Published in final edited form as:
J Pain Symptom Manage. 2009 September ; 38(3): 418–425. doi:10.1016/j.jpainsymman.2009.06.002.

Establishing "Best Practices" for Opioid Rotation: Conclusions of an Expert Panel

Perry G. Fine, MD, **Russell K. Portenoy, MD**, and **the Ad Hoc Expert Panel on Evidence Review and Guidelines for Opioid Rotation***
Pain Research Center (P.G.F.), Department of Anesthesiology, University of Utah School of Medicine, Salt Lake City, Utah; and Department of Pain Medicine and Palliative Care (R.K.P.), Beth Israel Medical Center, New York, New York, USA

Abstract

Opioid rotation is a strategy applied during opioid therapy for pain that refers to a switch from one opioid to another in an effort to improve clinical outcomes (benefits or harms). It begins with the selection of a new drug at a starting dose that minimizes potential risks while ideally maintaining analgesic efficacy. The selection of a starting dose must be informed by an estimate of the relative potency between the existing opioid and the new one. Clinically relevant estimates of relative analgesic potency have been codified on the "equianalgesic dose table," which has been used with little modification for more than 40 years. New information about relative potency and the growing implementation of long-term opioid therapy for chronic pain provided a strong rationale for the convening of an expert panel to discuss the scientific foundation to opioid rotation and the elements that now should inform a clinical guideline for this practice. The panel affirmed both the value and the limitations of the current equianlagesic dose table and proposed a guideline intended to promote safety during opioid rotation.

Keywords

Opioid; opioid rotation; relative potency; equianalgesic dose; pain management

Introduction

Opioid therapy for acute or chronic pain requires individualization of the dose, with the objective of identifying a favorable balance between analgesia and side effects. Opioid-related adverse effects are common and may be treatment-limiting. "Opioid rotation," a planned switch from one opioid to another in an effort to improve outcomes, is one strategy

Address correspondence to: Perry G. Fine, MD, Pain Research Center, Department of Anesthesiology, University of Utah School of Medicine, 615 Arapeen Drive, Suite 200, Salt Lake City, UT 84108, USA, perry.fine@hsc.utah.edu.
*See Appendix for members of the Ad Hoc Expert Panel.

The authors declare no financial conflicts with respect to this work.

in this setting. Widespread use of the approach has evolved over many years despite the lack of evidence-based guidelines or a uniformly-accepted “best practice” derived from expert opinion (1).

Opioid rotation begins with the selection of a safe and reasonably effective starting dose for the new opioid. Once initiated, the new therapy must be individualized through the process of dose titration and treatment of adverse effects. Given the large differences in potency among opioid drugs, the selection of a starting dose must be informed by an estimate of the relative potency between the existing opioid and the new one. Ideally, clinicians should implement the opioid switch at an initial dose that does not result in adverse effects or abstinence, and maintains efficacy. In clinical practice, determination of the optimal initial dose when rotating opioids is a challenge.

More than 40 years ago, methods for measuring relative opioid potency were developed (2). Data from numerous studies based on this methodology were subsequently adapted into “equianalgesic dose tables” to help guide conversions between opioids. However, the original relative potency assays had limitations and new evidence on relative potency is now available. The purpose of this article is to summarize the findings of an expert panel (see Appendix) that reviewed the evidence pertaining to relative opioid potency in order to develop guidelines that comport with the circumstances of everyday clinical practice.

Methods

An interdisciplinary expert panel with clinical and research expertise in opioid pharmacology was convened to review the evidence and formulate recommendations. The existing literature on relative potency was collated and critiqued as background information (3). The panel met for a full day of discussions, which were taped and transcribed. The transcript was then reviewed for key conclusions related to the definition of opioid rotation, the strengths and limitations of the existing literature on relative potency, the clinical considerations relevant to the clinical application of relative potency estimates, and the elements of a new guideline for opioid rotation. Noting that there have been no prospective clinical trials to evaluate the impact of opioid rotation on clinical outcomes in patients with acute or chronic pain, the panel endorsed the need for a guideline based on best evidence and clinical experience, prioritizing safety in the practice of opioid rotation. All panel members provided independent editorial input and consensus views are summarized in this paper.

Conclusions of the Expert Panel

The interdisciplinary panel reached consensus on an array of issues related to the practice of opioid rotation. These areas of agreement supported the development of a guideline.

Definition of Opioid Rotation

The panel agreed that the goal of opioid rotation is to improve therapeutic effectiveness during opioid therapy. The following definition was proposed:

Opioid rotation (or switching) is a change in opioid drug or route of administration with the goal of improving outcomes.

The panel agreed on several points that may clarify or expand the definition:

- Opioid rotation is best viewed as one strategy among many to address unsatisfactory outcomes following opioid administration or dose escalation. As such, it is important to note that opioid rotation may or may not be the best approach at any point in time, that more than one switch may be required to obtain satisfactory therapeutic outcomes, and that some patients will not respond well even to trials of multiple opioid drugs (1). Given the lack of clear evidence regarding clinical benefits of opioid rotation, the decision to undergo a trial of opioid rotation should be based on a shared decision-making approach that emphasizes the substantial uncertainties in estimating benefits and harms.
- Both the immediate and long-range goals of opioid rotation are to establish an opioid regimen that is more effective than the prior therapy. Effectiveness encompasses improved analgesic efficacy, reduced adverse effects, and/or improved treatment-related outcomes associated with physical and/or psychosocial functioning or quality of life.
- The definition of opioid rotation is premised on treatment principles that should generalize to a broad population of patients and provide sufficient clinical flexibility to address the large degree of individual variation encountered in diverse clinical settings.

Indications for Opioid Rotation

The panel identified potential indications for a switch in the existing opioid therapy:

- Occurrence of intolerable adverse effects during dose titration;
- Poor analgesic efficacy despite aggressive dose titration;
- Problematic drug-drug interactions;
- Preference or need for a different route of administration;
- Change in clinical status (e.g., concern about drug abuse or the development of malabsorption syndrome) or clinical setting that suggests benefit from an opioid with different pharmacokinetic properties;
- Financial or drug availability considerations.

The group excluded pain crises from the list of potential indications because the management of these complex clinical scenarios was beyond the scope of a guideline focused solely on opioid rotation. It also agreed that the term “poor opioid responsiveness” to describe a clinical situation that would justify a switch to an alternative opioid should be used cautiously because some clinicians perceive this term to imply that a patient is not responsive to opioids in general.

Clinical Considerations in the Practice of Opioid Rotation

The expert panel next focused on a number of clinical considerations relevant to the practice of opioid rotation:

- To optimize outcomes, the approach should begin with an assessment of an array of factors that may influence decision making relevant to the selection of a new drug and initial dose, the process of dose individualization, and other factors that may help ensure that the new therapy is optimized. These include demographic factors such as age and race, relevant disease-related and treatment-related factors, comorbid medical conditions, and concomitant pharmacotherapy.
- Implementation of opioid rotation also must consider the clinical care environment (e.g., outpatient, inpatient, long-term care, hospice) and psychosocial circumstances.
- In considering which specific opioid should be tried next, clinicians should weigh the patient's history of any drug sensitivities or experience with specific drugs, drug characteristics that may increase or decrease safety or efficacy given the patient's clinical status, drug characteristics that may offer previously unrealized benefits unrelated to pain relief (e.g. convenience, improved adherence, less reliance on oral administration, or access to a regular non-opioid drug in a combination product), and problems related to financial issues or insurance.
- If an opioid is selected that may require enhanced knowledge for safe prescribing, such as methadone or buprenorphine, clinicians should ensure that skills are adequate, obtain appropriate consultation, or refer to persons with expertise in prescribing these drugs.

In discussing these considerations, panel members emphasized several specific observations. For example, the distinction between acute and chronic pain has not been previously emphasized in clinical discussions of opioid rotation, but may represent an important issue. To reduce the risk of unintentional overdose when pain intensity may be changing quickly or rapid titration may be needed after a change in drugs, opioid rotation in the setting of acute pain management usually should employ a short-acting drug, rather than an extended-release formulation or methadone.

The panel also discussed the myriad of social circumstances that may influence drug selection, starting dose, or the protocol applied to dose titration. The decision to recommend one drug over another may be influenced, for example, by recognition that a patient lives with a substance abuser who may complicate efforts to protect the prescription, or an elderly caregiver who may not be able to monitor the patient. It was noted that the need for opioid switching may be driven by formulary restrictions, commonly encountered in Medicaid programs, managed care plans, long-term care facilities or hospice programs. Clinicians who practice in those settings should have opioid rotation guidelines that protect their patients.

The panel also observed that withdrawal immediately after the switch to a new opioid has received little attention in the literature. Most clinicians have little experience in managing acute withdrawal and many appear to have little recognition of the more subtle

manifestations of protracted withdrawal, such as dysphoria, fatigue, or sleep disturbance (4). The panel advised that clinicians who frequently offer opioid rotation should be prepared to recognize and manage opioid withdrawal syndrome and they may need additional education about this issue.

The final observation highlighted by the panel was that opioid rotation must be viewed in the larger context of opioid therapy for pain. Long-term therapy for chronic non-cancer pain remains controversial, and recent evidence-based guidelines indicate the importance of linking routine risk assessment to optimal pharmacotherapy (5). This type of guidance is foundational to any of the best practices that together comprise the therapy, including opioid rotation.

Need to Re-Evaluate the Equianalgesic Dose Table

The panel recognized the importance of the equianalgesic dose table, and the value of having the table represent the results of well-controlled trials. An extensive review of relative potency studies, however, highlighted both the limitations of the existing data and the challenges inherent in applying them to opioid rotation in the clinical setting (3). For example, almost all trials of relative potency were short-term trials conducted in patients with acute postoperative pain or patients with cancer pain on low-dose opioids, and may not be directly applicable to patients with chronic non-cancer pain on relatively high doses. Although the panel agreed that the current equianalgesic dose table should be used until an alternative is created, it also concluded that the use of the conventionally-accepted conversion ratios without adjustments for the individual patient would be dangerous, and that a modern guideline for opioid rotation must emphasize the goal of safety by specifying the potential for dose adjustments after calculation of the equianalgesic dose. The conversion ratios included in the table are merely a broad indicator of relative analgesic potency, which must be considered in tandem with other factors when switching from one opioid regimen to another.

The expert panel discussed the viability of a new equianalgesic dose table that would include all the opioids now used in practice and would have conversion ratios that incorporated the type of dose adjustments that might be included in a modern guideline for opioid rotation. Although these “adjusted” ratios would no longer be directly representative of data from randomized controlled trials, they could be applied to opioid rotation without requiring step-wise calculations, and for this reason, should reduce the risk of error. Given the complexity of this pharmacology, a new equianalgesic dose table would likely replace the single conversion ratio with a matrix of frequently applied ratios, and would presumably be best suited for an electronic medium.

The panel identified numerous gaps in the literature on relative potency, each of which complicates efforts to create a new equianalgesic dose table. Some drug pairs have been evaluated in several trials, which have yielded inconsistent relative potency ratios, or ratios shown to change with direction of the switch or the duration of treatment (3). Many influences on potency, such as genetically-determined differences in drug metabolism (6), have not yet been evaluated in relative potency studies, and their impact can only be inferred. Although the current opioid dose is likely to have an effect on the ratio necessary to

select an equianalgesic dose of any opioid, this has been confirmed only for conversions to methadone (7,8), and in the case of this drug, the effect of dose on relative potency is assumed to be greater than would be the case with other drugs. Due to the lack of data from studies of these and other factors, a revised table would necessarily include ratios largely informed by clinical judgment and experience, rather than evidence.

These challenges notwithstanding, the expert panel concluded that there would be value in pursuing the development of a more sophisticated equianalgesic table that would incorporate a guideline for dose adjustment based on the existence of factors that could influence relative potency. If created, studies could be designed to validate the model incorporated into the table, thereby demonstrating its utility overall while potentially testing the validity of each element.

Guideline for Opioid Rotation

In the absence of a simple approach to revising the equianalgesic dose table, the expert panel emphasized the need for a guideline focused on opioid rotation that would continue to rely on the existing equianalgesic dose table but promote safety through dose adjustments based on the best evidence available and expert opinion. In publications that include reference to the use of equianalgesic doses to switch opioid drugs, reference to an appended guideline should be encouraged (Table 1).

The guideline for opioid rotation uses existing equianalgesic dose tables as a reasonable starting point, though whether an individual patient will react to an opioid switch as anticipated is difficult to predict (3). To reduce the risk of unintentional overdose, the conversion ratio calculated for a patient undergoing opioid rotation should be adjusted based on clinical assessment of risk (9). To address risk, strategies for safe use of the equianalgesic dose table should involve a two-step process:

- Step 1: calculate an automatic safety factor
- Step 2: calculate an additional dose adjustment based on assessed patient characteristics

The safety factor (Step 1) may be conceptualized as an automatic reduction in the equianalgesic dose within a narrow window. This automatic reduction is justified on the basis of extensive experience demonstrating that the calculated equianalgesic dose commonly understates the actual potency of the new drug because of individual variation and the impact of incomplete cross-tolerance in the chronic treatment setting (1,9). Based on panel consensus, the window to apply to most switches is a reduction of 25-50% of the calculated equianalgesic dose.

The expert panel endorsed three exceptions to this automatic 25-50% reduction in the calculated equianalgesic dose. First, when switching to methadone, evidence of higher-than-anticipated potency in the clinical setting suggests that the automatic reduction in the calculated dose should be substantially greater, usually 75-90% (10). Although this steep reduction probably is not needed when the switch to methadone is occurring from a relatively low-dose opioid regimen, the decision to employ a smaller reduction requires

particularly careful monitoring after the change. Many clinicians use the 75-90% reduction in all cases, recognizing that initial underdosing is likely and that dose titration will be necessary. Some clinicians opt to alter the automatic reduction by applying a stepwise reduction based on the dose of the regimen prior to the switch to methadone, using standard low, medium and high conversion ratios depending on the current opioid dose (3,7).

Second, the original studies of transdermal fentanyl led to the development of a conversion table from oral or parenteral opioids to transdermal fentanyl. This one-way conversion chart incorporated a safety factor and subsequent experience supported the conclusion that the equianalgesic ratios printed in the label were conservative enough that an additional automatic reduction in the calculated equianalgesic dose was not required (11).

Third, studies have confirmed that a large proportion of patients obtain satisfactory results when treatment with the newer oral transmucosal fentanyl citrate formulations are initiated at the lowest available doses, irrespective of the baseline opioid regimen (12). This observation suggests that these formulations, which are used as supplemental treatments for breakthrough pain, should not be included in an opioid rotation guideline and always should be initiated at one of the lower doses in practice.

How much to adjust the calculated equianalgesic dose (i.e., a reduction of 25-50% of the calculated equianalgesic dose) should be based on a clinical judgment about the likelihood that the dose ratio in the equianalgesic table applies to the patient in question. Many characteristics of the patient or the analgesic regimen suggest that the conversion ratio included in the table may not be fully applicable (3). A larger reduction (e.g., 50% reduction in most cases) might be appropriate, for example, if the current opioid regimen uses a relatively high dose or if the patient has advanced age or renal disease. Patients of non-Caucasian race may be more sensitive to opioid effects for various reasons (3) and this characteristic also may suggest the use of this higher dose reduction. In contrast, a smaller reduction (e.g., 25% reduction in most cases) might be appropriate when the patient is on a relatively low dose regimen and is perceived to have characteristics comparable to the clinical populations that were studied in the early relative potency assays. Adjustment closer to the lower bound also is reasonable when the switch to a new regimen involves changing routes of administration without changing the drug.

The expert panel supported the use of a second evaluation (Step 2) for dose adjustment, which would be applied after the automatic reduction in the calculated equianalgesic dose is selected. This second step requires an assessment focusing on the severity of the pain at the time of the change and the existence of other medical or psychosocial factors that potentially alter potency or shift the likelihood that the initial dose of the new drug will be analgesic, relatively free of adverse effects, and unlikely to precipitate withdrawal. In many cases, the second assessment will conclude that the initial adjusted dose (Step 1) can be used as the starting dose. In some cases, however, the second evaluation may suggest that an additional change in this dose, usually in the range of 15-30% would be prudent.

For example, a patient undergoing a switch from morphine to hydromorphone may first be considered for an initial (Step 1) automatic 25% reduction in the calculated equianalgesic

dose. If the second assessment (Step 2) indicates that pain is very severe, however, a reasonable judgment would be to eliminate this reduction. In another case, a patient undergoing a switch to hydromorphone may first be considered for an initial (Step 1) automatic 25% reduction in the calculated equianalgesic dose and the second assessment reveals moderate pain, mild confusion, and the use of multiple other drugs. These patient-specific observations from the second evaluation (Step 2) may lead to the decision to reduce the dose by an additional 15%.

The expert panel acknowledged that these elements of the guideline were likely to be variably implemented, given the lack of high-quality evidence to determine relative opioid potency in individual patients. The recommendations are intended to reduce risks associated with opioid rotation, but provide no guarantee that the initial dose of the new drug is adequate. Accordingly, the panel also emphasized that a guideline for opioid rotation must present a strategy for titration of the dose after the change to a new drug is initiated. Depending on the approach selected by the clinician, this may or may not involve a co-administered short-acting supplemental dose, often termed the “rescue” dose. If a rescue dose is used, it conventionally is initiated at 5-15% of the total daily dose of the new medication and titrated as the baseline dose is increased. As noted, however, the oral transmucosal fentanyl formulations represent an important exception to this empirical approach, and usually are started at one of the lower doses irrespective of the baseline opioid dose.

Need for Research

Well-designed studies that compare outcomes among persons who undergo opioid rotation and those who are managed with dose escalations of the current opioid, opioid withdrawal, or other strategies are needed to clarify risks and benefits of opioid rotation. Studies should be conducted to determine who is more likely to benefit from opioid rotation and effects of applying different dose conversion strategies. Studies that assess relative potency estimates in different populations, during treatment with newer formulations, during very short (e.g., acute pain settings) versus long-term therapy and in patients on relatively high doses of opioids would be valuable. The impact of prior opioid dose on the potency of a new drug that appears to be particularly important when methadone (10) is administered should be studied with other drugs as well. The potential for bi-directional change in relative potency should be investigated across varied pairs of drugs. Sources of variation that may systematically alter potency, including demography, pain-related factors and disease-related factors, remain to be investigated (3).

Summary

Although opioid rotation is a common practice, review of the existing literature and discussion by an expert panel revealed substantial limitations in the pertinent evidence and a lack of clear consensus about a “best practice” approach. This effort has yielded a proposed 2-step guideline for opioid rotation, which emphasizes a safe strategy for switching drugs in diverse populations that is tailored to assessments of potential benefits and harms in individual patients. Future studies are needed to expand the evidence base and refine the guideline.

Acknowledgments

This project, including the convening of an expert panel and the preparation of this paper, was supported by an unrestricted grant from Endo Pharmaceuticals to the Department of Pain Medicine and Palliative Care, Beth Israel Medical Center, New York, NY.

Appendix

Ad Hoc Expert Panel on Evidence Review and Guidelines for Opioid Rotation

Panel members and authors:

Russell K. Portenoy, MD, Co-Chair (Beth Israel Medical Center, New York, NY)

Perry G. Fine, MD, Co-Chair (University of Utah, Salt Lake City, UT)

Roger Chou, MD, (Oregon Health Sciences University, Portland, OR)

Ricardo A. Cruciani, MD, PhD (Beth Israel Medical Center, New York, NY)

Deborah Gordon, RN, MS, FAAN (University of Wisconsin Hospitals and Clinics, Madison, WI)

Charles E. Inturrisi, PhD (Weill Cornell Medical College, New York, NY)

Kenneth Jackson, PharmD (Pacific University, Hillsboro, OR)

Michael Moskowitz, MD (Bay Area Pain Medical Associates, Mill Valley, CA)

Gavril Pasternak, MD, PhD (Memorial Sloan-Kettering Cancer Center, New York, NY)

Srinivasa Raja, MD (John Hopkins School of Medicine, Baltimore, MD)

Lynn Webster, MD (Lifetree Medical, Inc., Salt Lake City, UT)

Donna S. Zhukovsky, MD (M. D. Anderson Cancer Center, Houston, TX)

References

1. Quigley C. Opioid switching to improve pain relief and drug tolerability. Cochrane Database Syst Rev. 2004; (3) CD004847.
2. Houde R, Wallenstein S, Beaver W. Evaluation of analgesics in patients with cancer pain. Clin Pharm. 1966; 1:59–97.
3. Knotkova H, Fine PG, Portenoy RK. Opioid rotation: the science and the limitations of equianalgesic dose table. J Pain Symptom Manage. 2009; 38(3)
4. Shi J, Zhao LY, Epstein DH, Zhang XL, Lu L. Long-term methadone maintenance reduces protracted symptoms of heroin abstinence and cue-induced craving in Chinese heroin abusers. Pharmacol Biochem Behav. 2007; 87:141–145. [PubMed: 17532034]
5. Chou R, Fanciullo GJ, Fine PG, et al. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. J Pain. 2009 in press.

6. Caraco Y, Sheller J, Wood AJ. Impact of ethnic origin and quinidine coadministration on codeine disposition and pharmacodynamic effects. J Pharmacol Exp Ther. 1999; 290:413–422. [PubMed: 10381807]

7. Lawlor PG, Turner KS, Hanson J, Bruera ED. Dose ratio between morphine and methadone in patients with cancer pain: a retrospective study. Cancer. 1998; 82(6):1167–1173. [PubMed: 9506365]

8. Ripamonti C, Groff L, Brunelli C, et al. Switching from morphine to oral methadone in treating cancer pain: what is the equianalgesic dose ratio? J Clin Oncol. 1998; 16(10):3216–3221. [PubMed: 9779694]

9. Pereira J, Lawlor P, Vigano A, Dorgan M, Bruera E. Equianalgesic dose ratios of opioids: a critical review and proposals for long-term dosing. J Pain Symptom Manage. 2001; 22:672–687. [PubMed: 11495714]

10. Gazelle G, Fine PG. Methadone for pain. J Palliat Med. 2004; 7(2):303–304. [PubMed: 15130209]

11. Duragesic® (Fentanyl Transdermal System). Full Prescribing Information: Ortho-McNeil-Janssen Pharmaceuticals, Inc.; 2008.

12. Portenoy RK, Taylor D, Messina J, Tremmel L. A randomized, placebo-controlled study of fentanyl buccal tablet for breakthrough pain in opioid-treated patients with cancer. Clin J Pain. 2006; 22:805–811. [PubMed: 17057563]

Table 1

Guideline for Opioid Rotation

Step 1

- Calculate the equianalgesic dose of the new opioid based on the equianalgesic table.
- If switching to any opioid other than methadone or fentanyl, identify an "automatic dose reduction window" of 25% to 50% lower than the calculated equianalgesic dose.
    - ◇ If switching to methadone, identify this window at 75% to 90% lower than the calculated equianalgesic dose. For individuals on very high opioid doses (e.g., 1,000 mg morphine equivalents/day or higher), great caution should be exercised in converting to methadone at doses of 100 mg or greater per day; consider inpatient monitoring, including serial EKG monitoring.
    - ◇ If switching to transdermal fentanyl, calculate dose conversions based on the equianalgesic dose ratios included in the package insert for these formulations.
- Select a dose closer to the lower bound (25% reduction) or the upper bound (50% reduction) of this automatic dose reduction window on the basis of a clinical judgment that the equianalgesic dose table is relatively more or less applicable, respectively, to the specific characteristics of the opioid regimen or patient.
    - ◇ Select a dose closer to the upper bound (50% reduction) of the reduction if the patient is receiving a relatively high dose of the current opioid regimen, is not Caucasian, or is elderly or medically frail.
    - ◇ Select a dose closer to the lower bound (25% reduction) of the reduction if the patient does not have these characteristics or is undergoing a switch to a different route of systemic drug administration using the same drug.

Step 2

- Perform a second assessment of pain severity and other medical or psychosocial characteristics to determine whether to apply an additional increase or decrease of 15-30% to enhance the likelihood that the initial dose will be effective for pain, or conversely, unlikely to cause withdrawal or opioid-related side effects.
- Have a strategy to frequently assess initial response and titrate the dose of the new opioid regimen to optimize outcomes.
- If a supplemental "rescue dose" is used for titration, calculate this at 5-15% of the total daily opioid dose and administer at an appropriate interval; if an oral transmucosal fentanyl formulation is used as a rescue dose, begin dosing at one of the lower doses irrespective of the baseline opioid dose.