SPECIAL ARTICLE

Strategies to Manage the Adverse Effects of Oral Morphine: An Evidence-Based Report

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Abstract: Successful pain management with opioids requires that adequate analgesia be achieved without excessive adverse effects. By these criteria, a substantial minority of patients treated with oral morphine (10% to 30%) do not have a successful outcome because of (1) excessive adverse effects, (2) inadequate analgesia, or (3) a combination of both excessive adverse effects along with inadequate analgesia. The management of excessive adverse effects remains a major clinical challenge. Multiple approaches have been described to address this problem. The clinical challenge of selecting the best option is enhanced by the lack of definitive, evidence-based comparative data. Indeed, this aspect of opioid therapeutics has become a focus of substantial controversy. This study presents evidence-based recommendations for clinical-practice formulated by an Expert Working Group of the European Association of Palliative Care (EAPC) Research Network. These recommendations highlight the need for careful evaluation to distinguish between morphine adverse effects from comorbidity, dehydration, or drug interactions, and initial consideration of dose reduction (possibly by the addition of a co analgesic). If side effects persist, the clinician should consider options of symptomatic management of the adverse effect, opioid rotation, or switching route of systemic administration. The approaches are described and guidelines are provided to aid in selecting between therapeutic options.

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ACCORDING TO THE World Health Organization guidelines for patients with pain of moderate severity or greater, opioid analgesics are the mainstay of cancer pain management.[1] For patients with moderate to severe pain, oral morphine is conventionally the opioid of choice.[1] This recommendation was derived by virtue of availability, familiarity to clinicians, established effectiveness, simplicity of administration, and relative inexpensive cost. It is not based on proven therapeutic superiority over other options. Guidelines for the use of oral morphine have been presented by a previous expert working group,[2] and an update is in preparation.

Successful pain management with opioids requires that adequate analgesia be achieved without excessive adverse effects. By these criteria, a substantial minority of patients treated with oral morphine (10% to 30%) do not have a successful outcome because of (1) excessive adverse effects, (2) inadequate analgesia, or (3) a combination of both excessive adverse effects along with inadequate analgesia.[2]

The management of excessive adverse effects remains a major clinical challenge. Multiple approaches have been described to address this problem. The clinical challenge of selecting the best option is enhanced by the lack of studies comparing various therapeutic approaches to manage these problems. Indeed, this aspect of opioid therapeutics has become a focus of substantial controversy.

Given this situation, the Steering Committee of the European Association of Palliative Care (EAPC) Research Network felt that clinicians would benefit from evidence-based clinical-practice recommendations by an Expert Working Group. A panel of experts including Carla Ripamonti (cochair), Nathan Cherny (cochair), Jose Pereira, Henry McQuay, Gavril Pasternak, Sebastiano Mercadante, Vittorio Ventafridda, Carol Davis, and Marie Fallon were invited to participate. They met in Oporto, Portugal, in February 1998, where they reviewed all the available data, discussed the evidence, and discussed what practical recommendations could be derived from it. On the basis of the

Table 1. Common Opioid-Induced Adverse Effects

Gastrointestinal	Nausea
	Vomiting
	Constipation
Autonomic	Xerostomia
	Urinary retention
	Postural hypotension
CNS	Drowsiness
	Cognitive impairment
	Hallucinations
	Delirium
	Respiratory depression
	Myoclonus
	Seizure disorder
	Hyperalgesia
Cutaneous	Itch
	Sweating

content and conclusions of that meeting, Drs Cherny and Ripamonti drafted these recommendations that have since been approved by all participating experts.

OPIOID-INDUCED ADVERSE EFFECTS

Successful opioid therapy requires that the benefits of analgesia clearly outweigh treatment-related adverse effects. This implies that a detailed understanding of adverse opioid effects and the strategies used to prevent and manage them are essential skills for all involved in cancer pain management. The adverse effects that are frequently observed in patients receiving oral morphine and other opioids are summarized in Table 1.

FACTORS PREDICTIVE OF OPIOID ADVERSE EFFECTS

Drug Related

Overall, there is very little reproducible evidence suggesting that any one opioid agonist has a substantially better adverse effect profile than any other does.

Pethidine (meperidine) is not recommended in the management of chronic cancer pain because of concerns regarding its side effect profile. Accumulation of norpethidine after repetitive dosing of pethidine can result in CNS toxicity characterized by subtle adverse mood effects, tremulousness, multifocal myoclonus and, occasionally, seizures.[3,4] Although accumulation of norpethidine is most likely to affect the elderly and patients with overt renal disease, toxicity is sometimes observed in younger patients with normal renal function.[5,6] The most serious toxicity associated with pethidine is norpethidine-induced seizures. Naloxone does not reverse this effect, and indeed, could theoretically precipitate seizures in patients receiving pethi-

dine by blocking the depressant action of pethidine and allowing the convulsant activity of norpethidine to become manifest.[7,8] If naloxone must be administered to a patient receiving pethidine, it should be diluted and slowly titrated while appropriate seizure precautions are taken.

Route Related

There is very limited evidence to suggest differences in adverse effects associated with specific routes of systemic administration. Compared with oral morphine administration, small studies have demonstrated less nausea and vomiting with rectal[9] and subcutaneous administration.[10] Three studies comparing transdermal fentanyl to oral morphine demonstrated less constipation among the patients receiving transdermal fentanyl. It is not clear as to whether this is a route- or drug-related effect.[11-13]

Patient Related

For reasons that are not well explained, there is striking interindividual variability in the sensitivity to adverse effects from morphine and other opioid drugs. Genetic variability clearly affects the sensitivity to opioid analgesia, particularly related to codeine,[14,15] dihydrocodeine[16] and, possibly, oxycodone,[17] and it is reasonable to assume that the genetic background plays a similarly important role in the predisposition to adverse effects.

Some of this variability is related to comorbidity. Aging is associated with altered pharmacokinetics particularly characterized by diminished clearance and volume of distribution. This has been well evaluated for morphine[18] and fentanyl.[19,20] In studies of morphine use among elderly patients with chronic cancer pain, the older patients required lower doses than their younger counterparts, but they did not exhibit an enhanced risk for opioid-induced adverse effects.[21,22] Studies among patients with postoperative pain similarly found that age was a major predictor of lower morphine dose requirement.[23] In patients with impaired renal function there is delayed clearance of an active metabolite of morphine, morphine-6-glucuronide.[24] Anecdotally, high concentrations of morphine-6-glucuronide have been associated with toxicity[25-27]; however, in a prospective study of patients with opioid-induced delirium or myoclonus, no relationship to renal function was observed.[28] Patients with liver disease may have decreased clearance of meperidine, pentazocine, and propoxyphene that may result in increased bioavailability and prolonged half-lives, which may result in plasma concentrations higher than normal.[29,30] Regarding morphine, mild or moderate hepatic impairment has only minor impact on morphine clearance[31,32]; however, advanced disease may be associated with reduced elimination.[33]

Table 2. Comorbidity That May Mimic Opioid-Induced Adverse Effects

Cause	Adverse Effects
CNS	
Cerebral metastases	Drowsiness, cognitive impairment, nausea, vomiting
Leptomeningeal metastases	Drowsiness, cognitive impairment, nausea, vomiting
Cerebrovascular event	Drowsiness, cognitive impairment
Extradural hemorrhage	Drowsiness, cognitive impairment
Metabolic	
Dehydration	Drowsiness, cognitive impairment
Hypercalcemia	Drowsiness, cognitive impairment, nausea, vomiting
Hyponatremia	Drowsiness, cognitive impairment
Renal failure	Drowsiness, cognitive impairment, nausea, vomiting, myoclonus
Liver failure	Drowsiness, cognitive impairment, nausea, vomiting, myoclonus
Hypoxemia	Drowsiness, cognitive impairment
Sepsis/infection	Drowsiness, cognitive impairment, nausea, vomiting
Mechanical	
Bowel obstruction	Nausea, vomiting
Iatrogenic	
Tricyclics	Drowsiness, cognitive impairment, constipation
Benzodiazepines	Drowsiness, cognitive impairment
Antibiotics	Nausea and vomiting
Vinca alkaloids	Constipation
Flutamide	Constipation
Corticosteroids	Agitated delirium
Nonsteroidal anti-inflammatory drugs	Nausea, drowsiness
Chemotherapy	Nausea, vomiting, drowsiness, cognitive impairment
Radiotherapy	Nausea, vomiting, drowsiness

Drug Interactions

Patients who require opioid analgesia for chronic pain related to cancer or other chronic disorders commonly suffer from conditions requiring other medications that may increase the likelihood of adverse effects by several distinct mechanisms. Commonly, the adverse effects of the other medication may be synergistic or cumulative to those associated with opioid medications (Table 2). Drugs that may alter opioid absorption, metabolism, or clearance of opioid analgesics have recently been reviewed.[34]

Dose Related

Among adverse effects, there is substantial variability in their dose response. A dose-response relationship is most commonly evident regarding the CNS adverse effects of sedation, cognitive impairment, hallucinations, myoclonus, and respiratory depression. Even among these, however, there is very substantial interindividual variability to many of these effects. Additionally, as tolerance develops to some effects, the spectrum of adverse effects varies with prolonged use. Commonly, patients who have had prolonged opioid exposure have a lesser tendency to develop sedation or respiratory depression, and the predominant CNS effects become the neuroexcitatory ones of delirium and myoclo-

nus. Gastrointestinal adverse effects generally have a weaker dose-response relationship. Some, like nausea and vomiting, are common with the initiation with therapy but are subsequently unpredictable with resolution among some patients and persistence among others. Constipation is virtually universal, and it demonstrates a very weak dose relationship and no tolerance over time.

Opioid Initiation and Dose Escalation

After the initiation of an opioid or after dose escalation some adverse effects appear transiently and spontaneously abate. This phenomenon has been well demonstrated in a prospective study on the effect of morphine dose escalation on cognitive performance.[35] This study demonstrated that cognitive impairment associated with the initiation of opioid therapy or dose escalation commonly improved after 7 days. This phenomenon, although often described, has not been formally studied regarding other adverse effects such as nausea, vomiting, and delirium.

DIFFERENTIAL DIAGNOSIS

Adverse changes in patient well-being among patients receiving opioids are not always caused by the opioid. Adverse effects must be differentiated from other causes of

comorbidity that may develop in the treated patient and from drug interactions. Common causes of comorbidity that may mimic opioid-induced adverse effects are presented in Table 2.

Indeed, the appearance of a new adverse change in patient well-being that occurs in the setting of stable opioid dosing is rarely caused by the opioid alone, and an alternate explanation should be vigorously sought. Since polypharmacy is common among patients with advanced cancer, it is essential to scrutinize medication records and patient reports of drug administration to evaluate for possible drug interactions or some other drug-related explanation for the reported symptoms.

OVERVIEW OF ALTERNATIVE APPROACHES TO TREATING OPIOID ADVERSE EFFECTS

In general, four different approaches to the management of opioid adverse effects have been described:

1. Dose reduction of systemic opioid
2. Symptomatic management of the adverse effect
3. Opioid rotation (or switching)
4. Switching route of systemic administration

Dose Reduction of Systemic Opioid

Reducing the dose of administered opioid usually results in a reduction in dose-related adverse effects. When patients have well controlled pain, gradual reduction in the opioid dose will often result in the resolution of dose-related adverse effects while preserving adequate pain relief.[36]

When opioid doses cannot be reduced without the loss of pain control, reduction in dose must be accompanied by the addition of an accompanying synergistic approach. Four approaches are commonly applied:

1. The addition of a nonopioid coanalgesic. The analgesia achieved from nonopioid coanalgesics from the nonsteroidal anti-inflammatory class of agents is additive and often synergistic with that achieved by opioids. This is supported from a number of prospective studies[37-40] and from one retrospective drug utilization survey.[41] Nonopioid coanalgesics, particularly the nonsteroidal anti-inflammatory agents, have the potential to cause side effects that may be additive to the opioid-induced adverse effects that are already problematic. In evaluating the utility of one of these agents in a particular patient setting, one must consider the likelihood of benefit, the risk of adverse effects, the ease of administration, and patient convenience.

2. The addition of an adjuvant analgesic that is appropriate to the pain syndrome and mechanism. Adjuvant analgesics, drugs that have a primary indication other than pain but which are analgesic in some conditions, may be combined with primary analgesics to improve the outcome

for patients who cannot otherwise attain an acceptable balance between relief and side effects.[42] There is great interindividual variability in the response to all adjuvant analgesics and, for most, the likelihood of benefit is limited. Furthermore, many of the adjuvant analgesics have the potential to cause side effects that may be additive to the opioid-induced adverse effects that are already problematic. In evaluating the utility of an adjuvant agent in a particular patient setting, one must consider the likelihood of benefit, the risk of adverse effects, the ease of administration, and patient convenience.

3. The application of a therapy targeting the cause of the pain. Specific antitumor therapies, such as radiotherapy, chemotherapy, or surgery targeting the cause of cancer-related pain can provide substantial relief and thus lower the need for opioid analgesia. The analgesic effectiveness of radiotherapy is documented by abundant data and a favorable clinical experience in the treatment of painful bone metastases,[43-45] epidural neoplasm,[44] and headache attributable to cerebral metastases.[46-48] In other settings, however, there is a lack of data, and the use of radiotherapy is largely anecdotal. Despite a paucity of data concerning the specific analgesic benefits of chemotherapy,[49,50] there is a strong clinical impression that tumor shrinkage is generally associated with relief of pain. Although there are some reports of analgesic effect even in the absence of significant tumor shrinkage,[51-53] the likelihood of a favorable effect on pain is generally related to the likelihood of tumor response. Surgery may have a role in the relief of symptoms caused by specific problems, such as obstruction of a hollow viscus,[54-57] unstable bony structures,[58-60] and compression of neural tissues.[61-63] Bone pain may similarly be relieved by systemically administered local treatments, including bisphosphonates[64,65] or radiopharmaceuticals such as strontium-89.[66]

4. The application of a regional anesthetic or neuroablative intervention. The results of the World Health Organization "analgesic ladder" validation studies suggest that 10% to 30% of patients with cancer pain do not achieve a satisfactory balance between relief and side effects using systemic pharmacotherapy alone.[67-72] Anesthetic and neurosurgical techniques may reduce or eliminate the requirement for systemically administered opioids to achieve adequate analgesia. In general, regional analgesic techniques such as intraspinal opioid and local anesthetic administration or intrapleural local anesthetic administration are usually considered first because they can achieve this end without compromising neurologic integrity. Neurodestructive procedures, however, are valuable in a small subset of patients; and some of these procedures, such as celiac plexus blockade in patients with pancreatic cancer,

may have a favorable enough risk:benefit ratio that early treatment is warranted. The application of these approaches will be the subject for future Expert Working Group reports. In general, consideration of invasive approaches requires a word of caution. Interpretation of data regarding the use of alternative analgesic approaches and extrapolation to the presenting clinical problem requires care. The literature is characterized by the lack of uniformity in patient selection, inadequate reporting of previous analgesic therapies, inconsistencies in outcome evaluation, and paucity of long-term follow-up. Furthermore, reported outcomes in the literature may not predict the outcomes of a procedure performed on a medically ill patient by a physician who has more limited experience with the techniques involved.

Symptomatic Management of the Adverse Effect

Symptomatic drugs used to prevent or control opioid adverse effects are commonly employed. Most of these approaches are based on cumulative anecdotal experience. With few exceptions, the literature describing these approaches is anecdotal or "expert opinion." Very few studies have prospectively evaluated efficacy, and no studies have evaluated the toxicity of these approaches over the long term. In general, this approach involves the addition of a new medication. Implicitly, polypharmacy adds to medication burden and invokes associated risks of adverse effects, drug interaction, and diminished compliance.[73]

Opioid Rotation (Also Called Opioid Switching or Substitution)

Over the past 10 years, numerous clinicians and cancer pain services have reported successful reduction in opioid side effects by switching from the currently administered opioid to an alternative opioid.[74-88] This approach has been termed opioid rotation,[78,89] and it is also commonly referred to as opioid switching or opioid substitution. Using this approach, the reporting clinicians have described improvements in cognitive impairment, sedation, hallucinations, nausea, vomiting, and myoclonus.

The biologic basis for the observed intraindividual variability in sensitivity to opioid analgesia and adverse effects is multifactorial. Preclinical studies show that opioids can act on different receptors or subtype receptors,[78,90-99] and individual receptor profiles may influence the analgesia as well as the side effects. The genetic makeup of the individual plays and important role in analgesia for some opioids,[14-16,100-103] and similar phenomena may contribute to variability in adverse-effect sensitivity.

This approach requires familiarity with a range of opioid agonists and with the use of the opioid dose conversion tables when switching between opioids. It is important to appreciate, however, that doses calculated using such tables may not be accurate among patients tolerant to opioids. This inaccuracy is explained to some extent by the large SDs observed in many of the initial relative potency studies that formed the scientific basis for the development of these tables.[104] Furthermore, the phenomenon of incomplete cross-tolerance can lead to unanticipated potency in a new agent, even when from the same general class of opioid analgesic. The use of the opioid dose conversion tables is critical to this strategy. Guidelines for switching and rotating opioids are presented in Appendix A, and a dose conversion table appears in Appendix B.

While opioid rotation has the practical advantage of minimizing polypharmacy, outcomes are variable and somewhat unpredictable. While 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% of patients needed to undergo two or more switches until a satisfactory outcome was achieved.[77]

Switching Route of Systemic Administration

Limited data indicates that some adverse effects among patients receiving oral morphine can be relieved by switching the route of admission to the subcutaneous route. In one small study, this phenomenon was reported for nausea and vomiting[10]; in another study, there was less constipation, drowsiness, and nausea.[105]

INITIAL MANAGEMENT OF THE PATIENT RECEIVING ORAL MORPHINE WHO PRESENTS WITH ADVERSE EFFECTS

Among the experts, there was consensus regarding the initial steps in the management of adverse effects.

Distinguish Between Morphine Adverse Effects From Comorbidity or Drug Interactions

This step requires careful evaluation of the patient for factors outlined in Table 2. If present, these factors should be redressed. Metabolic disorders, dehydration, or sepsis should be treated, nonessential drugs that may be producing an adverse interaction should be discontinued. This situation requires a high level of clinical vigilance with close follow-up. Often, symptomatic measures to provide relief of the distressing symptoms will be required until improvement in patient well-being is observed.

Consider Dose Reduction

If the patient has good pain control, consider reducing the morphine dose. If the adverse effect is mild to moderate,

this may be achieved by reducing the morphine dose by 25% to 50%. This recommendation is based on the known dose-response relationship for some opioid adverse effects such as drowsiness, delirium and myoclonus as derived from pharmacokinetic/pharmacodynamic studies[106-108] and clinical observations.[87,109-113] In the setting of severe adverse effects, particularly neurotoxicity, often a complete cessation of morphine will be needed to allow circulating morphine levels to fall sufficiently for the adverse effects to resolve. Once resolution has occurred, consideration can be given to recommencing morphine at a lower dose or switching to an alternative opioid in accordance with the data presented below.

SPECIFIC ADVERSE EFFECTS: BEYOND THE INITIAL STEPS

Beyond these initial steps, the Expert Working Group concluded that a range of reasonable options commonly coexisted. In the sections below, the Expert Working Group summarizes the existing data regarding symptomatic management, opioid rotation, and switching the route of systemic opioid administration in the management of specific adverse effects and presents a rational approach to prudent decision making.

Nausea and Vomiting

Scope of the problem. Data from prospective studies indicates that chronic nausea is observed in 15% to 30% of patient receiving oral morphine for chronic cancer pain.[9,11,13,114-121]

Symptomatic management. These are no studies to indicate the superiority of one antiemetic over another in the management of opioid-induced nausea. Commonly, recommendations have been made on the basis of the inferred mechanism of opioid-induced nausea. These recommendations are unsupported by any prospective study or even systematic evaluation of retrospective data. Among the agents that have been suggested are metoclopramide, haloperidol, prochlorperazine, dimenhydrinate, phenothiazine, transdermal scopolamine, cisapride, ondansetron (and other 5-HT3 antagonists), and dexamethasone (and other corticosteroids).

Opioid rotation. In five reports, the prevalence and severity of nausea and vomiting were substantially reduced by switching to an alternative opioid.[77,78,83,84,86]

Switching route. In two small studies, the switch from oral to subcutaneous morphine produced significantly less nausea[10,105] and vomiting.[10] There is conflicting data regarding the effect of switching to the rectal route.[9,122,123] If present, this effect is small.

Constipation

Scope of the problem. Data from prospective studies indicates that chronic constipation is observed in 40% to 70% of patient receiving oral morphine for chronic cancer pain.[9,11,13,114-121] Opioid-induced constipation can be exacerbated by metabolic alterations (diabetes, hypercalcemia, hypokalemia, uremia, hypothyroidism), dehydration, advanced age, reduced physical activity/immobility, low-fluid and/or low-fiber diet intake, difficulty reaching the bathroom, mechanical obstruction, neurologic disorders, autonomic failure, drugs with anticholinergic action such as ondansetron, diuretics, anticonvulsants, iron, vinca alkaloids, and some antihypertensive drugs.[124,125]

Symptomatic management. These are no studies to indicate the superiority of one laxative over another in the management of opioid-induced constipation. Commonly, recommendations have been made on the basis of personal experience and clinical observations. These recommendations are generally unsupported by any prospective study or even systematic evaluation of retrospective data. Among the agents that have been suggested are docusate, senna, bisacodyl, phenophthalein, and lactulose. Prospective data has demonstrated efficacy of senna[126] and oral naloxone.[127-129]

Opioid rotation. In one small series, opioid rotation of morphine to methadone resulted in a reduction in constipation.[130]

Switching route. Reduction in constipation was not reported in any of the studies on changes in morphine route of administration.

Switching drug and route. Three recent crossover studies have demonstrated a reduced tendency to constipation among patients treated with transdermal fentanyl compared with oral morphine.[11-13]

Sedation

Scope of the problem. Data from prospective studies indicates that sedation or drowsiness is observed in 20% to 60% of patients receiving oral morphine for chronic cancer pain.[9,11,13,114-121]

Symptomatic management. The data indicating the merit of amphetamine psychostimulants is limited. In a single-dose study, dextroamphetamine antagonized opioid-induced sedation and cognitive impairment in postsurgical patients.[131] Several small controlled clinical trials of methylphenidate demonstrated efficacy in reducing drowsiness and confusion.[132-137] Positive outcomes were also observed in a small open label study of these agents in adolescents with chronic cancer pain.[138] All authors note that these agents can produce adverse effects such as hallucinations, delirium or psychosis, decreased appetite, tremor, and

tachycardia. These drugs are contraindicated in patients with a history of psychiatric disorders and are relatively contraindicated in patients with a history of substance abuse or with paroxysmal tachyarrhythmias.

Switching route. In one small study, the switch from oral to subcutaneous morphine produced significantly less drowsiness.[105]

Opioid rotation. In five reports, the prevalence and severity of drowsiness and/or sedation were substantially reduced by opioid rotation.[76,78,80,84,86]

Cognitive Failure

Scope of the problem. Mild cognitive impairment is common after the initiation of opioid therapy or dose escalation.[35,139] There is no data on the prevalence of severe opioid-induced cognitive failure or delirium.

Symptomatic therapy. Neuroleptics, specifically haloperidol, are most commonly recommended in the symptomatic management of patients with delirium. When associated with severe agitation, a benzodiazepine is often coadministered.[140] These recommendations largely derive from the extensive experience and studies in the management of acute delirium in the medically ill.[140-145] Anecdotal experience among cancer patients supports this approach.[146,147]

Opioid rotation. Delirium or agitated confusion was reported to improve after opioid rotation in five retrospective series.[77,78,80,85,86] In the only prospective study of its type, Maddocks et al[83] switched patients who developed delirium while taking oral or subcutaneous morphine to a continuous subcutaneous infusion of oxycodone, with resolution of the delirium in eight of 13 patients.

Switching route. Reduction in delirium was not reported in any of the studies on changes in morphine route of administration.

Myoclonus

Scope of the problem. Myoclonus may occur in patients on chronic opioid therapy, and it seems to be dose related in a unpredictable manner. In a small study of patients receiving more than 500 mg morphine per day, 12 of 19 had significant myoclonus.[148] A study of patients with morphine-related adverse effects indicated that the prevalence of myoclonus was threefold higher among patients receiving oral morphine than among those receiving parenteral morphine, suggesting a role of metabolite production by the liver.[28]

Symptomatic management. There are no prospective studies on the treatment of opioid-induced myoclonus. Consequently, current recommendations for the treatment of myoclonus are empiric and anecdotal. Agents that have been recommended include baclofen,[149-151] diazepam[152,153]

and clonazepam,[154-156] midazolam,[157,158] valproic acid,[155,156] and dantrolene sodium.[159]

Opiod rotation. Improvement in myoclonus after opioid rotation, commonly with total resolution of the symptom, is reported in five retrospective series.[77,78,84,86,87]

Switching route. Reduction in myoclonus was not reported in any of the studies on changes in morphine route of administration.

Pruritus

Scope of the problem. Data from prospective studies indicate that chronic itch is observed in 2% to 10% of patient receiving oral morphine for chronic cancer pain.[9,11,13,114-121]

Symptomatic management. There are no prospective studies on the treatment of opioid-induced pruritus. Consequently, current recommendations for the treatment of pruritus are empiric and anecdotal. Antihistamines are commonly recommended. Anecdotal positive experience has been reported with paroxetine.[160]

Opioid rotation. There are conflicting data suggesting that fentanyl and oxymorphone are less likely to produce histamine release.[161,162] A case where persistent morphine-induced itch resolved after switching opioid has been reported.[163]

Switching route. Reduction in pruritus was not reported in any of the studies on changes in morphine route of administration.

SELECTING BETWEEN THERAPEUTIC OPTIONS IN THE MANAGEMENT OF OPIOID ADVERSE EFFECTS

The members of the Expert Working Group concluded that there were inadequate data to formulate specific recommendations regarding the management of morphine side effects, and they recognized that even among expert clinicians there is considerable variability in individual practices. Despite this, they agreed on six factors to be taken into consideration when considering therapeutic options in the management of morphine adverse effects:

1. Convenience: Compliance with analgesic therapy is enhanced when the treatment program is simple.[73] In general, polypharmacy should be minimized whenever possible.

2. Availability: Drug availability is highly variable between countries and the range of available therapeutic options strongly influences clinical decision making.

3. Cost: Some opioid formulations, nonsteroidal anti-inflammatory drugs, adjuvant analgesics, and symptomatic remedies are expensive. This must be considered when budgetary constraints exist, and when insurance coverage is limited.

4. Familiarity: Clinician bias favors the selecting of options with which the clinician has greatest familiarity and experience. Since the most familiar option may not be the best option, clinicians should be sensitive to this bias and should familiarize themselves with a range of therapeutic options, including facility with all of the opioid drugs available in their country. Of critical issue is the need to be familiar with the use of the dose conversion tables in the calculation of doses when switching between different opioids and between routes of opioid administration.

5. Availability of appropriate experience and expertise: If invasive procedures are considered, it is important to consider the availability of local expertise. The outcome of invasive techniques is very operator-dependent, and outcomes reported in the literature may not predict the outcomes of a procedure performed by a physician who has more limited experience with the techniques involved.

6. Patient preference: In some situations, patients may have strong preference for an option of adding another medication or switching to an alternative monotherapy. Therapeutic options should be presented to the patient, and patient preferences should weigh into final decision making.

DIRECTIONS FOR FUTURE RESEARCH

The Expert Working Group identified the need for prospective research using validated outcome measures of pain and adverse effects to evaluate:

1. The efficacy of opioid-sparing approaches with the use of nonopioid and adjuvant analgesics and invasive approaches, including regional drug delivery and neuroablative techniques

2. The efficacy of dose reduction in the management of adverse effects

3. The efficacy of specific strategies in the symptomatic management of adverse effects

4. The efficacy of opioid rotation in management of adverse effects

5. The efficacy of switching routes of administration in management of adverse effects

6. Comparative studies randomizing patients between various approaches

In summary, the following conclusions can be drawn from this study:

1. There is no sound evidence from well-designed clinical trials of the superiority of one opioid over another regarding the side effect profile and/or analgesic profile.

2. There are now numerous reports describing improvement or resolution in adverse effects from morphine after switching to an alternative opioid. Data derived from observational studies and reports of opioid rotation indicate substantial intraindividual variability in analgesic effect and propensity to adverse effects.

3. 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 such as oxycodone, methadone, hydromorphone, and fentanyl is recommended. The outcome is not predictable and several different agents may need to be tried sequentially.

4. Despite the presence of multiple recommendations for the symptomatic management of opioid-induced adverse effects, the level of evidence supporting specific efficacy is very low.

5. Clinical research is needed to more formally evaluate the relative merits of these approaches.

ACKNOWLEDGMENT

APPENDIX A

Guidelines for Switching and Rotating Opioids

1. *Use dose conversion tables.* 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.

2. *Dose conversion tables are guidelines only.* 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%. 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.

3. *Dosing with the new opioid.* The initial goal when switching opioids is to convert the patient to the new drug safely. As noted above, 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.

APPENDIX B
Dose Conversion Table of Opioids in the Setting of Cancer Pain Management

Opioid	Relative Equianalgesic Doses
Morphine[122,123,164-166]	10 mg PO: 7-10 mg PR 10 mg PO: 3-5 mg SC or IV
Hydromorphone[74,75,167,168]	Morphine 10 mg PO: hydromorphone 2 mg PO Hydromorphone 2 mg PO: hydromorphone 1 mg SC or IV
Oxycodone[120,166,169,170]	Morphine 10 mg PO: oxycodone 7.5 mg PO Oxycodone 10 mg PO: oxycodone 5 mg SC or IV
Methadone[82]	N.B.—the ratio depends on the dose of previous opioid. → If morphine 30 mg to 90 mg PO use ratio of 4:1 (ie, morphine 30 mg is approximately equivalent to 7 mg of methadone → If morphine 90 to 300 mg PO use ratio of 8:1 (ie, morphine 300 mg PO is approximately equivalent to 35 mg methadone PO) → If morphine > 300 mg PO use ratio of 12:1 (ie, morphine 400 mg PO is approximately equivalent to 35 mg methadone PO) If previous morphine dose is *much* higher than 300 mg, the dose ratio will be higher than 12:1
Fentanyl[171,172]	Readers are referred to tables distributed by the manufactures for dose ratios related to transdermal fentanyl. Wide ranges are noted in these tables. A dose ratio of morphine SC: fentanyl SC of 100:1 is suggested for parenteral fentanyl.

NOTE. Doses are depicted to indicate relative potency, ie, morphine 10 mg PO is approximately equivalent in potency to hydromorphone 2 mg PO. This would give an equianalgesic dose ratio of morphine to hydromorphone of 5:1.

Abbreviations: PO, oral route; SC, subcutaneous route; IV, intravenous route; PR, rectal route.

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