Opioid rotation in patients with cancer: A review of the current literature

Athina Vadalouca, MD, PhD, FIPP
Eleni Moka, MD
Erifilli Argyra, MD, PhD
Panayiota Sikioti, MD
Ioanna Siafaka, MD, PhD

ABSTRACT

Cancer is a public health problem worldwide and a major cause of death or disability. Pain is one of the most common and feared symptoms in patients with cancer with marked impact on quality of life. According to the WHO analgesic ladder, opioids are the mainstay of cancer pain management, if well-accepted guidelines are systematically applied. Oral morphine has been widely used in treating cancer pain of moderate to severe intensity and remains the preferred first choice to many clinicians for its familiarity/availability/costs. However, a significant proportion of patients under oral morphine do not have successful outcomes, often switched to alternative strong opioids. Opioid rotation is a therapeutic maneuver aiming in improving analgesic response and/or reducing adverse effects, including change to different medication using the same administration route, maintaining the current medication but altering administration route, or both. In this review, a detailed presentation of the available literature, regarding opioid rotation strategy, up to now is performed. Indications, principles, opioid dose-conversion recommendations, and guidelines in oncology patients are presented. An outline of the evidence supporting the use of this therapeutic modality on clinical benefit/outcome is attempted. Mechanisms contributing to patients' variable opioid response are underlined. Since 1/3 of population will die from cancer (80 percent with severe pain in their final year of life), effective pain control remains an ongoing challenge. Opioid rotation may be useful in opening the therapeutic window and establishing a more advantageous analgesia/toxicity relationship. However, too much work is to be done to further individualize analgesic therapy for patients with cancer.

Key words: opioid rotation/opioid switching/opioid substitution, guidelines/recommendations/decision making, cancer pain, morphine, genetic polymorphism/intraindividual variability in response, alternative opioids, methadone, opioid rotation/outcome

“Pain must be regarded as a disease . . . and the physician’s first duty is action—heroic action—to fight disease . . .”

Benjamin Rush

CANCER AND CANCER-RELATED PAIN: PREVALENCE AND EPIDEMIOLOGICAL DATA

Cancer is a public health problem worldwide, being a major cause of death and disability and affecting all people: the young and old, the rich and poor, men, women, and children. Since 2002 and 2003, when GLOBOCAN (Global Burden of Cancer) project of International Agency for Research on Cancer (IARC) and the World Health Organization (WHO), respectively, published the last updates of the cancer estimates all over world, the cancer burden has not dwindled. Nowadays, over 20 million of people live with cancer and the World Cancer Report underlines that cancer rates are set to increase at an alarming rate globally, with more than 10 million new cases each year. It is estimated that the number of new cancer cases each year could rise even by 50 percent, from nearly 11 million in 2002 to 15 million in 2020 and 19 million by 2030, with more than a quarter of deaths being attributable to cancer, chiefly because of the ageing population. The WHO's cancer Research Agency scientists estimate that in 2006, there were 3.2 million new cases of cancer (up from 2.9 million in 2004) and 1.7 million deaths from the disease in the whole of Europe, with 300,000 new cases diagnosed each year, according to the new estimates published by IARC in Annals of Oncology, in February 2007.

In patients with cancer, pain is probably the most common and one of the most feared and burdensome
symptoms. Tragically, in our society, cancer pain is undertreated, due to fear of using opioid therapy. Patients with cancer are faced with multiple painful diagnostic-therapeutic events and pain problems occur in the long interval between disease diagnosis and termination of treatment, with many terminally ill patients experiencing severe pain in the last weeks or days of their life. Early reports on the prevalence of cancer pain draw attention to high figures ranging from 52 to 77 percent (24-60 percent in patients on active anticancer treatment and 62-86 percent in patients with advanced cancer). In 1985, Bonica et al. evaluated the prevalence of cancer pain worldwide by extrapolating the prevalence rates retrieved from 47 selected reports published in 15 countries. The mean pain prevalence in patients with various stages of cancer was 50 percent. In patients with advanced/metastatic/terminal cancer, the percentage was 71 percent. Almost two decades later, in a report combining weighted mean prevalence of pain in patients with all/various stages versus patients with metastatic or terminal disease, prevalence rates of pain were 40 percent (range 18-100 percent) and 74 percent (range 53-100 percent) in the referred categories, respectively.

In 2007, van den Beuken-van Everdingen et al. aimed to present a literature overview of epidemiological data on cancer-related pain during the period 1966 to 2005. They concluded that pain prevalence rates were 53 percent in patients with cancer of all stages, 59 percent in patients after anticancer treatment, 64 percent in patients with advanced, metastatic or terminal disease and surprisingly more than 30 percent (33 percent) in patients after curative treatment, with more than one-third of the patients grading their pain as moderate or severe. At present, no definite conclusions can be drawn about the real extent of the pain suffered by oncology patients, but it can be for sure that analgesic treatment is inadequate in a proportion of up to 42-51 percent of patients, whereas 30 percent of them receive no analgesics at all.

These high prevalence figures contrast sharply with the rapidly increasing interest in pain and pain relief in the past decade. Apparently, the greater insight into the pathophysiological mechanisms of pain and the wider availability of antinociceptive therapies has not influenced the prevalence of pain in patients with cancer. Moreover, WHO introduced a pain ladder, which is accepted worldwide (1986). (Figure 1) Combined with appropriate dosage guidelines, it should be able to provide tools for adequate pain relief in 70-90 percent of the patients. Despite clear WHO recommendations, cancer pain remains a major problem with a marked or even destructive impact on the quality of life of people with malignant disease and of their families. Since one-third of population will die from cancer, and of these up to 80 percent will experience severe pain in the final year of life, effective treatment of cancer related pain remains a priority and an ongoing challenge in clinical practice.

PRINCIPLES OF EFFECTIVE PAIN CONTROL IN PATIENTS WITH CANCER—THE NEED FOR OPIOID ROTATION

But is significant pain with cancer inevitable? No. The majority of patients can obtain pain relief if available drug and non-drug treatments are used properly. Three principles should be followed in pain control provision in patients with cancer. First, pain can be controlled in most patients by following the WHO step-care approach. Second, acute or escalating pain is a medical emergency requiring prompt attention. A delay in responding to this pain makes it more difficult to control. Third, addiction is not an issue in patients with terminal illness. When pain is treated appropriately, addiction problems are rare.

WHO analgesic ladder sought to promote a universal stepwise increase in potency of analgesics prescribed. In addition, emphasis was placed on tailoring prescribing to each individual and encouraging the use of regular analgesia, by the oral route, with regular review and dose escalation, in order to achieve and maintain good pain control. To maintain freedom from pain, drugs should be given “by the clock,” that is every 3-6 hours, rather than “on demand.” Although the recommendations for each step of the analgesic ladder have not been individually evaluated in random, controlled clinical trials (RCTs), the use of the analgesic ladder as a treatment strategy has been validated in the clinical setting, with up to 88 percent of patients obtaining satisfactory relief from pain. It is now widely accepted in clinical practice.

Individuals with moderate to severe cancer-related pain require treatment with strong analgesics, namely opioids. According to the WHO guidelines, opioid analgesics are the mainstay of cancer pain management. Most patients can be effectively managed if guidelines are systematically applied. One of the most important of these guidelines calls for individualization of the opioid dose through a process of gradual dose titration. Specifically, the dose should be increased in steps until,
either adequate analgesia is attained, or intolerable and unmanageable side effects occur.\(^{21,22}\)

Oral morphine has been widely used for treating pain of moderate to severe intensity, and remains the preferred first choice to many clinicians for its familiarity, availability and costs, rather than proven superiority. However, at present, there is little evidence to support the use of one strong opioid over another in the treatment of cancer related pain,\(^{23}\) as few RCTs have been undertaken to directly compare opioids and smaller trials are underpowered.

Drug company trials have focused on acute and/or chronic nonmalignant pain and care should be taken when extrapolating data from those trials to support use in patients with cancer who by nature are less well and often taking multiple concomitant medications. Therefore, the decision by WHO and the European Association for Palliative Care (EAPC) to recommend morphine as the opioid of choice is based largely on clinical expertise and pragmatic reasons, such as the general availability of morphine sulfate worldwide and the considerable experience in using this drug.\(^{20,23}\) A significant proportion of patients treated with oral morphine do not have successful outcomes, either because of intolerable adverse effects, inadequate analgesia, or a combination of both, because of drug-related, dose-related, route-related and patient-related factors, in addition to drug interactions.\(^{20,24}\) These patients are often "switched" to alternative strong opioids. Using this approach, the reporting clinicians have described improvement in cognitive impairment, sedation, hallucinations, nausea, vomiting, and myoclonus.\(^{24}\)

Opioid switching, or changing from morphine to an alternative opioid, is a therapeutic maneuver that is gaining popularity and is becoming established clinical practice in pain management, as a method of improving analgesic response, and/or reducing adverse side effects.\(^{25}\) Sequential therapeutic trials with different opioids can be useful in identifying the most favorable drug.\(^{26}\) The strategy of switching should not be confused with opioid rotation, which also includes the practice of simply switching to an alternative drug, either to change the route of administration or because of patient or clinician preference.\(^{20}\) However, the substitution of another opioid for a previous one, to obtain a more favorable response, largely has been reported as opioid rotation. In most terminally ill patients, escalating pain is related to progression of their disease. Tolerance of orally or parenterally administered opioids develops in some of these patients. When pain is no longer controlled on a specific regimen, or and gradual dose titration yields treatment-limiting toxicity, opioid rotation is a possible solution, with the aim of achieving a more favorable balance between analgesia and side effects. The keystone to the success of this approach is the concept of incomplete cross-tolerance between opioids.\(^{18,20,22,24,26}\)

**OPIOID ROTATION—DEFINITIONS**

In an effort to establish a broad and easy understandable definition, one could say that opioid rotation/switching/substitution is a strategy that includes changing to a different medication by using the same route of administration, maintaining the current medication, but changing the route of administration, or changing both the medication and the route of administration, because of insufficient pain management, intolerable adverse effects, need for change the administration route and economics, when treatment limiting toxicity establishes poor responsiveness. This approach is based on the clinical observation that intraindividual response varies remarkably from opioid to opioid and that a change to an alternative drug may yield a far better balance between analgesia and side effects.\(^{27,29}\)

Although opioids have no ceiling effect associated with their dosing, a more liberal use has resulted in clinical reports of very high morphine doses causing new forms of opioid neuroexcitatory toxicity in these cases. Clinicians should be prepared to be skilled in using alternative opioids. The frequency of opioid switching tends to increase in acute palliative care units, probably as a consequence of a better knowledge and an improved monitoring of the cognitive function in patients who receive higher doses of opioids than in the past.\(^{30}\) Sequential opioid trials, also called opioid rotation, or opioid switching may be needed to identify the drug that opens the therapeutic window and establishes the most acceptable and balanced analgesia/toxicity relationship.\(^{31}\)

**OPIOID RESPONSIVENESS AND OPIOID ROTATION: INDICATIONS FOR CHANGING THE DRUG OR THE ROUTE OF ADMINISTRATION**

Opioid responsiveness can be defined by the degree of analgesia achieved during dose escalation, either to intolerable side effects or to the development of adequate analgesia.\(^{26}\) Several factors can interfere with an appropriate opioid analgesic response in the course of the illness. These include the progression of the disease and the development of tolerance, the appearance of intractable side effects, the type and temporal pattern of pain, morphine metabolites, pharmacokinetic and pharmacodynamic factors, and individual factors that are not well known. Different methodologies capable of accurately predicting or monitoring opioid response have been suggested in an effort to allow researchers to speak "a common language." Tolerance is a component of the concept of opioid responsiveness. However, the assessment of analgesic tolerance in patients with cancer is constrained by numerous difficulties because of changes in the noxious stimuli with increasing activity in nociceptive pathways.\(^{26,32}\)
Consequently, the term opioid responsiveness includes the extremely large variability that characterizes the continuum of responses, going from the easy and immediate achievement of analgesia to unresponsiveness. Opioid responsiveness should not be judged on the analgesic response to one opioid and should be assessed after a trial of one or more alternative opioids. When the pain is relieved inadequately by opioid analgesics given in a dose that causes intolerable side effects, despite routine measures to control them, patients should be considered for treatment, with the same opioid by an alternative route, or with an alternative opioid administered by the same route.\textsuperscript{36,38,33}

The need to change opioid occurs in the following clinical conditions:

1. Pain is controlled but the patient experiences intolerable adverse effects.

2. Pain is not adequately controlled, but it is impossible to increase the dose due to adverse effects.

3. Pain is not adequately controlled by rapid increasing the dose of opioids, although the drug does not produce adverse effects. This last point remains controversial, as further increasing doses could potentially allow achieving the appropriate analgesia. However, a rapid opioid escalation has been recognized as a negative factor for the clinical response.\textsuperscript{30,34}

Apparently, the major indication for switching opioids is represented by poorly controlled pain with unacceptable adverse effects due to opioid toxicity, rapid development of tolerance, refractory pain, or difficult pain syndromes (Table 1). In 1995, in the first large survey on opioid rotation conducted by de Stoutz et al., the indications for opioid rotation included cognitive failure in 39 percent of patients, hallucinations in 24 percent, uncontrolled pain in 16 percent, myoclonus in 11 percent, nausea in 9 percent, and local irritation from methadone suppositories in 1 percent of patients. Furthermore, in the same study, which included 80 patients undergoing 111 episodes of opioid rotation, it was indicated that patients requiring opioid rotation had significantly more difficult pain syndromes than the patients who did not require opioid substitution. Accordingly, higher doses of opioids were used to control their pain, creating a higher risk of developing late opioid toxicity. The leading symptoms improved in 73 percent cases (69 percent in patients with cognitive failure, 66 percent in patients with hallucinations, 70 percent in patients with uncontrolled pain, 50 percent in patients with nausea and 100 percent in patients with myoclonus).\textsuperscript{35}

In a more recent systematic review of 31 reports on opioid switching, Mercadante and Bruera concluded that the more frequent indication for opioid switching was uncontrolled pain with/or adverse effects, although the distinction was not clear among studies.\textsuperscript{30} In a large multicenter survey about 12 percent of patients required a true opioid switch (excluding changes of route), because of the insufficient efficacy (64 percent), adverse effects (51 percent), or application problems (22 percent). Patient's wish, interactions between drugs, scientific or economic reasons were randomly named. Five of the six cases, in which myocloni were reported, had a true opioid switch. In only 54 of the 107 patients, with a change of the route of administration, application problems were named as a reason. Patients with little or without pain changed the upload or the route of administration less often. Patients who died during follow-up were more likely to stay on the baseline opioid and more likely to change the route of administration. Although this is far less than expected, this finding reflects the different settings, typical of palliative care. Outpatients are more likely to undergo a switch because of insufficient analgesia, whereas inpatients may switch more often because of more complex clinical conditions.\textsuperscript{36}

The decision to switch routes of administration may be driven by factors related to feasibility or responsiveness. The oral route may become unavailable because of disease-related impairments, such as dysphagia, decline in consciousness, or changes in gastrointestinal absorption. The latter concern may be relevant even in patients who retain oral intake. The influence of disorders such as peritoneal carcinomatosis, ascites, severe constipation, bowel dysmobility, and generalized mucositis on opioid absorption is undefined, and a switch to nonoral administration can eliminate this concern during a period of poorly controlled pain. Sometimes, a nonoral route is indicated despite the ongoing availability of the oral route. From a practical standpoint, a change in route might be considered to reduce the burden imposed by the need to consume large number of tablets or, possibly, improve patient compliance. From the perspective of responsiveness, a switch in route may be indicated to implement a trial of a new drug (specifically, a change to the transdermal route to provide a trial of fentanyl) as follows:

1. Try intraspinal administration when toxicity precludes systemic opioids,

2. Provide access for parenteral supplemental doses to treat breakthrough pains that have a rapid onset.\textsuperscript{37}

3. A thorough assessment will assist the clinician in determining the severity of pain and the type of pain (worsening of the same pain, development
Table 1. Clinical reasons for changing opioids

<table>
<thead>
<tr>
<th>Reasons for Changing Opioids</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Lack of efficacy</td>
<td>Worsening of existing pain or underlying disease process</td>
</tr>
<tr>
<td></td>
<td>Development of opioid analgesic tolerance</td>
</tr>
<tr>
<td></td>
<td>Inability to tolerate side effects</td>
</tr>
<tr>
<td></td>
<td>Dose required to produce analgesia exceeds APAP maximum daily dose recommendations (4 g/day) in patients on combination products (hydrocodone/APAP)</td>
</tr>
<tr>
<td>2. Development of intolerable side effects</td>
<td>Gastrointestinal (constipation, nausea, vomiting)</td>
</tr>
<tr>
<td></td>
<td>CNS (sedation, somnolence, dysphoria, hallucinations, myoclonus)</td>
</tr>
<tr>
<td></td>
<td>Cardiovascular (orthostatic hypotension due to histamine release)</td>
</tr>
<tr>
<td>3. Change in patient’s status</td>
<td>Inability to swallow</td>
</tr>
<tr>
<td></td>
<td>Poor peripheral vascular status</td>
</tr>
<tr>
<td></td>
<td>Poor absorption of transdermal medications</td>
</tr>
<tr>
<td></td>
<td>Requirements of high-dose opioids not practically administered by oral, rectal, transdermal routes</td>
</tr>
<tr>
<td>4. Practical considerations</td>
<td>Availability in local pharmacies</td>
</tr>
<tr>
<td></td>
<td>Cost</td>
</tr>
<tr>
<td></td>
<td>Amount of opioid needed</td>
</tr>
<tr>
<td></td>
<td>Route of administration</td>
</tr>
<tr>
<td></td>
<td>Opiophobia (fear of one or more of the opioids, e.g., “morphine” that may be associated with death or addiction)</td>
</tr>
</tbody>
</table>

of new pain which may not be as responsive to opioid analgesics).

If lack of efficacy is the issue, it is crucial that the clinician reassesses the patient and gives prerequisite thought to the addition of a new therapeutic class (tricyclic antidepressant, anticonvulsant) versus changing the opioid analgesic. An appropriate assessment should include a review of the clinical situation and pain syndromes, the use of an adjuvant analgesic to deal with the altered sensorium, secondary to opioid toxicity and the correction of any contributing abnormal biochemistry, including hydration status. The evaluation of the patient in pain should take into consideration physiologic characteristics as well as the impact of pain on the patient’s quality of life. The patient’s self-report should be the primary source of information, such as description, intensity, pattern, and temporal pain nature. These aspects give the clinicians the clues as to what may be the underlying pathology or mechanism of pain. The degree to which pain interferes with activities of daily living should serve as marker for how aggressively to approach this intervention.

The increasing number of reports from many centres regarding the problematic adverse effects of commonly used opioids such as morphine, particularly at high doses, and the increasing popularity and controversy over the concept of opioid rotation resulted in the European Association of Palliative Care (EAPC) forming a Working Group. This group attempted to develop evidence-based recommendations on strategies to manage adverse effects of morphine. This working group concluded that in the proportion of cancer patients who develop intolerable side
effects before achieving adequate pain relief (in conjunction with a nonopioid and adjuvant analgesic as appropriate), a change to an alternative opioid or a change in the route of administration should be considered, with a strength and consistency of evidence supporting grade of B.24

**OPIOID ROTATION—GUIDELINES AND RECOMMENDATIONS**

Opioid equianalgesic doses—Dose conversion charts

Converting from one opioid to another in opioid-responsive patients is often necessary, as dose limits of short-acting combination products are reached, or the use of a long-acting agent is desired. Knowledge of relative potency estimates is the foundation for the well-tolerated and effective conversion from one opioid to another and between routes of administration. The potency of a drug indicates the dose required to produce a given effect. Relative analgesic potency refers to the ratio of doses required, such that two analgesic drugs (actually, drugs administered by specific routes) produce the same effect.37

Thus, to find the initial dose of the new opioid, it is necessary to calculate the “equianalgesic dose,” or the dose most likely to provide the same pain relief.

The most important problem raised from opioid switching literature is the conversion ratio among opioids in patients presenting a poor opioid response, with an unfavorable balance between analgesia and adverse effects. Most equianalgesic conversion data presented in reference tables are derived from older studies, not optimally designed for clinical application in dose conversion, including single dose studies and studies that were not designed for the detection of relative opioid potencies.30,36

Many times opioid equianalgesic conversion dosing recommendations emerged as secondary observations, made by the investigators.38

Equianalgesia refers to the ratio of the doses of two opioids, required to produce the same analgesic effect. Experience from bioequivalence testing suggests that is useful to distinguish two clinical settings, termed prescribability and switchability.39 The former refers to prescription of a drug for the first time. In this case the response to the drug has been well characterized, including the large variability in individual response. The latter refers to transferring a patient from one drug to another. Different criteria, termed population and individual criteria, can address prescribing and switching equivalence questions respectively.40 In clinical setting, equianalgesia is an impractical concept, as it refers to the same analgesia level when passing from one opioid to another, which is not the real clinical goal in daily practice and also because it does not take into account adverse effect changes. An initial conversion ratio is a more acceptable definition to apply to opioid switching.26

If one accepts opioid switching as a recommended therapeutic maneuver, the underlying implication is that there is a true clinical difference among different opioids. Guidelines for opioid rotation are intended to reduce the risk of relative overdosing or underdosing, as one opioid is discontinued and another is administered. These guidelines require a working knowledge of an equianalgesic dose table/initial conversion ratio table, as it is very well depicted in Tables 2 and 3.18,20,22,30-32,36,41-45 Such a table “ideally” provides evidence-based values for the relative potencies among different opioid drugs and routes of administration. The values were derived from well-controlled, single-dose assays conducted in cancer populations with limited opioid exposure.33,46 The dose table simplifies comparisons by describing all potencies relative to a standard, which is defined as morphine 10 mg parenterally.18,22

Nevertheless, equianalgesic doses are recommendations for the initial dose selection,44 and should be used only as an initial estimate due to the following reasons:

1. Ratios are primarily derived from studies not originally designed to evaluate equianalgesic dosing.

2. Most have wide confidence intervals and large standard deviations (SDs).

3. There exists a large interpatient variability. Some patients need much lower or higher doses than expected.

4. There is incomplete cross tolerance among opioids. Patients who have been on chronic, high-dose opioid therapy may be particularly sensitive to a new opioid.

In clinical practice, a dose ratio of oral morphine:oxycodone of 2 is often used. In a study of 44 patients who were recruited as part of a retrospective clinical trial to evaluate opioid switching, the median dose ratio of morphine:oxycodone was 1.7, the range from the individual patient data was large, 0.25-12.47 This illustrates the need to use conversion tables as a guide, in addition to doses titration for individual patients. Such problems are accentuated with opioids such as methadone, which is stored in the adipose tissue and has a rapid distribution phase following oral administration, followed by a slow elimination phase, with slow transfer between tissue stores and plasma.20

In addition to the lack of relative potency information during long-term therapy, other factors underscore the tentative nature of the equianalgesic dose table. The relative potencies codified in the tables mentioned above, were derived from data that were acquired from selected populations and then interpreted to yield meaningful
Table 2. Opioid analgesics used for severe cancer pain: Equianalgesic doses

<table>
<thead>
<tr>
<th>Agents</th>
<th>Duration of action (hours)</th>
<th>Half-life (hours)</th>
<th>Parenteral dose (mg) im = sc = iv</th>
<th>Oral/rectal dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>2-4 to 3-6, 8-12 for morphine CR, 24 for morphine SR</td>
<td>1.5/2-3</td>
<td>10</td>
<td>20-30 up to 60*</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>4-6 to 8-12 for oxycodone SR</td>
<td>2-3</td>
<td>15</td>
<td>20-30</td>
</tr>
<tr>
<td>Hydromorphone**</td>
<td>4-5</td>
<td>2-3</td>
<td>1.3-1.5</td>
<td>4-7.5, mostly 7.5</td>
</tr>
<tr>
<td>Levorphanol***</td>
<td>6-8</td>
<td>12-15/16</td>
<td>2 for acute setting and 1 for chronic users</td>
<td>4 for acute setting and 1 for chronic users</td>
</tr>
<tr>
<td>Oxymorphone*</td>
<td>4-6</td>
<td>2-3</td>
<td>1</td>
<td>2-20*; short-term use; 20 chronic dosing 2-4*</td>
</tr>
<tr>
<td>Methadone†</td>
<td>4-6</td>
<td>15-30 to 150</td>
<td>1-10 (mostly im); short-term use; 5-10 chronic use 1-4*</td>
<td>N/A</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>4-8</td>
<td>3.3-4.5</td>
<td>N/A</td>
<td>20-30</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>1-3 to 4, 48-72 for TTS</td>
<td>1.5-6, 16-24 for TTS</td>
<td>0.1-0.2 (im, iv) can be administered as continuous iv or sc infusion</td>
<td>N/A 100 µg/h fentanyl TTS = 4 mg/h morphine iv TTS fentanyl^A; 1 µg fentanyl TTS = 2 mg/day morphine po IONSYS iontophoretic transdermal system ACTIQ sublingual fentanyl</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>N/A</td>
<td>N/A</td>
<td>0.4</td>
<td>0.8</td>
</tr>
<tr>
<td>Codeine</td>
<td>4-6</td>
<td>3</td>
<td>120-130</td>
<td>200</td>
</tr>
<tr>
<td>Propoxyphene</td>
<td>4-6</td>
<td>6-12</td>
<td>N/A</td>
<td>130-200^IV</td>
</tr>
<tr>
<td>Meperidine†</td>
<td>2-4</td>
<td>3-4</td>
<td>75</td>
<td>300</td>
</tr>
</tbody>
</table>

Abbreviations: im, intramuscular; iv, intravenous; sc, subcutaneous; po, oral; N/A: not available for administration by that route. Morphine is the standard for comparison of opioids with multiple formulations available. The equianalgesic dose is the dose that provides analgesia equivalent to 10 mg of parenteral morphine. In clinical practice, the potency of the intramuscular route is considered to be identical to the intravenous and subcutaneous routes. iv route is the most common route used in clinical practice. The most common side effects of morphine are constipation, nausea, sedation. Respiratory depression is rare in cancer patients. Equianalgesic table is used on the horizontal axis to switch route of administration and on the vertical axis to switch between opioids.

*Extensive survey data suggest that the relative potency of intramuscular: oral morphine, which has been shown to be 1:6 in an acute dosing study, is 1:2-3 with chronic dosing.

**Survey data suggest that the relative potency of hydromorphone intramuscular: oral is 5:1 in an acute dosing setting but may change to 3:7:1 with chronic dosing.

***Long half-life with accumulation occurring after treatment beginning or dose increase.

†Oxymorphone immediate release and oxymorphone extended released tablets have been approved by the FDA.

‡Racemic mixture contains d-isomer, an NMDA antagonist that is probably the cause of potency greater than indicated by the equianalgesic table. Try to reduce equianalgesic dose by 75-90 percent and be aware that long half-life can lead to delayed toxicity after beginning treatment or increasing dose, particularly when patients have been receiving other opioids for long periods of times and at high doses. Estimates put the equianalgesic ratio of po morphine to po methadone at 1:4-1:1.

^Oxymorphone immediate release and oxymorphone extended released tablets have been approved by the FDA.

^A The dose of transdermal fentanyl in µg/h is approximately 1/2 the 24-hour dose of oral morphine. A ratio of oral morphine: TTS fentanyl is indicated to be 70:1 (previously it was supposed to be 100:1).
<table>
<thead>
<tr>
<th>Drug name</th>
<th>Available dosage</th>
<th>Equianalgesic dose</th>
<th>Oral to perenteral dose ratio</th>
<th>Dosing interval (hours)</th>
<th>Strengths of products (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>30, 10</td>
<td>3:1</td>
<td>CR 12</td>
<td>MSContin 15, 30, 60, 100, 200 mg tablets; Oramorph 15, 30, 60, 100 mg tablets</td>
<td></td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>7.5, 1.5</td>
<td>5:1</td>
<td>IR 4</td>
<td>Dilaudid 1, 2, 3, 4 mg Tab., Liq., Supp.</td>
<td></td>
</tr>
<tr>
<td>Oxycodone</td>
<td>15</td>
<td>N/A</td>
<td>N/A</td>
<td>CR 12</td>
<td>Oxycontin 10, 20, 40, 80 mg</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>30</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Vicodin (hydrocodone bitartrate, acetaminophen); Vicodin 5 (5 mg/500 mg); Vicodin 7.5 (7.5 mg/750 mg); Vicodin 10 (10 mg/660 mg)</td>
</tr>
<tr>
<td>Codeine</td>
<td>200, 130</td>
<td>1.5:1</td>
<td>N/A</td>
<td>15, 20, 60 mg tablets. Doses exceeding 65 mg are not recommended due to increasing constipation side effects.</td>
<td></td>
</tr>
<tr>
<td>Meperidine</td>
<td>300, 75</td>
<td>4:1</td>
<td>N/A</td>
<td>Demerol 50, 100 mg tablets, syrup. Not recommended for administration &gt;48 hours, or for cancer pain management.</td>
<td></td>
</tr>
<tr>
<td>Levorphanol</td>
<td>4, 2</td>
<td>2:1</td>
<td>6-8</td>
<td>Levo-Dromorar 2 mg tablets. Long half-life: must be used with caution to avoid delayed accumulation.</td>
<td></td>
</tr>
<tr>
<td>Methadone</td>
<td>Variable during titration</td>
<td>N/A</td>
<td>5, 10, 40 mg Tab., Liq. Very good for neuropathic pain. Long half-life must be used with extreme caution to avoid accumulation.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fentanyl</td>
<td>Refer to conversion</td>
<td>Refer to conversion</td>
<td>N/A</td>
<td>72 hours</td>
<td>Duragesic 25, 50, 75, 100 μg patch. It is necessary to also use a breakthrough medication.</td>
</tr>
</tbody>
</table>

**Principles of Administration**

- **WHO Ladder**
  - For mild pain (unless contraindicated) use aspirin, acetaminophen, or nonsteroidal anti-inflammatory agents.
  - If pain persists from mild to moderate pain use Percocet, Tylenol #3, Vicodin, or Oxycodone.
  - If pain continues or becomes moderate to severe, increase the opioid (i.e., morphine, dilaudid, and oxycontin).
  - Adjuvant medications are added to medication regimen as indicated on adjuvant medication list.
  - Breakthrough dose: 1/3 to 1/2 of the 12-hour dose or 10-15 percent of the 24-hour dose.
  - Titrating dosage:
    - Calculate increase based upon total opioid dose (ATC + Breakthrough) taken in the previous 24-hour period.
    - Increase both the ATC and breakthrough doses.
  
  Or
  
  B. Use the following guidelines:

<table>
<thead>
<tr>
<th>Pain</th>
<th>Increase dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 7</td>
<td>by 50 to 100 percent</td>
</tr>
<tr>
<td>4-7</td>
<td>by 25 to 50 percent</td>
</tr>
<tr>
<td>&lt; 4</td>
<td>by 25 percent</td>
</tr>
</tbody>
</table>

  - Once a patient has 2 or less breakthrough doses and a steady state of medication has been reached, then a continuous release equianalgesic opioid may be initiated. Always start with an instant release before switching to continuous release.

  - Switch from fixed combination opioids to a single-entity opioid when acetaminophen dose > 4000 mg/day.

  - **Conversion equation:**
    - Equianalgesic dose (route) Current opioid = Equianalgesic dose (route) Desired new opioid
    - 24h dose (route) current opioid
    - 24h dose (route) desired new opioid

  

  CR, continuous release; IR, instant release.

Created by the Safe Conduct Team of the Safe Conduct Project, Ireland Cancer Center, The Hospice of Western Reserve Copyright 2000 RWJ Foundation Demonstration Project, Reprinted with permission.
estimates from broad distributions, which could then refer to total effect, peak effect, or duration of effect. The data pertaining to parenteral administration were largely acquired through studies of the intramuscular route and subsequently extrapolated to the intravenous and subcutaneous routes. Thus, although the studies that provided the data for the equianalgesic dose tables were carefully controlled, and still represent the state of the art in single-dose analgesic trials methodology, the extrapolation of these data to the clinical settings requires caution. The findings of other studies that have provided relative potency estimates also must be interpreted cautiously. A very small number of studies suggest that the potency of rectally administered opioids is comparable with that achieved when the drugs are given by the oral route. Few rectally administered drugs have been studied, the influence of long term therapy is unknown and the impact of various physiological factors (such as variability in rectal venous drainage) has not been empirically evaluated.\(^\text{37,46}\)

The reason for switching may influence the doses to be chosen. Patients switched due to convenience are different from patients switched due to uncontrolled pain, which are different from patients with adverse effects and controlled pain, who are different from patients with uncontrolled pain and adverse effects. Opioid conversion should not be a mere mathematical calculation, but just a part of a more comprehensive patients' assessment of the actual opioid therapy, evaluating the underlying clinical situation, pain and adverse effect intensity, comorbidity, concomitant drugs, and excluding any possible pharmacokinetic factor that limits the effectiveness of a certain drug.\(^\text{30,38}\) Furthermore, one should have in mind patients' age, since elderly patients with cancer require a lower amount of opioid analgesia than younger adults, with a ratio for age <65, 65-74, and 75 about 1:1/2:1/3.\(^\text{48}\)

Nevertheless, questions concerning the validity of relative potency estimates should not be construed as justification to dismiss the utility of this information when converting from one opioid drug or route administration to another. Rather, they are a reminder to the clinician about the need for prudence and careful monitoring of effects when changing opioid therapy.\(^\text{37}\) Monitoring is crucial, particularly when patients are switched from high doses of opioids.\(^\text{30,40}\) Prudence and monitoring are foundations for all aspects of opioid therapy and indeed, would be required during dose and route conversions, even if there were no concerns about the validity of relative potency estimates.\(^\text{37}\) Given the wide conversion ratios reported in the literature, the process of reaching an optimal dose should be highly individualized.\(^\text{30}\)

**Opioid rotation: Principles, protocols and dose-conversion steps selecting a starting dose and a new administration regimen: general principles**

The primary goal of opioid rotation protocols is to find a safe starting dose of the new opioid. The regimen is then titrated to the individual patient's needs using a combination of a scheduled dose and liberal use of "rescue" doses. Safe opioid rotation adheres to specific principles, which are presented as sequential steps in Tables 4-6.\(^\text{22,24,37}\) The process of decision making that

<table>
<thead>
<tr>
<th>Table 4. Guidelines for switching and rotating opioids</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Guidelines for Switching and Rotating Opioids</strong></td>
</tr>
<tr>
<td><strong>1. Use dose-conversion tables.</strong> When switching from one opioid to another in naïve patients, dose-conversion tables are used to calculate the dose of the new opioid. Ensure that the table being used relates to the management of chronic pain. Tables used in acute pain management generally depict single-dosing, which cannot be applied in the chronic pain setting. In tolerant patients, the possibility of incomplete cross-tolerance makes the use of a simple conversion on the basis of dose-conversion tables potentially hazardous.</td>
</tr>
<tr>
<td><strong>2. Dose-conversion tables are guidelines only.</strong> It must be noted that the values depicted in dose conversion tables are guidelines only. There exists large interindividual variability in response to various opioids and this variability cannot be captured in these tables. Recent studies indicate a wide range of dose ratios relative to morphine. However, with the exception of methadone, current literature does not clarify the exact ranges. A suggestion, which is not supported by strong evidence, would be to decrease the dose of the new opioid by an additional 30 to 50 percent. This would accommodate the variability in most cases and address the phenomenon of a lack of complete cross-tolerance when switching from one opioid to another.</td>
</tr>
<tr>
<td><strong>3. Dosing with the new opioid.</strong> The initial goal when switching opioids is to convert the patient to the new drug safely. As noted earlier, incomplete cross-tolerance may result in a patient who is far more sensitive to the new agent than expected. Thus, it is suggested that clinicians be conservative in their calculations when switching between opioids. It is advisable to start at doses of the new opioid lower than those predicted by the dose-conversion tables, monitor patients closely during the switch-over period and titrate to clinical effect. If pain is not well controlled, the dose can be increased, whereas if the patient experiences adverse effects such as excessive somnolence, the dose may need to be titrated down. It is always better to start at a lower dose and then titrate upward than to start with a dose that is too high. Close monitoring of patients during the switch is crucial.</td>
</tr>
</tbody>
</table>

From Cherny et al., J Clin Oncol 2001; 19: 2542-2554.\(^\text{24}\) Reprinted with permission © 2008 American Society of Clinical Oncology. All rights reserved.
### Table 5. Principles—Empirical steps for opioid rotation

| Step 1 | Use a consistent method or protocol |
| Step 2 | Detailed Patient Assessment |
| Step 3 | Calculate the total daily dose of the current opioid |

#### Starting Cutoff Point

Select a new opioid.

#### Calculate the equianalgesic dose (ED) of the new opioid using an equianalgesic dose-conversion table.

Consistently use the same equianalgesic table for dose calculating.

There may be slight differences from one table to another.

#### Determine the clinically relevant starting point

If switching to any opioid other than methadone or fentanyl, decrease the equianalgesic dose by a standard percentage (25 to 50 percent), which is the 24-hour starting dose. This is done to account for the following: Incomplete cross-tolerance between opioids, Variations in patients’ metabolism, Limitations of equianalgesic tables.

If switching to methadone, reduce the dose by 75 to 90 percent.

If switching to transdermal fentanyl, do not reduce the equianalgesic dose.

Reducing the calculated dose may not be necessary when route alone is being changed.

When rounding, round downward.

#### Daily Dose and Dose Unit

Establish the regular daily dose of the new opioid.

Divide the 24-hour starting equianalgesic dose (ED) by number of doses per day

This is the scheduled dose or equianalgesic dose unit (EDU).

#### Dose Adjustment

Consider further changes in the adjusted equianalgesic dose based on medical condition and pain.

If the patient is elderly or has significant cardiopulmonary, hepatic, renal disease, consider further dose reduction.

If the patient has severe pain, consider a lesser dose reduction, if there is no substantial risk of exaggerated opioid toxicity.

Reduce more if the patient experiences significant opioid adverse effects or is medically frail.

#### Continuous Frequent Pain

Drug administration on an “around-the-clock” basis.

(continued)
<table>
<thead>
<tr>
<th>Step</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Breakthrough Pain</strong></td>
<td>Order liberal and adequate breakthrough dosing and titrate to comfort. Coadminister rescue dose using the same drug if feasible, use an alternative short-acting drug if necessary. Calculate a rescue dose as 5 to 15 percent of the total daily (24 hours) opioid dose and administer at an appropriate interval (usually available at q1 hour). When administering a continuous infusion, rescue dose is 25 up to 50 percent of the hourly rate. The exception is oral transmucosal fentanyl citrate (ACTIQ), which should always be started at a dose of 200 or 400 μg.</td>
</tr>
<tr>
<td><strong>Step 9</strong></td>
<td><strong>Monitoring</strong></td>
</tr>
<tr>
<td></td>
<td>Monitor patient closely for the following: balance of analgesia, function, side effects.</td>
</tr>
<tr>
<td><strong>Step 10</strong></td>
<td><strong>Dose Adjustment—New Scheduled Dose</strong></td>
</tr>
<tr>
<td></td>
<td>Adjust the scheduled dose after 24 hours based on total opioid intake (scheduled and rescue doses) over the previous day. Recalculate scheduled dose of total opioid in 24 hours (scheduled + rescue)/doses per day = new scheduled dose.</td>
</tr>
<tr>
<td><strong>Step 11</strong></td>
<td><strong>Dosage Escalation</strong></td>
</tr>
<tr>
<td></td>
<td>At an interval appropriate to the severity of the pain and the pharmacology of the drug and route. Increase the dosage at intervals long enough to ensure steady state has been approached since the last dosage change. Increase the dosage by the quantity of rescue drug consumed or by 30-50 percent.</td>
</tr>
<tr>
<td><strong>Step 12</strong></td>
<td><strong>Reassessment—Titration</strong></td>
</tr>
<tr>
<td></td>
<td>Reassess and titrate the new opioids according to the therapeutic response, side effects. Titrate the dosage until adequate analgesia appears. Or intolerable and unmanageable side effects supervene. Titrates rescue doses proportionally to the total 24-hour dose.</td>
</tr>
<tr>
<td><strong>Step 13</strong></td>
<td><strong>Continue Frequent Assessment—Adverse Effects Assessment and Treatment</strong></td>
</tr>
</tbody>
</table>
ultimately leads to the selection of a new opioid drug or route of administration must be filtered through the complex vagaries, which is inherent in the long-term management of patients with chronic medical illness. The overall objective, which is to provide comfort in a manner that enhances the quality of life and is consistent with the goals of care, will be more attainable if all these considerations are addressed on an ongoing basis.37

An important step in opioid rotation is to determine the patient's current total daily opioid utilization. This can be accomplished by adding up the doses of all long-acting and short-acting opioid doses consumed per day. If the patient is on multiple opioids, it is wise to convert all to morphine equivalents using standard equianalgesic tables.38 The equianalgesic dose table provides only a broad guide for dose selection, when a switch from one opioid to another is contemplated.37,49 Then each one is added together to derive a total daily dose in morphine equivalents. This method is usually chosen, as most equianalgesic data in reference tables are derived from multiple studies, which often used morphine as the sole comparator.38,45

Next, the clinician needs to ask the patient about previous experiences, if any, with other opioids, before deciding which will be the next opioid considered. During this line of questioning it may be possible to determine both the potential efficacy of and the patient's ability to tolerate other opioids. Ultimate selection of the opioid will also be based on several additional patient considerations, including route of administration, possibility of drug-drug or drug-disease interactions, dosage forms, relative cost and availability of the same drug in either, or both, a long-acting and short acting form.38 Once the previously calculated total daily opioid dose, in morphine equivalents, has been used to determine the dose range of the new opioid, acquired patient specific information should serve as a guide for making patient specific adjustments to dose.21,38,41

In most cases, the calculated dose equivalent of a new drug must be reduced to ensure safety. Based on clinical experience, the starting point for dose reduction from the calculated equianalgesic dose is 25-50 percent. There are several reasons for this. First, there is a potential for incomplete cross tolerance between opioid drugs. This would lead to effects (including adverse effects) that would be greater than expected, when a switch to a new drug is made. Second, because of the large interindividual variability in the relative potencies among opioids, the ratios listed in the equianalgesic table may be more or less than the ratio that would be found if a single-dose study was performed in the individual patient. Third, there is a need to adjust treatment for conditions that increase opioid risk, such as advanced age and medical co morbidities.

There are two exceptions to the guideline that dose reduction from the calculated equianalgesic dose should start at 25-50 percent. The first exception occurs with conversion to a transdermal fentanyl system (TFS or TTS fentanyl or fentanyl patch). As it will be analyzed later on, in the development of this formulation, conversion guidelines were developed that incorporated a safety factor, obviating the need for additional dose reductions in most patients.22

The second exception occurs with conversion to methadone. A larger reduction in the calculated equianalgesic dose, specifically 75-90 percent, is justified by data that demonstrate a much greater potency than expected, when switching to methadone from another pure mu agonist, such as morphine.22,29 Indeed, some data indicate that the potency of methadone following a switch to a new drug is depended on the dose of the prior drug.20

Once the calculated equianalgesic dose is reduced by 25-50 percent (75-90 percent in the case of methadone), further dose adjustments might be considered based on medical condition and the degree of unrelieved pain. For patients who are elderly or have significant cardiopulmonary, hepatic, or renal disease, the new opioid may be reduced by more than 50 percent. In contrast, if a patient reports severe pain, the new dosage may be administered at the calculated equianalgesic dosage, foregoing the usual percentage reduction, or even increasing the calculated dose of the new opioid by 25-50 percent.22,38 The ultimate decision of whether to be conservative or aggressive is

<table>
<thead>
<tr>
<th>Table 6. Switching from an IR opioid regimen to SR opioids and vice versa—Practical recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Changing from an IR opioid regimen to SR opioids</strong></td>
</tr>
<tr>
<td>Step 1</td>
</tr>
<tr>
<td>Step 2</td>
</tr>
<tr>
<td>Step 3</td>
</tr>
<tr>
<td>Step 4</td>
</tr>
</tbody>
</table>

| **Changing from an SR opioid regimen to IR opioids** |
| Step 1 | Calculate the total daily dose of the SR opioid. |
| Step 2 | Calculate the q4-hour and breakthrough dosing, based on the SR opioid daily total. |
| Step 3 | Start the IR opioid 12 hours after the last SR opioid dose. |
| Step 4 | Order available breakthrough dosing to cover the transition interval. |

Abbreviations: IR opioid: instant release opioid; SR opioid: slow release opioid; q4: every 4 hours.
dependent upon the acuity of the situation, the degree of 
existing opioid tolerance and the patient’s environment,
such as whether or not a trustworthy caregiver is avail-
able to help in evaluation of opioid-related adverse 
effects (eg excessive sedation). \textsuperscript{38}

Patients should be continually reassessed to determine 
both response to therapy and tolerability of the new 
agent. Patients should be followed closely for the first 
7 to 14 days after a medication change takes place. It is 
common for the need to adjust a new long acting opioid 
dose up or down during the initial 24 to 48 hours after 
conversion. It is helpful to have patients keep a diary of 
the amount of short acting medication they use each day,
as rescue or breakthrough pain dosing, their average 
daily pain intensity and the amount provided by break-
through doses. This information is paramount to assisting 
with early dosage adjustments in the period immediately 
following opioid transition, to permit fine tuning of the 
new regimen.

Rescue and breakthrough pain dosing

Once the total daily dose of the new opioid, or the 
previous opioid by a new route, is selected, an adminis-
tration regiment should be designed to accommodate the 
specific needs of the patient.\textsuperscript{21,28} Patients with continuous 
or frequently recurring pain should receive a scheduled 
dose ("around the clock"), or if parenteral therapy is initi-
ated, a continuous subcutaneous or intravenous infusion.
A key component of the redesigned regimen is the provi-
sion of access to an immediate release (short-acting) opi-
oid in the event the patient needs more relief during the 
first 24 to 48 hours after conversion. A short-acting opioid 
provides the patient a means to “rescue” for acute 
episodes of pain, which supercede the level of analgesia 
provided by the long-acting opioid during the titration 
phase, or to cover episodes of incident pain, end-of-dose 
failure, or breakthrough pain, three types of episodic pain.
Most patients benefit from access to supplemental dose, 
which is offered on an “as needed” basis for the manage-
ment of intermittent breakthrough pain (often called a 
“rescue” dose). Usually the drug given around the clock 
is also used for the rescue dose. The exceptions to this 
practice are methadone and transdermal fentanyl, which 
are usually coadministered with an alternative short-acting 
opioid as the rescue dose.

As with opioid conversion, there is no standard accepted 
method for determining the exact rescue or breakthrough 
dosage. Expert consensus has derived rules of thumb to 
calculate a safe and effective dose. Oral rescue doses 
should be made available every one to two, up to 4 hours 
as needed, while parenteral doses can be offered every 
30-60 minutes. Based on clinical experience, the expert 
consensus suggests that the size of the rescue dose is 
usually calculated as 5-15 percent of the total daily opioid 
dose, or 25-30 percent of the incremental, single standing 
dose.\textsuperscript{31,37,38,50,51} Those patients with mild baseline pain 
and severe breakthrough pain may be treated with a 
relatively larger rescue dose, and the few patients who 
experience chronic pain appear to benefit from an “as 
needed” regimen alone.\textsuperscript{37} The ideal goal should be to 
have the patient on the same opioid, in both long-acting 
and short-acting form, to minimize the need to work with 
imprecise conversion ratios, if further titration is required.

Dose titration

At the start of the therapy with a new drug or route of 
administration, patients must be monitored carefully and 
frequently for pain relief and adverse effects. Dose titra-
tion is almost always needed soon after a switch. The rate 
of dose titration depends on pain severity, presence and 
degree of adverse effects, route of administration, phar-
macokinetic factors and the setting of treatment. The 
need to undertake rapid changes in the fixed schedule 
dose is usually obviated by the availability of the rescue 
dose. The availability of the rescue dose also reduces the 
risk of unrelieved pain that would otherwise be associ-
ated with the selection of a conservative dose at the time 
of conversion to a new drug or route.\textsuperscript{37}

Titration of the scheduled regimen should preferably 
be performed after a period that is long enough for the 
steady-state to be approached, following the previous 
change (4 to 5 half-lives for all immediate-release opioids 
and 2 to 3 days for controlled-release oral or transdermal 
formulations). The size of the increment in the scheduled 
regimen can be determined by the number of rescue 
doses required since the start of the therapy, or the last 
dose adjustment, or, often more conservatively, by arbi-
trarily choosing an increment of 30-50 percent. It is usu-
ally necessary to increase the rescue dose proportionately, 
so that it remains 5-15 percent of the total daily dose.\textsuperscript{37,38}

Dose titration, in this manner, is necessary whenever 
algesia is ineffective. There are no ceiling doses for the 
use of pure \mu-receptor agonists and dose escalation is limited 
only by the occurrence of adverse effects. The treatment 
of these effects, such as constipation, nausea and somno-
lence, is therefore essential to optimize opioid therapy. 
As it has been clearly mentioned and underlined up to 
now, the goal of dose escalation is to identify a regimen 
associated with a favorable balance between analgesic 
and adverse effects.\textsuperscript{37}

Frequency of opioid switching

In several retrospective studies rotation rates between 
20 and 44 percent were found without defining the kind 
of switches or the patient population.\textsuperscript{29,35,36} Comparing 
frequencies of opioid switches in different patient popu-
lations, reasons for changing the administration route
and/or switching the opioid must be differentiated from the true switch, in case of switching only long-acting opioids. Muller-Busch et al., in 2002, reported a switch rate of 15.7 percent with different frequencies in the respective baseline opioids in a retrospective study of patients in his palliative care unit.56

Opioid use was assessed in a prospective cohort study of 412 palliative care patients from 14 inpatient and outpatient palliative care facilities in Germany, by the team of Muller-Busch et al. They concluded that frequencies of changes in medications were found to be largely shaped by the setting reflecting patients' needs and clinical necessities. Nevertheless, in the palliative care setting, population additional aspects as patient's choice, cost effectiveness, and scientific reasons for a switch stayed back behind efficacy, tolerability, and application necessities.56

CLINICAL EXPERIENCE SWITCHING THE OPIOID

Drug selection

Few studies have evaluated the outcomes of sequential opioid trials and there are no specific data from which to infer the optimal order of administration.57 Generally, clinical observations suggest that the choice of the opioid depends on the intended route of administration, pain severity, evaluation of patients' compliance, concomitant symptomatology, as well as the availability and the costs of a specific opioid formulation in different settings of care.36,37,52,53 The selection of the baseline opioid, but also its change have to reflect all these aspects.

For example, the severity of pain may influence the selection of a new opioid. If pain is severe, the conventional short half-life opioid drugs, such as morphine, hydromorphone and oxycodone, are usually preferred. Rapid dose-titration is simplified when steady-state plasma concentration can be approached quickly. On the other hand, patients' characteristics must be assessed carefully if methadone treatment is being considered. Methadone, as it is extensively analyzed later on, is usually avoided in elderly patients, prone to opioid toxicity, also having problems of compliance or/and monitoring.57

Toxicity may increase over time without any change in the opioid dose. Patients with cancer can develop severe, persistent adverse effects, even if they are receiving only small doses of morphine. Opioid metabolites have been claimed to generate these late effects. Moreover, dehydration can lead to a reduced intravascular volume and slower glomelular filtration, resulting in renal failure. Hydration can reverse states of confusion and can facilitate metabolite elimination, promoting diuresis, when switching to an alternative opioid. The reduction of the opioid dose may result in symptom improvement. However, pain becomes uncontrolled in most cases. Dissimilar side effect profiles and completely different intensity of side effects at any given level of analgesia have been reported in patients undergoing treatment with apparently comparable drugs.26

Additionally, a potential disadvantage of morphine up to now is that it is not available in a transdermal formulation. Transdermal fentanyl and buprenorphine were included in the group of long-acting opioids, in spite of their different route of administration and were considered equivalent to other formulations of opioids. Levomethadone, which might have advantages in certain forms of neuropathic pain, but is associated with difficulties in dose titration, also inducing cumulation effects, was rarely used in this study signifying a reserved attitude towards this drug.54,55 The clinical value of the newer long acting opioids, or other formulations could not be established in this or other retrospective studies, because of the low number of patients receiving these drugs in the respective groups to compare. Nevertheless though, most retrospective studies support the notion that opioid rotation must be retained as an essential therapeutic option, even with optimized adjuvant and co analgesic regimens.56

Switching from morphine to hydromorphone and vice versa

Hydromorphone is a semisynthetic congener (derivative) of morphine and a potent µ-selective agonist, similar to morphine, sharing some particularities from the metabolic point of view, for example the production of metabolites, which may interfere with the global effect of the drugs, particularly in patients with renal failure. It is between 5 and 10 times as potent as morphine, thus, appearing no major differences between hydromorphone and morphine in terms of efficacy and adverse effects, when equianalgesic doses are used.23,30 Hydromorphone, if available in both normal release and modified release formulations for oral administration, is an effective alternative to oral morphine, according to EAPC recommendations, with strength of evidence grade A.23

No correlation between the dose of the previous opioid and the final ratio between hydromorphone and morphine has been found. In a previous study by Bruera et al., 36 patients, presenting adverse effects, or uncontrolled pain during opioid titration, changed from oral or subcutaneous morphine to oral or subcutaneous hydromorphone, and 12 patients from oral or subcutaneous hydromorphone to oral or subcutaneous morphine. The dose ratio for both morphine and hydromorphone did not change significantly over a wide range of dosages, suggesting that complete or almost complete cross tolerance develops to both opioids.29

The dose ratios between morphine and hydromorphone and vice versa were found to be 5.3 and 0.28, respectively. In a subsequent retrospective study the lack
of correlation between dose ratios and previous opioid dose was confirmed. Forty-four patients with cancer were switched, because of the occurrence of adverse effects, during opioid titration from morphine to hydromorphone (34 and 10 patients by subcutaneous and oral route, respectively), and 47 patients from hydromorphone to morphine (35 and 12 patients by subcutaneous and oral route, respectively). Median time to stabilization was 2-3 days. No change in pain intensity was reported. Of interest, while the morphine-hydromorphone ratio was 4.9 and 5.7, subcutaneously and orally, respectively, in the other direction (hydromorphone to morphine), morphine-hydromorphone ratio was 4 and 3.45, respectively, suggesting that tolerance was more pronounced in one direction.

Wirz et al., in a prospective clinical trial examined the technique of opioid rotation to oral sustained-release hydromorphone, for controlling unrelieved pain and symptoms in outpatients with cancer pain. Fifty patients were assessed and rotation was successful in 64 percent of them experiencing untreaptable pain (60 percent), as well as gastrointestinal (32 percent) and central (26 percent) symptoms, under oral morphine (38 percent), transdermal fentanyl (22 percent), tramadol (20 percent), oxycodone (12 percent) and sublingual buprenorphine (8 percent). Pain intensity, gastrointestinal symptoms, especially defecation rates, and incidence of insomnia improved after an increase in morphine-equivalent doses from 108.9 to 137.6 mg/day, without modifying concomitant analgesics or co analgesics. The authors concluded that switching the opioid to oral hydromorphone may be a helpful technique to alleviate pain and several symptoms, but it is still not clear to what extent the underlying mechanisms, such as rotation technique itself, better dose adjustment, or using a different opioid have an impact.

Furthermore, extended-release hydromorphone hydrochloride (ER hydromorphone HCl) capsules have been developed for administration every 24 hours. A prospective evaluation focused on the first (conversion) phase of two identically designed, randomized, controlled trials that compared the efficacy of once-daily ER hydromorphone HCl capsules with immediate release hydromorphone hydrochloride (IR hydromorphone HCl) tablets, administered four times daily, in the treatment of cancer and noncancer-related pain. In a total of 343 patients (79 percent with cancer-related pain), a conversion ratio of 8:1 mg of oral morphine to oral ER hydromorphone HCl was found to be clinically useful in patients with cancer-related moderate to severe persistent pain.

The reported change of equianalgesic ratios of hydromorphone over time has led to skepticism about hydromorphone. The presence of an agonist metabolite, acting in concert with the opioid to produce maximal analgesia, could account for this change over time. If an active metabolite is subject to slow accumulation and elimination, this could account for a changing dose ratio, unaccompanied by the expected clinical consequences of using an inappropriate dose ratio for conversion. When converting from morphine to hydromorphone using a 7:1, a slow elimination of an agonist metabolite could prevent a situation of undermedication. Conversely, conversion from hydromorphone to morphine using 7:1, with the expected repercussion of overdose, could be attenuated by the slow accumulation of the agonist metabolite. This explanation may be problematic, considering that the primary hydromorphone metabolites include both a 3- and a 6-glucuronide species, the same as morphine. Whether these metabolites behave in similar fashion to those of morphine remains to be fully clarified.

Additional research supports the lower dose ratio and directional influence observed when converting between morphine and hydromorphone. Lawlor et al., in their study of subcutaneous and oral conversions, found no significant differences in the dose ratio, determined by route of administration. However, there was a significant directional influence, suggesting that the new opioid was more potent. The presence and activity of active and proanalgesic metabolites of morphine and possibly hydromorphone, account for this directional phenomena. However, until the concept of incomplete cross-tolerance is better understood, clarification will remain speculative. Corroborating the findings of Bruera E et al., prior opioid exposure did not influence the dose ratio between the two agents. The recommendations of these investigators to use a dose ratio of 5:1 for morphine to hydromorphone and a dose ratio of 3.7:1 for hydromorphone to morphine conversion would appear to be judicious in light of the available medical literature.

Switching to oxycodone

Oxycodone is a semisynthetic congener of morphine, which has been used clinically for pain relief for over 80 years and which until recently was most often prescribed in low-dose combination products with a nonopioid, for oral administration, or as rectal suppository. In some countries, it has been more widely used as single agent to treat postoperative pain and cancer pain. It has now become available in new oral formulations (normal and modified release, such as controlled release, CR, and immediate release, IR preparations). Oxycodone, according to EAPC recommendations, in both formulations for oral administration, is effective alternative to morphine, with strength of evidence grade of A. The CR and IR preparations have been shown to exhibit equivalent analgesia, with the major advantage of the CR product being the convenience of decreased dosing frequency. The major metabolites of oxycodone include noroxycodone and oxymorphone. Noroxycodone does not exhibit
Appreciating the precise influence of incomplete cross-tolerance is currently not feasible. Given these data, it would seem prudent to use the more conservative dose ratios as high as 3:1 for patients with widely varying opioid requirements. Bioavailability differences could theoretically account for ratios as high as 3:1 for patients with widely variable morphine/oxycodone oral bioavailability. Appreciating the precise influence of incomplete cross-tolerance is currently not feasible. Given these data, it would seem prudent to use the more conservative dose ratio in determining a conversion to an around-the-clock dose, while providing ample and frequent breakthrough medication. Thus, when converting from morphine to oxycodone, a 2:1 ratio could be used, versus using a 1:1 ratio when converting from oxycodone to morphine.

Switching from morphine to fentanyl and sufentanil

Fentanyl is a semisynthetic, pure opioid agonist notable for a rapid onset of action, a highly lipophilic nature and inactive metabolites. It is an established anaesthetic and analgesic drug, which is about 80 times as potent as parenteral morphine. It is not usually used by mouth, because it rapidly undergoes extensive first-pass metabolism. The low molecular weight and high lipid solubility of fentanyl facilitate absorption through the skin. These properties have led to development of novel transdermal and sublingual formulations for the delivery of fentanyl analgesia. After application, fentanyl is undetectable in the systemic circulation for 1-2 hours, but then serum levels rise with analgesic effects, evident within 8 to 16 hours, and steady-state is achieved at 72 hours. Each patch is applied for 3 days. An intradermal depot develops, so that following removal of the patch, serum levels take about 16 hours to drop to 50 percent. Medical reports on the clinical use of fentanyl for cancer-related pain are limited and conversion data regarding fentanyl and other opioids is equally sparse.

Transdermal fentanyl is effective and well tolerated in the management of cancer pain, but is generally less flexible than shorter-acting preparations. Although the 3-day duration of action is an important advantage of patients with stable opioid requirements, it can complicate management of patients with unstable pain, whose opioid requirements are fluctuating. According to EAPC recommendations, fentanyl patch is an effective alternative to oral morphine, but is best reserved for patients whose opioid requirements are stable. It may have particular advantages for such patients, if they are unable to take oral morphine, as an alternative to subcutaneous infusion. There is some experimental and clinical evidence that transdermal fentanyl is associated with less constipation than morphine.

The manufacturer provides a conversion tool with its transdermal product, but it is very broad and may be based on other dose conversions that are problematic. The dose ratio of oral morphine to transdermal fentanyl ranges from 75 to 225 mg morphine to 1 mg fentanyl for the 25 µg/h patch. The range of this ratio decreases, as the dose of the transdermal patch increases, so for 300 µg/h of fentanyl, the range is 144-156 mg of morphine per mg of fentanyl. As a result of these ranges, especially at the smaller fentanyl doses, these conversion guidelines should be used with caution. These conversion data also convert oral to parenteral morphine at a 6:1 ratio, convert oral morphine to oral hydromorphone at an 8:1 ratio and...
consider methadone to be three times more potent than morphine orally and equipotent, when given parenterally. These conversions are in conflict with available medical literature. As conversions, using this tool, made between more than two agents, the risk of error increases dramatically. 40,49,65

Switching to fentanyl is not advisable, unless other methods of analgesia are provided in the meantime, due to slow onset of transdermal analgesia. Although different studies have been performed to compare fentanyl and morphine, the exact conversion ratio between these drugs remains unclear, considering the conservative recommendation by manufacturers' (150:1), which could expose patients to unnecessary suffering. One multicenter, prospective study was performed in 98 patients with controlled cancer pain, with the aim of studying the most convenient conversion ratio when switching from oral morphine to transdermal fentanyl. The initial oral morphine/transdermal fentanyl ratio was 100:1. Pain control after switching was similar, although many patients required higher doses than those calculated and more rescue doses were required with transdermal fentanyl. The final ratio was 70:1. Constipation and laxative consumption decreased in comparison with morphine treatment. 30,40,49,66

In a survey of 321 patients treated with oral morphine, on a mean dose of 122 mg, the mean initial dose of transdermal fentanyl was 50.3 µg/h (about 1.2 mg/day) and the mean conversion ratio was 100:1. Pain control improved between 2 and 7 days after switching. In this short term period (the study was long-term) constipation also improved. Sixteen patients withdrew due to uncontrolled pain. However, this was not the primary outcome of the study and patients were switched probably for unclear reasons, rather than for adverse effects and/or poor pain control. 30

In a prospective study, 19 patients, presenting morphine-induced toxicity, were switched to transdermal fentanyl, using a ratio of 150:1. Over the 14 days study period, doses were increased for most patients, although no data were provided about the final ratio, reached at stabilization. An improvement in well-being and cognitive function was statistically observed after switching. Only nine patients completed the study period. Despite improvement in global well-being, patients developed several adverse effects and one experienced respiratory depression. Four patients were excluded because of adverse effects or insufficient response and two were severely ill. 30,40,49,67

In a recent prospective, open-label study 20 patients, presenting morphine-induced delirium, were gradually switched to transdermal (9 patients) or intravenous fentanyl (11 patients), using a conversion ratio of parenteral morphine 10 mg-fentanyl 0.150 mg/day. Considering an oral-parenteral morphine ratio of 3:1, 23 the initial transdermal fentanyl-oral morphine ratio used was relatively high, 200:1, as confirmed by the need to increase the dose in the subsequent days, with a final conversion ratio of 89, which is similar to that reported in other studies. The treatment was effective in reducing the pain and delirium score in 13 patients, within 3 days, and in 18 patients within 7 days. 30,68

A retrospective study examined the effects of switching to subcutaneous fentanyl, in patients who had experienced uncontrolled pain, while receiving transdermal fentanyl (4 patients), or who had experienced toxicity on other opioids, such as morphine or hydromorphone (17 patients), using doses similar to transdermal fentanyl, assuming the same bioavailability, or starting a dose ratio of morphine to fentanyl of 50-100:1, respectively. In the 10 patients who reached stabilization, in a mean of 2.8 days, the four patients switched from morphine had a mean morphine-fentanyl ratio of 85:1, while the six patients switched from hydromorphone had a ratio of 23:1. This group of patients improved cognitive impairment, myoclonus, hallucinations, and agitation. The other patients were switched to other opioids, or died before achieving stability. 30,49,60

Hunt et al. compared subcutaneous morphine to subcutaneous fentanyl, in a trial designed to evaluate toxicity and efficacy. In this study, they used and then confirmed a conversion ratio of 10 mg subcutaneous morphine:150 µg subcutaneous fentanyl. This equates to a parenteral morphine:fentanyl conversion ratio of 70:1, suggesting the oral morphine:transdermal fentanyl ratio would be approximately 140:1. The small number of subjects in this report limits the conclusions that can be made. However, to ensure favorable safety outcomes, a reasonable conversion from oral morphine to transdermal or subcutaneous fentanyl would be 100:1. If appropriate breakthrough medications were made available, any adverse consequences of using this lower ratio would be minimized. 30,40,49,70 Conversion rates suggested are demonstrated in Tables 7 and 8.

The usefulness of fentanyl patch is very well documented in the current literature, especially when rotating from morphine preparations. It seems it controls severe cancer pain, because of excellent analgesic effect, less adverse effects and more convenience, especially when morphine's undesirable characteristics are considered, or oral administration should be avoided, when transitioning patients to home care setting. 71 However, according to Clemens et al., in patients switched from fentanyl patch to morphine, sufficient pain relief was achieved by lower equianalgesic morphine doses, when compared with the doses at admission. Patients with far advanced cancer often suffer from sweating and cachexia, which may have negative effects on the absorption of transdermal fentanyl. 72,75 Furthermore, despite the introduction of the minimum sized fentanyl patch against the recommended
Table 7. Switching from another opioid to transdermal fentanyl (TTS Fentanyl) or discontinuing transdermal fentanyl—A practical guide

<table>
<thead>
<tr>
<th>Changing from another opioid to TTS fentanyl</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Step 1</strong></td>
<td>Calculate the total daily dose of the current opioid.</td>
</tr>
<tr>
<td><strong>Step 2</strong></td>
<td>Calculate the equianalgesic 24-hour morphine parenteral dose.</td>
</tr>
<tr>
<td><strong>Step 3</strong></td>
<td>Determine the equivalent transdermal fentanyl dose.</td>
</tr>
<tr>
<td><strong>Step 4</strong></td>
<td>Continue the previous opioid for 8-12 hours.</td>
</tr>
<tr>
<td><strong>Step 5</strong></td>
<td>Order adequate breakthrough dosing based on the calculated total.</td>
</tr>
<tr>
<td><strong>Step 6</strong></td>
<td>Change the fentanyl patch every 72 hours.</td>
</tr>
</tbody>
</table>

Discontinuing TTS fentanyl

| **Step 1** | Calculate the equivalent dose of the new opioid. |
| **Step 2** | Calculate the scheduled interval and breakthrough dose of the new opioid. |
| **Step 3** | Remove the patch and start the new opioid 12 hours later. |
| **Step 4** | Order adequate breakthrough dosing to cover the patient in the interval. |

Table 8. Switching from oral morphine to TTS fentanyl: Practical advice and information

<table>
<thead>
<tr>
<th>Equivalency ratio 100:1 (oral morphine mg/24 hours; TTS fentanyl mg/24 hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>iv/sc Morphine (mg)</strong></td>
</tr>
<tr>
<td>--------------------------</td>
</tr>
<tr>
<td>20</td>
</tr>
<tr>
<td>40</td>
</tr>
<tr>
<td>60</td>
</tr>
<tr>
<td>80</td>
</tr>
</tbody>
</table>

Abbreviations: iv, intravenous; sc, subcutaneous; TTS fentanyl, transdermal fentanyl.

Note: Transdermal fentanyl dosage (µg/h) is easily converted from oral morphine (mg/day) by approximately dividing the oral morphine dose by 2.

minimum dose of morphine, which served to decrease pain intensity, side effects on the respiratory system in the Japanese population, were raised, even when prescribed by palliative care specialists. Therefore, the recommended minimum dose regulation is not for general practitioners from a medical safety standpoint.74

Moreover, fentanyl patch in reservoir and matrix systems have been compared in terms of pain alleviation, skin compatibility, adhesive properties, wearability/comfort and general satisfaction. In a multicenter pilot study, published in 2005, 91 percent of patients preferred the matrix system. According to the authors, reservoir and matrix systems appear to have comparable efficacy and safety, so that outpatients can be switched directly from the reservoir to the matrix system, without difficulties and new dose titration. Thus, matrix systems for transdermal fentanyl seem that they will replace the reservoir systems in the future, in the European countries.75

Sufentanil is a synthetic phenylpiperidine analogue of fentanyl with very little literature examining a dose ratio to fentanyl and other opioids. In the prospective pain setting, with short-term use, sufentanil was found to be 2.5-5 times more potent than fentanyl.49 In a retrospective survey of 11 patients on subcutaneous morphine (9), epidural morphine (1) and mild analgesics (1) reporting significant adverse effect, subcutaneous fentanyl improved opioid-related adverse effects, and in some cases pain intensity. The initial conversion ratio from subcutaneous morphine to subcutaneous fentanyl was variable, ranging from 10 to 600:1 (that is from 30 to 1800:1, in oral equivalents of morphine). Doses of fentanyl were then increased in most cases, to reach a clinically derived conversion ratio of 68:1 (that is approximately 200:1 with oral morphine). Other investigators employed a 10:1 relative dose potency between fentanyl and sufentanil.30,40,49,76

Finally, regarding fentanyl formulations available, oral transmucosal fentanyl citrate (OTFC) is an effective treatment for “breakthrough pain” in patients stabilized on regular oral morphine or an alternative opioid of the Step 3 in the WHO analgesic ladder. (EFIC recommendation, strength of evidence graded A)23 OTFC produces a rapid onset of analgesia in 5-15 minutes with a short duration of action of about 2 hours. OTFC provides rapid systemic dosing, via absorption through oral mucosa. As far as equianalgesic doses, OTFC of 200 and 800 µg produce the same analgesic effect with 2 and 10 mg of intravenous morphine, with a ratio of iv morphine:OTFC of 1:0.08-0.1.77,78 More safety data are required from wider and longer term clinical use.25,79 The fentanyl buccal tablet (FBT), a new formulation of fentanyl that uses an effervescent drug delivery system, enhances penetration across the buccal mucosa for the treatment of breakthrough pain, in opioid-tolerant patients. FBT is well tolerated by patients and in well designed phase III trial in opioid-tolerant, oncology patients, a single dose of FBT...
100-800 μg provided clinically significant improvement in pain intensity from 15 to 60 minutes after the dose, with the majority of side effects being atypical of those associated with opioids and mild to moderate in nature. Recent studies have demonstrated superior pharmacokinetic profiles when compared with other available transmucosal opioids (OTFC), however, pharmacodynamic data are still somehow limiting.82

Switching to methadone

Morphine and hydromorphone have similar pharmacological properties that facilitate switching from one to the other. Methadone has major pharmacokinetic and pharmacodynamic differences capable of making the switching more complex. It is a racemic mixture, comprised of a dextro- and a levo-rotatory isomer Its bioavailability is estimated to be approximately 80 percent with a range of 41-99 percent. Initial reports and later surveys of switching to methadone have seen a dramatic dose reduction, as well as frequent improvement in pain intensity and decrease in neurotoxicity.30,40,49,83

Figure 2 shows a theoretical model for the effects of switching from morphine (or hydromorphone) to methadone. Morphine and hydromorphone undergo liver metabolism to a number of active metabolites, such as 3-glucuronide, 6-glucuronide, and others. In prolonged treatment, progressive renal failure, dose escalation, or dehydration, these hydrosoluble metabolites accumulate, leading to opioid-induced neurotoxicity. Chronic administration of morphine results in NMDA receptor activation, largely responsible for decreased analgesic effectiveness and progressive dose escalation. When patients undergo a switch over to methadone, there is progressive elimination of the active opioid metabolites of morphine, hydromorphone, or other similar opioids, and also a decreased NMDA receptor activity, due to its weak anti-NMDA activity. As a consequence, there is a trend for an improvement in pain intensity, with a reduction in neurotoxicity and opioid dose escalation.30,40,49,84

These pharmacokinetic characteristics of methadone have significant consequences with chronic dosing. Although it is an instant release preparation, the long half-life allows for twice or three times daily dosing schedules, which may enhance compliance. The liquid formulation provides long acting analgesia for patients who cannot swallow, but have a feeding tube in place. There are no known metabolites associated with methadone, circumventing the toxicities seen, following accumulation of metabolites, associated with morphine and probably other opioids. The lipophilic nature of the drug allows for increased sublingual and buccal absorption. Apart from pharmacokinetic considerations, methadone is relatively inexpensive, compared with costs for sustained or continuous release formulations.49,85-87

There are, however, disadvantages associated with this pharmacokinetic profile. Methadone's long, unpredictable half-life and its propensity for tissue accumulation raise the potential for serious, even life-threatening, toxicity. This, coupled with the limited knowledge concerning titration, dose schedule and equianalgesic conversion, demands highly individualized, time-intensive therapy, being directed at patients converted to methadone.49,88-90

The dose ratios for morphine:methadone, depicted in most equianalgesic tables, are basically based on single dose studies, which found an approximate equivalent analgesic potency of the two agents.90 Equivalency ratios comparing morphine and other opioids to methadone are dose-dependent. The ratio may range from 1:1 at low doses of oral morphine, up to 20:1 for patients receiving oral morphine in excess of 300 mg/day.30,40

In a study conducted by the team of Bruera E, 37 advanced patients with cancer, with poor pain control, were switched from subcutaneous hydromorphone to methadone. The initial conversion ratio between hydromorphone and methadone, orally or rectally, was 1:5, based on previous tables recommended at that time, and switch-over took place progressively, reducing hydromorphone dose and increasing the methadone dose. The mean time to complete the switch-over was 3.2 days for rectal methadone and 6.5 days for oral methadone, with a final subcutaneous hydromorphone-methadone conversion ratio of 1.2:1 for the oral route and 3:1 for the rectal route, which suggests incomplete tolerance and greater bioavailability of methadone by the oral route.30,40,91

In a large retrospective study of 113 patients undergoing opioid switching, due to adverse effects and/or uncontrolled pain, 65 changed from subcutaneous hydromorphone to oral or rectal methadone. In this study methadone was found more potent than initially thought. The median conversion ratio between subcutaneous hydromorphone and methadone (orally and rectally) was 1.14, a ratio 5-10 times higher than expected, if available equianalgesic tables were used. In a further analysis, the dose...
Table 9. Calculated median dose ratios for methadone and morphine sulfate or hydromorphone

<table>
<thead>
<tr>
<th>Rotation</th>
<th>Median dose ratio</th>
<th>P-value</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>MS:ME (po)</td>
<td>11.36:1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ME:MS (po)</td>
<td>8.25:1</td>
<td>NS</td>
<td>37</td>
</tr>
<tr>
<td>MS:ME (po)</td>
<td>5.42:1</td>
<td>0.007</td>
<td>37</td>
</tr>
<tr>
<td>&lt;1165 mg MS/day</td>
<td>16.8:1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;1165 mg MS/day</td>
<td>12.25:1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MS:ME (po)</td>
<td>5.42:1</td>
<td>0.007</td>
<td>37</td>
</tr>
<tr>
<td>&lt;330 mg HM/day</td>
<td>0.95:1</td>
<td>0.023</td>
<td>30</td>
</tr>
<tr>
<td>&gt;330 mg HM/day</td>
<td>1.6:1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MS:ME (sq:po)</td>
<td>4.5:1</td>
<td>NS</td>
<td>46</td>
</tr>
</tbody>
</table>

MS, morphine; HM, hydromorphone; ME, methadone; po, oral; sq, subcutaneous; NS, not significant; NR, not reported.

"Expressed as MS:ME.
From Bruera et al., Cancer 1996; 78: 852-857."

Ratio between hydromorphone and methadone was significantly higher when patients were receiving higher opioid doses before the switch, differently from what was observed between hydromorphone and morphine, on both directions. However, for all the three drugs, a wide range in ratio was observed, which is presented in Table 9. These data led to the conclusion that only a partial cross-tolerance developed between hydromorphone and methadone. Of interest, 12 percent patients developed respiratory depression, and three of them required naloxone, despite the change took place over 3 days (the dose of the first opioid was progressively reduced, while the second one was correspondently increased).

A subsequent retrospective study described a conversion strategy, based on clinical experience with converting opioids to methadone. Dosing of methadone was based on their observation that the relative potency of methadone, following chronic dosing of morphine was much higher. Thus, conversion was determined from the total daily dose of morphine; as the dose of morphine increased, the conversion factor (percent of morphine dose) decreased. Patients taking 60 mg/day of morphine were converted to 15 mg/day of methadone, those taking 60-90 mg/day of morphine received 25 percent of their morphine dose as methadone, and those on 100 mg/day morphine were converted to 16 percent of their morphine dose as methadone. They concluded that, while methadone is a valuable drug for pain control, administration schedules should be individualized.

According to EAPC recommendation on opioid rotation, methadone is an effective alternative, but may be more complicated to use, in comparison with other opioids, because of pronounced interindividual differences in its plasma half life, relative analgesic potency and duration of action. Candidates for a trial of methadone might include, but are not limited to: Patients with poor pain control, who have received an adequate trial of other strong opioids (especially if neuropathic pain is a component of the pain syndrome), patients experiencing severe or multiple toxicities to other strong opioids and patients, receiving high opioid doses, but have also difficulties in swallowing, due to numerous tablets per dose. (Level of strength of evidence: C). According to Fredheim et al., autoinduction of methadone metabolism does not take place during long term treatment, a fact that supports that a 3-day opioid switch from morphine to methadone, followed by a one week titration, seems pharmacologically sound.

Recommendations from the investigators include using a ratio of 10:1 morphine: methadone (oral) for patients taking <1,000 mg morphine/day and increasing the ratio to 15:1 for those taking >1,000 mg of oral morphine/24 hours.

Eighty-eight advanced patients with cancer with pain were switched from different opioids to oral methadone. The previous opioid included subcutaneous hydromorphone in 37 patients and other opioids in 51 patients (doses expressed as mean equivalent parenteral hydromorphone, 3 mg/day). Patients were switched for different reasons, including poor pain control at dose limiting toxicity, toxicity and good pain control, and convenience, but were not analyzed separately according to these indications. A subgroup of 37 patients, receiving a median equivalent daily dose of hydromorphone of 236 mg, had a methadone conversion ratio of 1.4, while a subgroup of 51 patients, receiving a median equivalent daily dose of 3 mg, had a methadone conversion ratio of 0.25. Pain control improved, possibly without relevant adverse effects. Time to stabilization was not reported. A highly significant association was found between previous opioid exposure and hydromorphone-methadone ratio.

In a cross-sectional study, 38 consecutive patients with cancer, on stable doses of morphine, for a week, were
switched to methadone, despite reporting mild adverse effects or poor pain control. About one-third of patients were switched for convenience. The patients, receiving a median dose of oral morphine 145 mg/day, were progressively switched, reducing the dose of morphine and replacing it with methadone in 3 days. The median time to stabilization was 3 days. Patients took three days to achieve the same preswitching level of analgesia, and improve their symptom intensity. The final dose of oral methadone was 21 mg/day (median ratio 7.7). A strong linear negative relationship between previous morphine dose and final ratio of conversion was found. The lower the morphine dose previously administered, the fewer days it took to achieve equianalgesia. However, no distinction was made according to the indication for switching. It is not clear the outcome of patients with poor pain control.96,97

An ad libitum schedule for conversion of morphine to methadone has been proposed. Thirty-three inpatients, who did not respond to two increases in opioids (79 percent), or those with intolerable adverse effects and uncontrolled pain (21 percent), were switched from oral morphine (19 patients), subcutaneous diamorphine, or transdermal fentanyl to methadone. An initial 10:1 morphine-methadone conversion ratio, up to a maximum of 40 mg, given at intervals of 3 hours or more as required, was used. When daily methadone requirements were stable, the daily methadone consumption was then divided in two doses, given twice a day. Eighty-eight percent of patients stabilized on a regular dose of methadone, within 3 days on average (range 2-18 days). However, in the next days (not reported), about 50 percent required dose changes, prevalently increases, with a final dose of 80 mg, that is equivalent to a final morphine-methadone ratio of 6. A weak correlation between methadone and morphine dose was found.98

In 37 patients, who had intolerable adverse effects, or uncontrolled pain (10 patients withdrawn), one-twelfth of the previous total dose of oral morphine, instead of the original one-tenth ratio suggested,99 up to a maximum of 30 mg per dose, but not frequently than every 3 hours, was given as oral methadone on the patient's request and the ad libitum prescription continued, until demand for methadone was stabilized. Pain control was achieved in about 89 and 100 percent of patients within 7 and 11 days, respectively. The median time for achieving a stable dose of methadone (median 20 mg) was 3 days. The morphine-methadone conversion ratio was 6, and no trend in dose ratio in relation to the dose of morphine was detected, probably because of the relatively low morphine doses, before switching. Adverse effects resolved or improved in more than 90 percent of patients. Using this approach, some patients may require several days to achieve pain control (eight patients, about 30 percent, required five or more days).100

Differently from previous protocols proposed, where a loading dose was followed by other doses on patient's request, a loading dose of one-tenth of previous oral morphine dose, up to a maximum of 30 mg of methadone, was started, followed by regular administration of the same dose, divided and given twice daily. One-eighth of the loading dose of methadone was offered as needed and additional loading dose is given, up to a maximum of 30 mg, with severe uncontrolled pain. However, not all the patients followed this regimen exactly. In the seven patients switched from morphine to methadone, the conversion ratio was 11.8.101 Of interest, starting morphine-methadone ratio, relatively higher in comparison with previous approaches, did not changed, maintaining the initial 5:1 conversion ratio, although patients on relatively high doses of morphine had to reduce of one-third doses of methadone.102

The rationale of this approach was confirmed, analyzing opioid plasma concentration during switch-over in 10 patients. Using a fixed morphine-methadone ratio of 5:1, "effective" methadone plasma concentration were achieved on the first day, to peak on the second day and a significant clinical effect was evident on the first day, in terms of pain control and improvement in adverse effect, although plasma concentration do not exactly reflect pharmacodynamics. Doses were changed according to the clinical situation, requiring an increase initially, and then a decrease in methadone doses in the following days, to produce a final morphine-methadone ratio of 6.46, in comparison with the initial 5:1. Of interest, the mean previous dose of morphine was 317 mg/day, which was relatively high.30,40,103

Methadone has been recently shown to possess a unique quality, namely NMDA antagonism, which may have in turn a suppressing effect of central sensitization and reversing opioid tolerance. According to this hypothesis patients with neuropathic pain would have more benefits when switching to methadone, influencing in some way the conversion ratio with other opioids. However, in a retrospective study of 40 patients requiring opioid switching for the occurrence of adverse effects during opioid escalation, no differences in conversion ratios were found in patients with neuropathic or non-neuropathic pain syndromes, suggesting no need to adjust the dosage of methadone in patients with neuropathic pain.104,105 However, a particular conversion ratio was not defined due to lack of achievement of stabilization, requiring further increasing doses to control pain. In another small case series, intravenous hydromorphone was switched to intravenous methadone, with different starting ratios, ranging from 1:1 to 1:10, to achieve final conversion ratios at clinical stabilization of 1:4-5, although the timing was variable.106

In a larger series, 18 consecutive patients, experiencing cancer pain, underwent opioid switching from intravenous
Methadone dose was then titrated every 3 days. A significant number of patients were switched for uncontrolled pain (about 40 percent) or neurotoxic adverse effects (about 60 percent). Methadone was started with a delay, from 8 to 24 hours, proportional to the previous dose of fentanyl. The final conversion ratio was 1:17. Additional boluses of 100-200 percent of the hourly infusion rate, every 60 min, were administered by nurses. There was a 10 percent increase in the median hourly infusion of methadone from Days 1 to 2; then, it remained stable to decrease on Day 4, at values less than those used at Day 1. The calculated final dose ratio between fentanyl and methadone was 1:4.5 across the 17 responsive patients. Satisfactory pain control, without significant adverse effects, was achieved in 16 patients (88.8 percent); fourteen were satisfied 24 hours after switching. Only one patient required an epidural treatment. Sedation score, as well as confusion, significantly decreased unless in a moribund patient. Of interest, no significant correlation between the total dose of fentanyl and the final conversion ratio was found, thus showing a certain cross-tolerance between the two drugs, differently from what was reported when switching from hydromorphone and morphine to methadone.

Intravenous administration of methadone provides better availability, compared with the oral route, as a different conversion ratio was reported when switching from transdermal fentanyl to oral methadone in 17 patients with cancer pain. According to Benitez-Rosario et al., opioid switching from TTS fentanyl to oral methadone in patients with cancer is a safe approach, improving the balance between analgesia and side effects. However, oral methadone availability is relatively good, about 80 percent, and intravenous-transdermal fentanyl ratio seems to be 1:1, so that these differences (1:4.5 and 1:17 with intravenous-intravenous and transdermal-oral, respectively) remain unexplained. Similar to previous work, the fentanyl dose did not affect the final fentanyl-methadone dose ratios, when switching from transdermal fentanyl to oral methadone, using an initial ratio of 1:20 (using an indirect conversion from fentanyl to morphine: 1:100, and then from morphine to methadone 5:1), and providing rescue doses of 10 percent of the daily methadone dose. The final conversion ratio was 1:17. Patients were switched for uncontrolled pain (about 40 percent) or neurotoxic adverse effects (about 60 percent). Methadone was started with a delay, from 8 to 24 hours, proportional to the previous dose of fentanyl. Methadone dose was then titrated every 3 days. A significant decrease in pain intensity was observed 4 days after starting methadone, and outcomes were considered effective in 80 percent of patients on day 7. This approach was intensive for the ratios chosen, but soft for timing, as after fentanyl withdrawal, methadone was started after 8-24 hours. This means that patients with uncontrolled pain were possibly suffering, waiting for methadone “arrival”, which is well-known to be delayed, for its pharmacokinetic characteristics. Data on the first days are not presented (24 hours after switching a significant proportion of patients had severe pain).

A rapid switching was provided in a subsequent study of 24 patients switched for inconvenient balance between analgesia and adverse effects. Furthermore, Mercadante et al., in 2007, published a study regarding opioid plasma concentrations during a switch from TTS fentanyl to methadone. The aim of their study was to assess pharmacokinetic changes of fentanyl and methadone underlying the clinical events occurring during opioid switching. They studies 18 patients with cancer, receiving transdermal fentanyl, with uncontrolled pain and/or moderate to severe opioid adverse effects, who were switched to oral methadone, using an initial fixation ratio of 1:20. TTS patches were removed and the first of the three daily doses of methadone was started concurrently. A successful switch was determined the day after in seven patients while four patients did not respond favourably (63 percent effective switching) five patients were considered too terminal for an appropriate evaluation. No differences in plasma concentration pattern of the two opioids were found between patients, considered responders and non responders. When switching between drugs with delayed effect, because of pharmacokinetic type of delivery, concerns will always exist about the correct timing of introducing the second drug, after stopping the previous one. According to the authors, starting methadone soon after removing fentanyl patches results in a rapid increase of methadone concentration, while the half life of the transdermal fentanyl is reached after 25 hours. As a result, the rapid achievement of a clinical effect is obtained, avoiding distressing therapeutic holes in patients with a clinical condition, mainly characterized by poor pain control and severe adverse effects, requiring an immediate intervention.

Switching from methadone to other opioids

Different experiences suggest that opioid switching shows directionality and therefore are not reciprocal, implicating that that conversion ratios for reverse rotation are even more difficult to predict. Available data are based on small series. In a retrospective study, six patients were switched from methadone (median dose 60 mg) to morphine, with an immediate substitution using a ratio of 1:10. The stable dose was achieved in a mean of
4 days. The final conversion ratio was 0.22 (morphine-methadone 5.2). The median morphine-methadone dose ratio of lower-upper quartile was 8.25. If median data are compared, not considering the lower-upper quartile median, the median morphine-methadone ratio seems to be halved when switching direction is from methadone to morphine (morphine-methadone 11.65 versus methadone-morphine 5.2). Moreover, no correlation between previous doses of methadone and final conversion ratio after achieving the stable dose of morphine was observed. Such variability could be explained not only by the relatively low number of patients with wide individual responses, but also by limited cross-tolerance between morphine and methadone, the possible anti-NMDA properties of methadone, or as a result of elimination of metabolites having hyperalgesic properties, producing different effects depending on the direction of switching. In a small series, seven patients were successfully switched from oral methadone to transdermal fentanyl. About 30 percent higher final doses of fentanyl were found, with a methadone-fentanyl ratio of 13:1, from an initial ratio of 20:1. This occurred independently of the preswitching opioid dose.

In a recent series, a worsening pain with severe adverse effects after switching from methadone to another opioid has been reported. The second opioid was discontinued and methadone treatment restarted. Data on the outcome after this new rotation are not available. This observation is not substantiated by general experience by people using frequently opioid switching, even when switching from methadone to another opioid, which is less frequently used. This group of patients was receiving very high doses of intravenous methadone, eight of these patients were administered more than 300 mg/day (range 48-1,920 mg/day, mean 353/day), probably having a state of profound hyperalgesia, where further opioid escalation, or even opioid switching, may produce just worsening pain, regardless of the personal conversion ratios used. It is not clear the reason why patients who were poorly responsive to previous methadone could be rotated back, so excluding the indication to change therapy, unless presuming a rapid receptor restoration. Such megadoses of opioids have been subject of controversies, as they could be prevented with other available methods. According to the authors, who presented a study regarding pitfalls of opioid rotation to methadone, opioid from methadone to another opioid could be really complicated, with worsening of pain and excessive dysphoria. In these patients, conversion ratios of equianalgesic doses unfortunately are not available. At this level of opioid tolerance (and hyperalgesia), it is impossible to quantify any approximate dose conversion rate (it has been reported 1 percent of the equianalgesic dose of extraordinary doses of parenteral morphine, 21,600 mg/day). Switching to alternative opioid drugs

Buprenorphine is a semisynthetic opioid derived from thebaine and has been assessed as a therapy for chronic cancer pain, in both clinical and postmarketing surveillance studies. Data have shown efficacy, safety and good tolerability, over prolonged treatment periods, with a marked stability of doses. In a recent study, from the cancer population (134 patients), 20 percent stayed on transdermal buprenorphine until the end of their lives. Postmarketing surveillance study data from 13,179 patients, including 3,690 patients with cancer assessed during a 10-week observation period, showed that 81 percent of patients achieved good/very good pain relief with transdermal buprenorphine. Results from the Spanish Pain Society, also confirmed its beneficial efficacy and safety and showed that buprenorphine does not antagonize pain relief, or cause withdrawal when combined with full microagonists. When opioid rotation is indicated to improve pain relief or reduce adverse effects, equipotency ratios are important. After well established dose titration, no problems are confronted in switching patients from prior analgesic therapy with other opioids to transdermal buprenorphine. The equipotency ratio for morphine to buprenorphine, previously established as 75:1, is now being questioned, as new data from a retrospective cohort study were published indicating a ratio of 100:1. In another study, examining opioid rotation from high-dose morphine to transdermal buprenorphine in chronic pain patients, neither tolerance, nor refractory effect following rotation was noted. However, conversion tables with a fixed conversion ratio are of limited value in patients treated with high-dose morphine.

Extended-release tramadol (tramadol ER) is a once daily formulation of tramadol approved in the United States for moderate to severe chronic pain in adults. A model and simulation analysis was conducted to support dosing recommendations for switching patients receiving immediate-release tramadol (tramadol IR) to tramadol ER. This pharmacokinetic analysis supports switching patients from a daily dose of tramadol IR 200 or 300 mg directly to tramadol ER 200 and 300 mg once daily, respectively. Patients who take other doses of tramadol IR may switch to the next lower 100-mg increment of tramadol ER (from tramadol IR 225, 250, 275 mg daily to tramadol ER 200 mg once daily). Confirmation of these findings would require clinical studies, comparing the systemic exposure of tramadol upon switching from the IR to the ER formulation.

**CLINICAL EXPERIENCE ISSUES IN ROUTE SELECTION—SWITCHING THE ROUTE OF ADMINISTRATION**

Although the optimal route of morphine administration is by mouth, this route influences the morphine to...
metabolite ratio in both plasma and CSF. Despite the fact that the oral route is preferred due to its safety, low cost, ease of administration and patient acceptability, many patients require an alternative route of administration at some point during the course of their illness. These specific indications address concerns related to practicality and responsiveness. Concentrations of morphine metabolites were found to be greater after parenteral therapy in comparison with oral administration. Patients who received oral morphine had a threefold higher prevalence of myoclonus, than patients who received morphine by the parenteral route. Thus, switching from oral to parenteral administration may reduce metabolite formation and, thus, toxicity due to metabolite accumulation.

**Parenteral route**

Twenty-eight percent of patients with cancer with advanced disease, who were referred to a pain clinic, required parenteral opioids at some point during the course of their illness. In selecting the route of administration, the severity of pain and the rapidity with which relief was required, were found to be clinical considerations. The parenteral route facilitates rapid titration of the opioid dose. When stable pain control is achieved, patients can be switched to noninvasive routes of administration. Intravenous administration may be necessary to provide a quick onset of analgesia in the setting of rapidly worsening pain. Continuous intravenous or subcutaneous infusion may be a very useful route when oral administration is not feasible, particularly for those patients who can benefit from concurrent parenteral administration of rescue boluses. The decision to use one or the other of these routes for continuous infusion is influenced by the anticipated duration of treatment, the treatment setting and the availability of an indwelling venous access.

About 70 percent of patients will benefit from the use of an alternate nonoral route for opioid delivery before death, because cognitive failure and the inability to swallow make it impossible to continue oral administration. If patients are unable to take drugs orally, then the preferred alternative routes are subcutaneous, rectal and transdermal. Subcutaneous route appears to be safe and effective. It makes home management simple with the first-pass effect and is advantageous in some cases because the insertion of needles and the use of portable pumps are unnecessary. The differences found between the oral and rectal equianalgesic ratios support similar

and quality of life compared with conventional, intermittent, oral or subcutaneous morphine application. Side effects were infrequent and mild. Epidural and subcutaneous morphine provided better pain relief and fewer adverse effects compared with oral treatment. Both treatments were comparable in terms of effectiveness and acceptability. Thus, no additional significant benefits are achieved by administering epidural morphine in cancer pain, in comparison with the subcutaneous route.

However, subcutaneous administration may not be advisable in patients with generalized oedema, who easily develop erythema or abscess at the skin site, with coagulation disorders, or with poor peripheral circulation. Alternative opioids should be then preferred to morphine, when high dosages are required. A dose of 2 mL can dissolve about 1 g of hydromorphone or diamorphine. Although methadone administration subcutaneously has been shown to be effective, it results in topic adverse skin reactions, requiring either site change or discontinuation of the subcutaneous infusion.

Summarizing all the information presented above, EAPC suggested the following recommendations, which have strength of evidence supporting grade C:

1. If patients are unable to take morphine orally, the preferred alternative route is subcutaneous. There is generally no indication for giving morphine intramuscularly for chronic cancer pain, because subcutaneous administration is simpler and less painful.

2. The average relative potency ratio of oral to subcutaneous morphine is between 1:1 and 1:3, and this ratio is the same when converting oral to IV morphine.

3. In patients requiring continuous parenteral morphine, the preferred method of administration is by subcutaneous infusion.

4. Intravenous infusion of morphine may be preferred in patients who have already an indwelling intravenous line, develop erythema, soreness or sterile abscess with subcutaneous administration, have coagulation disorders, or poor peripheral circulation.

**Rectal and sublingual route**

The rectal route has the potential to partially avoid the first-pass effect and is advantageous in some cases because the insertion of needles and the use of portable pumps are unnecessary. The differences found between the oral and rectal equianalgesic ratios suggest lower bioavailability by the rectal route, although similar

---

**Note:** The text continues with further discussion and recommendations for opioid management. However, the provided excerpt focuses on the parenteral route and its advantages, including the use of subcutaneous administration. The rectal and sublingual routes are also briefly mentioned. Further details on the practical implications and specific patient considerations for these routes are integral to a comprehensive understanding of opioid administration in cancer care.
analgesic levels were achieved.\textsuperscript{26,29} The preparation, the use of surfactants and the presence of faeces inside the rectum, influence the bioavailability of the drugs administered by this route. Interindividual variability in rectal bioavailability is also due to drug adsorption in the faeces, spread of the drug to the upper part of rectum and transportation to the liver, poor drug delivery from the suppository, poor absorption from the rectal mucosa and poor dissolution in small volumes of rectal fluid. Rectal administration can be uncomfortable, thus, making progressive titration difficult, because of limited availability of commercial preparations.\textsuperscript{20,26,126} There is conflicting data regarding the effect of switching to the rectal route. If present, this effect is small. However, in some reports, the prevalence and severity of drowsiness and/or sedation were substantially reduced by route changing, although reduction in delirium and pruritus was not reported in any of the studies on changes in morphine route of administration.\textsuperscript{24}

According to EAPC recommendations for cancer pain management and opioid rotation, the buccal, sublingual and nebulized routes of administration of morphine are not recommended, because at present there is no evidence of clinical advantage over the conventional routes and the absorption seems to be unpredictable (grade of recommendation: B).\textsuperscript{23} In contrast, highly lipophilic drugs, like methadone, fentanyl and buprenorphine, are absorbed sufficiently sublingually and can be useful alternatives for patients who are not able to swallow. The sublingual administration of methadone results in a higher absorption than that of morphine (34 percent) due to its lipophilic characteristics.\textsuperscript{26,127} Sublingual buprenorphine may be a useful alternative to low-dose oral morphine for patients who have difficulty swallowing and is often used by this route, but experience of long-term use in cancer pain is limited.\textsuperscript{23}

Transdermal route

A revitalized interest in transdermal route of administration has developed recently. The indications for the transdermal fentanyl system are evolving, as experience with this formulation increases. Although the strongest indication is compromised swallowing or gastrointestinal absorption, other indications may be relevant in practice: severe constipation and the need for improved quality of life are other possible indications for this formulation. On the contrary, reduction in constipation was not reported in any of the studies on changes in morphine route of administration.\textsuperscript{28} Improved bowel function, relief of nausea and emesis, improved sleep quality, and morning vigilance associated with adequate pain relief have been reported. Most patients estimated that the transdermal fentanyl therapy was superior to the previous therapy with oral morphine.\textsuperscript{26,67}

Patients with stable pain, who already are receiving regular doses of opioids and with low to medium opioid dose requirements, are considered the ideal candidates for such a route of administration. Dysphagia and nausea and/or emesis due to tumoral involvement of the upper gastrointestinal tract may represent a useful indication.\textsuperscript{26,128} Nevertheless, more recent trials by Ripamonti et al. conclude that application of the fentanyl patch, as first-choice strong opioid in cancer pain, in the presence of unstable pain, and in the absence of dysphagia, or where the use of morphine is not contraindicated, is not contraindicated.\textsuperscript{129}

Opioid rotation and intrathecal drug delivery:
An alternative route for opioid administration

Despite increasing awareness, education and opioid rotation with drug and/or route switching according to guidelines and recommendations mentioned up to now, a substantial number of patients with cancer suffer considerable pain at some point during their disease, and approximately 25 percent of them die in pain. Intrathecal drug delivery offers an effective pain control approach for the small percentage of patients with cancer whose pain is not otherwise controlled, or who develop analgesic related toxicities. The goals of intrathecal therapy are to preserve quality of life, function, and independence regardless of prognosis. Furthermore, the availability of intrathecal therapy as a management option for uncontrolled pain or intolerable side effects offers significant reassurance to patients with cancer.\textsuperscript{130}

A 2002 randomized multicenter clinical trial investigated the efficacy of an intrathecal drug delivery system (IDDS) plus comprehensive medical management (CMM), versus CMM alone in refractory cancer pain. Patients receiving IDDS and CMM had reduced pain, fewer common drug toxicities and improved survival, compared with patients receiving CMM alone. Although the IDDS and CMM group achieved better outcomes than the control group, results from the trial also demonstrated that algorithm use by pain specialists in the control group receiving CMM alone also reduces cancer pain by 39 percent and pain medication toxicity by 17 percent. Other investigators found similar improvement in pain reduction, with algorithm use versus routine oncology care.\textsuperscript{132} A multidisciplinary panel of experts gathered in October 2003 to develop consensus recommendations of best clinical practice for the management of intractable pain in patients with cancer. Oncologists in this group noted that despite the expansion of knowledge about the benefits of intraspinal analgesia, there was a lack of guidelines for the adoption of advanced management techniques in appropriate clinical circumstances, and most specifically for the use of intraspinal drugs in cancer pain.\textsuperscript{130}
They concluded that administration of intrathecal opioids and adjuvant medications allows reductions of up to 200 percent in the amount of administered oral or parenteral medication. In addition to reduced dosages, intrathecal opioids plus adjuvants enhance pain control with minimal side effects. The receptors targeted are virtually the same as those targeted with oral, parenteral, and transdermal medications. They also stated that IDDS can be highly effective in a variety of patient settings, including cases of refractory pain, diminished performance status, poor tolerability of oral drugs, polyneuropathic for complex pain and inadequate dosing due to addiction concerns. However, because side effect profiles are dramatically improved with intrathecal delivery, drug titration requires hours instead of days, and pain can be aggressively treated with less risk of life threatening toxicities.

Thus, rapid pain relief also results in fewer hospitalizations for pain control and saves healthcare money. The panelists recommended different treatment approaches for patients with cancer, categorized as short-term and long-term survivors. As they suggested, long-term survivors should be treated according to the updated algorithm of the Polyneuropathic Consensus Conference in 2003, which developed recommendations for patients with chronic pain regardless of origin (mostly nonmalignant), which is shown in Figure 3. Maximal dosing and dosing recommendations for intrathecal medications for long-term survivors are depicted in Table 10. The panel agreed that a separate algorithm was needed for short-term cancer survivors, characterized as having a high disease stage or grade, incapacitation due to pain, and/or life-expectancy (1 year). Because end-of-life issues include...
Table 10. Recommended dosages and concentrations for medications used in the intrathecal cancer pain algorithm for long-term and short-term survivors

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage (mg/day)</th>
<th>Max concentration (mg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morphine</td>
<td>15</td>
<td>30</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>5-10</td>
<td>30</td>
</tr>
<tr>
<td>Bupivacaine</td>
<td>2-30</td>
<td>38</td>
</tr>
<tr>
<td>Clonidine</td>
<td>0.01-1.0</td>
<td>2</td>
</tr>
</tbody>
</table>

Recommended dosages and concentrations for medications utilized in the intrathecal cancer pain algorithm for short-term survivors

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage (mg/day)</th>
<th>Max Concentration (mg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>First-line medications (1-3 medications in mixture)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morphine</td>
<td>0.1-50</td>
<td>50</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>0.1-100</td>
<td>100</td>
</tr>
<tr>
<td>Bupivacaine</td>
<td>3-50</td>
<td>38</td>
</tr>
<tr>
<td>Droperidol (nausea indication)</td>
<td>0.025-0.15</td>
<td>0.5</td>
</tr>
<tr>
<td>Second-line medications (2-4 medications in mixture)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fentanyl</td>
<td>0.01-5</td>
<td>20</td>
</tr>
<tr>
<td>Sufentanil</td>
<td>0.001-0.5</td>
<td>2</td>
</tr>
<tr>
<td>Clonidine</td>
<td>0.025-0.8</td>
<td>2</td>
</tr>
<tr>
<td>Third-line medications (4-6 medications in mixture)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baclofen</td>
<td>10-1000</td>
<td>2</td>
</tr>
<tr>
<td>Second opioid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morphine</td>
<td>0.1-15</td>
<td>30</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>0.1-10</td>
<td>30</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>0.01-0.15</td>
<td>1</td>
</tr>
<tr>
<td>Fourth-line medications (more than 3 medications) possibly neurotoxic; use for rescue only</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tetracaine</td>
<td>30-85</td>
<td>100</td>
</tr>
<tr>
<td>Ketamine</td>
<td>0.025-1.0</td>
<td>2</td>
</tr>
<tr>
<td>Midazolam (HCl form only)</td>
<td>0.025-1.0</td>
<td>2</td>
</tr>
<tr>
<td>Droperidol (pain indication)</td>
<td>0.025-0.25</td>
<td>1</td>
</tr>
</tbody>
</table>

Abbreviation: HCl, hydrochloride.

The intent of the consensus was that increased understanding of available options for truly effective pain management in the oncology and palliative care arena and the benefits of the multidisciplinary cooperation, will translate into genuine improvements in patient quality of life and a measurable decrease in the number of patients who suffer needlessly in the final days of their life.

According to EAPC recommendations, spinal (epidural or intrathecal) administration of opioid analgesics in combination with local anaesthetics or clonidine should be considered in patients who derive inadequate analgesia or suffer intolerable side effects, despite the optimal use of systemic opioids and nonopioids (strength and consistency of evidence supporting grade: B). However, additional randomized controlled trials evaluating polyanalgesia and efficacy and safety of various agents in the spinal space are necessary to increase acceptance of intrathecal therapy in cancer pain management. Comparative studies of conventional medical management versus intrathecal drug delivery in patients with cancer, with a focus on performance scores and survivorship as end points, would also be of interest. As very well has been presented by the World Health Organization, IDDS could become the fourth step in therapeutic ladder for terminally ill patients with cancer (Figure 5). Finally, studies comparing cost-effectiveness of conventional medical management and intrathecal therapy, including hospital and nursing staff utilization costs, may provide insights regarding cases where financial considerations may otherwise limit access to therapy.

Opioid rotation: Does it work? Clinical outcome

Is there any evidence that patients who are switched achieve a better clinical outcome? A recent systematic review looked at the current level evidence for opioid switching, as a useful therapeutic maneuver in patients (adults and children, cancer and non cancer) with pain. The review highlights the lack of robust data available: no RCTs were located. Published data on opioid switching included case reports (52 studies), retrospective studies/audits (15 studies), and prospective controlled trials (14 studies). Not surprisingly, published reports tended to report positive results, improvement in pain and/or adverse effects, on switching opioids. In general, morphine tended to be the opioid of first choice (first-line escalating pain, that may require more rapid dose escalation and more complex polyanalgesia, as well as the need to maintain quality of life, the panel agreed that a revised management algorithm was needed to allow more flexibility and more aggressive therapy for such patients. The cancer pain algorithm developed by the expert committee is presented in Figure 4 and the maximal dosage and concentration recommendations for short-term survivors are also shown in Table 10.
opioid), with most initial switches involving methadone (second-line opioid). The authors referred to multiple consistencies of outcome, such as pain, adverse effects, analgesic requirements and breakthrough pain, patients' preference, quality of life and global improvement. They concluded that a robust evidence base for the practice of opioid switching does not exist, but for chronic cancer pain, opioid switching may be the only option for enhancing pain relief and minimizing toxicity.20,24 According to available data, as Mercadante et al. underline, opioid switching will result in clinical improvement at least in more than 50 percent of patients with chronic pain, presenting a poor response to one opioid. Despite the favorable effect reported with opioid switching, data are based on open studies, most of them being retrospective or small case series. Unfortunately, in the setting of uncontrolled pain, in the presence of adverse effects, it is quite difficult to conduct randomized controlled studies, and a formal approach according to evidence-based medicine is unlikely.30 Opioid switching may improve the balance between analgesia and adverse effects in about 70-80 percent of patients, using lower doses of opioid medications, although no data are available on long-term basis.
Unfortunately, the results of the opioid rotation are sometimes completely unpredictable. It is not unusual for a number of patients to deteriorate, following opioid switching. Infrequently, there have been reports of an opioid switch failing to improve symptoms.\textsuperscript{20,112} A variety of confounding variables, such as a change in route, as well as drug, grouping neuropathic and nociceptive pain together, and failure to exclude other potential causes of adverse effects, made it impossible to draw definitive conclusions in the review. The evidence based results are limited in order to support the opioid rotation pharmacologic strategy.\textsuperscript{20}

A more recent study, published since the systematic review, prospectively evaluated the clinical benefits of switching from morphine to an alternative opioid.\textsuperscript{47} One hundred eighty-six palliative care patients were recruited. Responders were treated with morphine for more than 4 weeks with good analgesia and minimal side effects. Nonresponders (switchers) either had uncontrolled pain or unacceptable morphine-related side effects. Forty-seven (of 186) patients were in the switchers group. Thirty-seven of these (79 percent) had a successful outcome with a second-line opioid, oxycodone. Furthermore, as Enting et al. comment in their published study, par­enteral opioids improved the balance between analgesia and side effects in patients with cancer with pain, who failed on conventional opioids, with an important improve­ment seen in 71 percent of them. On the basis of their study, it was concluded that parenteral opioids are a good alternative to spinal opioids. Moreover, it is suggested that a change in route alone is as effective as using an alternative drug through the same route of administration.\textsuperscript{194}

While opioid rotation has the practical advantage of minimizing polypharmacy, outcomes are variable and somehow unpredictable. Although many patients will have an improved balance between analgesia and side effects, in some cases, patients may have an unimproved or worse outcome, with the new agent that may necessi­tate a further trial of rotation or a change in therapeutic strategy. Indeed, in one prospective survey, 20 percent of patients needed to undergo two or more switches until a satisfactory outcome was achieved.\textsuperscript{24,28} Future studies are increasingly important to monitor the benefits from application of opioid rotation.

AETIOLOGY OF INTERINDIVIDUAL VARIABILITY IN OPIOID ANALGESIC RESPONSE

Implications in opioid rotation

Opioid responsiveness refers to the likelihood that a favorable balance between pain relief and side effects can be achieved during dose titration. Ten to 30 percent of patients demonstrate poor responsiveness to an opioid during routine administration. Poor responsiveness is a complex phenomenon that may be related to one or more of a diverse group of factors, including co morbid medical disorders that predispose to toxicity, a pain pathophysiology associated with relatively limited analgesic response, and pharmacologic effects, such as the accumulation of active metabolites caused by dehydration or renal insufficiency.\textsuperscript{20,22,47}

The concept of interindividual variability in morphine analgesic response is not a new one. In the 1950s, Lasagna and Beecher reported a 65 percent “success” rate with morphine in an experimental pain model.\textsuperscript{135} Similarly, a bimodal response to morphine analgesia has been described in dental extraction pain.\textsuperscript{136} Whereas, mild sedation, nausea and vomiting occur relatively frequently on initiation of opioids, with cautious dose titration these problems usually disappear within days. However, for a minority, these symptoms persist, preventing further dose titration and adequate analgesia. Persistent confusion, drowsiness, nausea, and nightmares are the most commonly reported adverse effects, which result in the need to switch to an alternative opioid.\textsuperscript{47} Less common side effects and reasons reported for switching include neuromuscular disturbances such as muscle spasm, myoclonus, and pruritus.\textsuperscript{20,22}

Clinically, it can be difficult to identify true opioid intolerance, particularly in patients with cancer, where symptoms such as drowsiness, nausea, and vomiting can have many causes. De Stoutz et al. identified adverse effects, primarily cognitive impairment, in 41 percent of patients with cancer on regular opioids. However, not all symptoms resolved on switching opioids, suggesting that nonopioid causes were important.\textsuperscript{35} In general, a pragmatic approach is usually taken, in which, if there is a clinical suspicion that symptoms are opioid related, a trial of an alternative opioid is instigated.

Scientific rationale for switching: Genetic variations in candidate genes

A patient’s response to a drug depends on multiple factors. Pharmacokinetic determinants include drug absorption, distribution, metabolism, and elimination. Pharmacodynamic factors—for example, drug concentration at the target site, number and morphology of target receptors, and variation in downstream events after receptor-ligand binding—all combine to influence overall response. Pharmacodynamic and pharmacokinetic variation in drug handling may be further influenced by age, concomitant medications, underlying disease, and various environmental factors, including diet. When comparing different opioids, it is useful to consider both their routes of metabolism and their receptor profiles.

Little of the interindividual variation in response to morphine can be attributed to age, gender, cancer diagnosis, or renal or liver function, and a number of authors have highlighted the potential importance of a genetic influence on morphine responsiveness. It would appear that, although some of the differences among individuals in terms of opioid sensitivity can be related to differences in environmental factors, age, pain severity, emotional state, and prior pain experience, much of this variation could be a result of genetic factors.

The genetic code, DNA, carries the complete genetic information of a cell and consists of thousands of genes. Each gene serves as a code or template for building a protein molecule, such as a receptor or an enzyme. Variation in the genetic code can alter protein expression and function. Given the broad spectrum of proteins involved in determining response to a drug, genetic variation in multiple genes could influence an individual’s response to different opioids. In addition, given the pharmacokinetic and pharmacodynamic differences among the opioids, such variation may favor treatment with one opioid versus another for a given individual. The evidence for genetic variation in a selection of candidate genes, influencing response to different opioids, is outlined below.

Drug transporters: P-glycoprotein

The membrane-bound drug transporter P-glycoprotein influences drug absorption and drug excretion. It regulates transfer of opioids across the blood-brain barrier and can actively pump opioids out of the central nervous system (CNS). P-glycoprotein knockout mice, which are completely devoid of P-glycoprotein activity, have enhanced absorption and high CNS concentrations of P-glycoprotein substrates (eg morphine, fentanyl, and methadone) with associated prolongation of analgesia. Administration of cyclosporine, a P-glycoprotein inhibitor, results in increased fentanyl- and morphine-induced analgesia. Interindividual variability in P-glycoprotein activity is well recognized and genetic variation in the multidrug resistance gene MDR-1, which encodes for P-glycoprotein, has been associated with resultant alterations in P-glycoprotein activity. Because P-glycoprotein modulation of opioid CNS levels varies substantially among different opioids, the effects of genetic variation altering P-glycoprotein activity are different, depending on the opioid in question. MDR-1, the gene that codes for P-glycoprotein, is therefore a good candidate gene for influencing analgesic response to opioids and the prevalence of opioid-induced CNS side effects. Whereas multiple single nucleotide polymorphisms (SNPs) have been identified in the MDR-1 gene, two mutations (C3435T and G2677T/A) have been associated with differences in P-glycoprotein expression or function. Variation in the G2677T/A genotype has also been shown to alter drug levels and drug-induced side effects. There are no studies to date reporting on analgesic response or opioid side-effect profiles in relation to variation in the MDR-1 genotype.

Opioid receptors

During the past 20 years, three opioid receptors have been identified (\( \mu, \kappa, \delta \)) and the genes coding for these receptors have now been cloned. Morphine and other commonly used opioids (fentanyl, oxycodone, hydromorphone, methadone) act primarily at the same receptor, the \( \mu \)-opioid receptor. Additionally, oxycodone, methadone, and buprenorphine may have clinically important activity at other opioid receptors too. The knowledge of these receptors aspects can be useful in explaining the differences in analgesic or adverse effect responses among opioids in the clinical setting. Binding studies to postmortem brain samples and in vivo positron-emission tomography radio-ligand analysis suggest 30-50 percent or even larger ranges of individual human differences \( \mu \)-opioid receptor densities. More than 100 polymorphisms have been identified in the human \( \mu \)-opioid receptor gene, and some of these variants have been shown to alter the binding affinities of different opioids. The most widely studied polymorphism in the \( \mu \)-opioid receptor gene is the A118G nucleotide substitution, which codes for the amino-acid change asparagine to aspartic acid. It has been reported in association with both addiction and pain studies. Addiction studies have published conflicting results. Although some studies have reported a protective effect of the mutant allele against drug and alcohol abuse, other studies found no such association. In pain studies, there have been suggestions that the mutant allele may decrease the potency of morphine or morphine-6-glucuronide (M6G) in patients with cancer. A study of 99 patients with controlled cancer pain reported that patients homozygous for the variant allele (n = 4) needed
more morphine to control pain than heterozygous (n = 17) and homozygous wild-type (n = 78) individuals. In a recent, prospective study in patients with cancer, we evaluated genetic variation in a number of candidate genes, including the μ-opioid receptor gene, in patients with cancer pain who responded to morphine versus those who were switched to an alternative opioid. No differences were seen in genotype or allelic frequencies for polymorphisms in the μ-opioid receptor gene.

The μ-opioid receptor is a G-protein-coupled receptor (GPCR). Opioid receptor signaling results in inhibition of neuronal transmission of painful stimuli, by a complex sequence of events. GPCR signaling is regulated by receptor desensitization, endocytosis, and down regulation. β-Arrestin-2 is an intracellular protein that is involved at multiple points in regulating receptor phosphorylation, desensitization, and internalization. In animal studies, the analgesic effect of morphine is both increased and prolonged in β-arrestin-2 knockout mice. Because rates of μ-opioid receptor internalization and desensitization differ according to which ligand binds, polymorphic variation affecting β-arrestin-2 may have a greater or lesser effect depending on the opioid given. Whereas the study by Ross et al. above showed no differences between controls and switchers for polymorphisms in the μ-opioid receptor gene, a significant difference was seen in genotype and allelic frequency for the T8622C polymorphism in the β-arrestin-2 gene. This SNP in exon 11 does not result in an amino-acid change but is at a “wobble position” and may therefore influence mRNA translation.

**Opioid metabolism**

There is no single common metabolic pathway for the metabolism of opioids. Codeine and oxycodone are metabolized by the cytochrome P450 (CYP) 2D6 enzyme. Oral morphine and hydromorphone are primarily metabolized in the liver through the uridine-diphosphoglucuronosyltransferase (UGT) system. Fentanyl and methadone are metabolized by the CYP3A4 enzyme, which is responsible for complete or partial metabolism of 50 percent of all known drugs. Genetic variation in CYP2D6 results in poor metabolism of the opioid codeine to its active metabolite morphine. Other studies have shown important pharmacogenetic influences in oxycodone and morphine metabolism.

Oral morphine is primarily metabolized in the liver by the UGT system. The pharmacology of morphine and these two main metabolites (M6G, M3G) in humans has been well documented. Both morphine and its metabolite levels vary greatly among individuals, not only because of differences in dosing, but also because of interindividual variability in pharmacokinetics. M6G has major analgesic properties, whereas M3G, the major metabolite of morphine, has a negligible affinity for opioid receptors and is considered to be devoid of analgesic activity. On the contrary, experimental studies have proven that M3G produces neuroexcitatory and antianalgesic effects. Controversies exist about its role in the development of tolerance to M6G antinociceptive effects. Faura et al. showed a high correlation, independent of clinical variables, between M3G and M6G, confirming that a single enzyme is responsible for metabolism of morphine, namely UGT2B7.

A number of SNPs in the promoter region of UGT2B7 have been reported, but their impact on enzyme function is debated. In vitro studies have demonstrated altered transcription factor binding to polymorphic regions, but these do not translate into altered promoter activity. Whereas one clinical study showed that genetic variation in the promoter region correlated with serum morphine and M6G concentrations, this was not confirmed in a subsequent larger study. One SNP, in exon 2, results in an amino-acid substitution, histidine to tyrosine, at the proposed location of the substrate-binding site. However, no relationship has been shown between this variant and morphine metabolism in patients with cancer. Although research continues in this area, it appears at the moment that polymorphisms in genes controlling the metabolism of morphine do not, in isolation, explain inter-individual variability in morphine response.

The CYP enzymes CYP3A4, CYP3A5, and CYP2D6 are important in the metabolism of a number of strong opioids, including oxycodone, fentanyl, and methadone. Multiple SNPs have been validated in the CYP3A4 gene, but less than 5 percent occur in the coding regions. None of the amino-acid changes have been shown to affect putative substrate-binding sites, but four have been shown to affect drug metabolism in functional studies. CYP3A5 demonstrates either high or low activity primarily as a result of polymorphic variation in intron 3, resulting in mRNA splicing and production of a nonfunctional protein (5-15 percent of whites). CYP2D6 is among the most widely studied of the CYP enzymes and has been extensively studied in relation to its role in codeine metabolism. Approximately 7 percent of whites have inactivating mutations in the gene encoding CYP2D6 or have complete deletion of the gene. The importance of CYP2D6 in determining analgesic efficacy of different opioids is debated (oxycodone, hydrocodone, dihydrocodeine), although clinical differences in response to the opioid tramadol have been shown between poor and rapid metabolizers.

On clinical grounds, the M6G concentration in plasma and CSF during morphine therapy, suggests that it makes an important contribution to the analgesic efficacy of the parent drug, although the degree to which M6G contributes to the clinical effects of morphine and its exact potency are yet to be quantified. Because M3G may...
oppose the analgesic effect of morphine or M6G, a negative relation between the degree of pain relief and CSF M3G concentration may be expected. Nonetheless, evidence showing that M3G may antagonize the analgesic actions of morphine or influence the severity of adverse effects is unsubstantiated.\textsuperscript{20,26}

The role of morphine metabolites in the mechanisms of analgesic response and in the pathogenesis of late toxicity has been described. It has been suggested that the accumulation of toxic metabolites during chronic opioid therapy can lead to severe adverse effects, even in patients with apparently normal renal function. If metabolites are considered to play a relevant role, then switching opioids may allow for the elimination of the responsible breakdown.

Control of gene expression: Transcription factors

A number of transcription factor recognition sites have been postulated in the human \( \mu \)-opioid receptor gene.\textsuperscript{200,201} One of these, signal transducer and activator of transcription 6 (STAT-6) has been shown to be functionally relevant.\textsuperscript{202} Whereas the \textit{stat-6} gene is known to be highly polymorphic, most of the validated SNPs lie in intronic, noncoding regions. Our study, comparing switchers who did not tolerate morphine with controls who responded to morphine, showed significant differences in the genotype of the \textit{stat-6} gene between switchers and controls.\textsuperscript{140} Research continues to examine other transcription factors that may be important in influencing response to different opioids.

Complexity of pain: Other pathways interact

Response to a painful stimulus is regulated by interactions between multiple regions within the brain via different neurochemical pathways.\textsuperscript{202} There is evidence to support interaction between dopaminergic and adrenergic pathways and opioid signaling pathways in the CNS.\textsuperscript{203} Catechol-O-methyltransferase (COMT) is one of the enzymes that metabolizes catecholamines and is an important modulator of neurotransmitters in the brain. Polymorphic variation in the \textit{COMT} gene has been shown to affect \( \mu \)-opioid neurotransmitter responses to a pain stressor\textsuperscript{203} and to influence interindividual variation in pain sensitivity.\textsuperscript{204} In addition, Rakvag et al.\textsuperscript{205} have demonstrated a correlation between \textit{COMT} genotype and morphine dose requirements in patients with cancer.

CONCLUSION

Opioid rotation involves changing from one opioid to another or one route of administration to another, using correct equianalgesic conversion techniques to achieve better analgesia and/or fewer side effects. The strategy appears to work because of significant interindividual variations in response to both analgesic activity and toxicity. Although there are many retrospective studies, few prospective controlled trials of opioid rotation have been published. The practical and theoretical advantages of opioid rotation include improved analgesia, reduced side effects, cost reduction, and improved compliance. Disadvantages include problems related to inaccurate conversion tables, limited availability of certain opioid formulations, drug interactions, and the possibility of increased expense. Weighing the advantages and disadvantages is essential prior to making a decision about opioid rotation selection.

However, there is no sound evidence from well-designed clinical trials of the superiority of one opioid over another, regarding the side effect and/or analgesic profile. Now, there are numerous reports describing improvement or resolution in adverse effects from morphine after switching to an alternative opioid. When opioid rotation is applied in the setting of unacceptable adverse effects, the selection of an alternative opioid is largely empiric. A pure opioid agonist is recommended. The outcome is not predictable and several different agents may need to be tried sequentially. Data derived from observational studies and reports indicate substantial intraintividual variability in analgesic effect and propensity to adverse effects. Literature review shows that approximately 500 genes have now been implicated in “pain”, in animal and human studies. In order to continue to evaluate the genetic contributions, to both pain susceptibility and analgesic response, further candidate genes need to be considered.

Opioid rotation has been shown to be useful in opening the therapeutic window and establishing a more advantageous analgesia/toxicity relation. Opioid responsiveness to difficult pain syndromes should not be based on the results obtained by a single drug. More studies are necessary to obtain more knowledge of the opioid response in patients with difficult pain syndromes. Opioid neurotoxicity, possible associated factors and drugs that limit excitatory symptoms are other research areas for future exploration. More information is needed about the appropriate dosage to use when switching from one opioid to another. Randomized trials, including “N of 1” studies, where a patient act as their own control, are needed: firstly to establish the true effectiveness of this clinical practice, secondly, to determine which opioid should be used first-line or second-line, and thirdly to standardize conversion ratios when switching from one opioid to another.

It is still true today that it is very easy to become judgmental when faced with a patient whose suffering is difficult to understand. Unfounded assumptions are harmful and can rob a suffering patient of hope. With our current knowledge of how pain is generated and alleviated, it is
both disrespectful to the patient and a breach of medical ethics not to provide what is clearly needed. When a patient in chronic pain seeks our help, the first question we should ask ourselves is not whether we should provide an analgesic but whether we can in good conscience leave that person in pain. Good pain control remains a high priority for clinicians and patients, and there is much work to be done to further individualize analgesic therapy for patients with cancer. To quote Marcia Angel, "Few things a doctor does are more important than relieving pain . . . pain is soul destroying. No patient should have to endure intense pain unnecessarily. The quality of mercy is essential to the practice of medicine; here, of all places it should not be strained."

Aithina Vadalouca, MD, PhD, FIPP, Associate Professor of Anaesthetics, Pain Therapy and Palliative Care, Aretaieion University Hospital, Athens, Greece.

Eleftheria Angyra, MD, PhD, Assistant Professor of Anaesthesiology, Pain Therapy and Palliative Care, Aretaieion University Hospital, Athens, Greece.

Panayiota Sikioti, MD, SHO in Psychiatry Scientific Collaborate of Pain Therapy and Palliative Care Unit, Aretaieion University Hospital, Athens, Greece.

Joanna Siafaka, MD, PhD, Assistant Professor of Anaesthesiology, Pain Therapy and Palliative Care, Aretaieion University Hospital, Athens, Greece.

REFERENCES


117. Murthy BP, Skee DM, Danyluk AP, et al.: Pharmacokinetic model and simulations of dose conversion from immediate-to-


