicians abandoned patients after the law took effect; and a closer look at a specific pain clinic, Payette Clinic in Vancouver, Washington, which links a nurse practitioner to deaths of pain patients from unintended methadone overdose.

Alex Cahana, MD, professor and chief of the Division of Pain Medicine in the Department of Anesthesiology and Pain Medicine, University of Washington (see *Conversation*, page 7 of this issue), said he was not interviewed for the series, although he offered to speak to a reporter, and that the paper would not print his opinion piece after the series ran.

Here are the articles that appeared each day of the series. To find the articles and some updates, go to *www.SeattleTimes.com* and type "methadone" in the search field.

Part 1: Silent deaths
(December 10, 2012)
- State pushes drug that saves money, costs lives
- Timeline: State defends methadone as deaths rise
- How we did it: our analysis

Part 2: Politics of pain
(December 11, 2012)
- New law leaves patients in pain
- Source documents

Part 3: A troubled clinic
(December 12, 2012)
- In pain clinic's wake: doubts, chaos, deaths. ■