Opioids and the management of cancer pain

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Opioid analgesic therapy is the cornerstone of the symptomatic management of cancer pain of moderate or greater severity. This holds true regardless of the pain mechanism. Although somatic and visceral pain appear to be relatively more responsive to opioid analgesics than neuropathic pain, neuropathic pain is not "opioid resistance", and appropriate dose escalation will identify many patients with neuropathic pain who can achieve adequate relief [1].

Optimal use of opioid analgesics requires a sound understanding of the general principles of opioid pharmacology, the pharmacological characteristics of each of the commonly used drugs, and principles of administration, including: drug selection, routes of administration, dosing and dose titration and the prevention and management of adverse effects.

Important principles in opioid drug therapy

Classification

Opioid compounds can be divided into agonist, agonist–antagonist and antagonist classes based on their interactions with the various receptor subtypes (Table 1). In the management of cancer pain, the pure agonists are most commonly used. The mixed agonist–antagonist opioids (pentazocine, nalbuphine and butorphanol) play a minor role in the management of cancer pain because of the existence of a ceiling effect for analgesia, the potential for precipitation of withdrawal in patients physically dependent to opioid agonists, and the problem of dose-dependent psychotomimetic side effects that exceed those of pure agonist drugs [2]. In recent years there has been a renewed interest in the partial agonist, buprenorphine, particular in its transdermal administration.

Table 1
Classification of opioid analgesics

Agonists	Partial agonists	Agonist/antagonists
Morphine	Buprenorphine	Pentazocine
Codeine	Dezocine	Butorphanol
Oxycodone		Nalbuphine
Heroin		
Oxymorphone		
Pethedine		
Levorphanol		
Hydromorphone		
Methadone		
Fentanyl		
Sufentanil		
Alfentanil		
Propoxyphene		

Dose–response relationship

The pure agonist drugs do not have a ceiling dose; as the dose is raised analgesic effect increases in a semi log-linear function, until either analgesia is achieved or the patient develops dose limiting adverse effects such as nausea, vomiting, confusion, sedation, myoclonus or respiratory depression.

The equianalgesic dose ratio

Relative analgesic potency of opioids is commonly expressed in terms of the equianalgesic dose ratio. This is the ratio of the dose of two analgesics required to produce the same analgesic effect. By convention, the relative potency of each of the commonly used opioids is based upon a comparison to 10 mg of parenteral morphine. Equianalgesic dose information (Table 2) provides guidelines for dose selection when the drug or route of administration is changed.

Several principles are critical in interpreting the data presented in equianalgesic dose tables. The commonly quoted values do not reflect the substantial variability that is observed in both single-dose and multidose crossover studies. Numerous variables may influence the appropriate dose for the individual patient, including pain severity, prior opioid exposure (and the degree of cross-tolerance this confers), age, route of administration, level of consciousness and genetically determined metabolic or receptor heterogeneity. For most agents the equianalgesic dose relationship to morphine is linear, for methadone

Table 2
Opioid agonist drugs

Drug	Dose (mg) equianalgesic to 10 mg IM morphine		Half-life (hr)	Duration of action (hr)	Comments
	IM	PO			
Codeine	130	200	2–3	2–4	Usually combined with a non-opioid
Oxycodone	7–10	15–20	2–3	2–4	
Propoxyphene	50	100	2–3	2–4	Usually combined with a non-opioid Norpropoxyphene toxicity may cause seizures
Morphine	10	30	2–3	3–4	Multiple routes of administration and formulations available M6G accumulation in renal failure
Hydromorphone	2–3	7.5	2–3	2–4	Multiple routes of administration and formulations available
Methadone	1–3	2–6	15–190	4–8	Plasma accumulation may lead to delayed toxicity Dosing should be initiated on a PRN basis.
Pethidine	75	300	2–3	2–4	Low oral bioavailability Norpethidine toxicity limits utility Contraindicated in patients with renal failure and those receiving mono-amine oxidase (MAO) inhibitors
Fentanyl transdermal system		Empirically transdermal fentanyl 100 $\mu g\,h^{-1}$ = 2–4 $mg\,h^{-1}$ intravenous morphine		48–72	Patches available to deliver 25, 50, 75 and 100 $\mu g\,hr^{-1}$

however, the relationship appears to be curvilinear with the equianalgesic dose ratio falling as the dose of prior morphine increases: at low doses of morphine (30–300 mg oral morphine) the equianalgesic ratio for oral methadone to oral morphine is 1:4–1:6 and at high doses (>300 mg oral morphine) 1:10–1:12 [3].

Opioid agonists

Codeine

Codeine is the most commonly used opioid analgesic for the management of mild to moderate pain. It is generally formulated in combination with aspirin or acetaminophen. Its plasma half-life and duration of action is usually in the range of 2–4 hr. The analgesic effect of codeine is at least partly dependent on the metabolism of codeine to morphine by the genetic polymorphic cytochrome P-450 CYP2D6 (sparteine oxygenase). Approximately 7% of Caucasians lack CYP2D6 activity (poor metabolisers) due to inheritance of two non-functional alleles and in these people codeine has a diminished analgesic effect [4,5]. Recently, a case of opioid toxicity was reported in a patient with ultrarapid CYP2D6 activity [6].

Dihydrocodeine

Dihydrocodeine is an equianalgesic codeine analog. In many places it is only available in combination with acetaminophen or aspirin. A single-agent sustained-release formulation has also been developed [7]. Similar to codeine, poor metabolisers of sparteine have a diminished analgesic effect with this agent [8].

Hydrocodone

Hydrocodone has an oral analgesic potency that is approximately half that of oral morphine. It is widely available in a combination tablet that incorporates 10 mg hydrocodone with 1000 mg acetaminophen [9]. Hydrocodone is metabolised to morphine by cytochrome P-450 and, consequently, poor metabolisers have a diminished analgesic effect.

Oxycodone

Oral oxycodone has a high bioavailability (60%) and an analgesic potency that is 25–50% greater than morphine [10]. It is metabolised by the cytochrome isoenzyme CYP2D6, which is severely impaired by liver dysfunction [11]. Oral oxycodone, in combination with aspirin or acetaminophen in products that

provide 5 mg of oxycodone per tablet, is commonly used for moderate pain in Step II of the "analgesic ladder". Single-agent tablet or syrup formulations are also available, and doses of these can be adjusted to effectively manage severe pain [12]. Sustained-release formulations have been developed which have an 8–12 hr duration of action and are suitable for the management of both moderate and severe pain [10,13]. In some countries oxycodone pectinate is available as a rectal suppository which has a delayed absorption and prolonged duration of effect [14].

Propoxyphene (Dextropropoxyphene)

Propoxyphene is a low potency congener of methadone. It is metabolised to norpropoxyphene, which has a long half-life and is associated with excitatory effects, including tremulousness and seizures [15]. These effects are dose-related and are not a clinical problem at the doses of propoxyphene typically administered for moderate pain (50–100 mg every 4 hr) [16]. In addition to the above, propoxyphene may rarely induce a hepatotoxic reaction [17]; potentially dangerous drug interactions have been reported when propoxyphene has been administered along with carbamazepine [18], warfarin [19] or alcohol.

Morphine

Based on its availability and clinician familiarity with its use, morphine has been designated as the prototypical agent for Step III of the "analgesic ladder". It is available in a very wide range of formulations: injectable, immediate- and controlled-release tablets, immediate- and controlled-release rectal suppositories, immediate-release syrup and controlled-release suspension.

Morphine has a half-life and duration of action of 2–4 hr. It undergoes hepatic glucuronidation at the 3 and 6 positions and the metabolites are excreted by the kidneys. Morphine-3-glucuronide (M3G) is the major metabolite [20]. M3G is not an analgesic, rather there is data to suggest a role in the production of dose-related adverse effects such as hyperalgesia/allodynia and myoclonus [21]. Morphine-6-glucuronide (M6G) binds to opioid receptors [22] and produces potent opioid effects in animals [22–24]. In humans the data is conflicting with analgesia observed with intrathecal administration [25] but not consistently after intravenous administration [26,27]. M6G excretion by the kidney is related to creatinine clearance [28] and in some patients with impaired renal function, high concentrations of M6G have been associated with toxicity [29–31], suggesting the need for enhanced vigilance when administering morphine to patients with renal impairment. The intramuscular (IM) to per Os (by mouth) (PO) relative potency of morphine is 1:3 or 1:2 [32].

Hydromorphone

Hydromorphone is a versatile, short half-life, opioid that can be administered by the oral, rectal, parenteral and intraspinal routes [33]. Its solubility, high bioavailability by continuous subcutaneous infusion (78%) [34] and the availability of a high concentration preparation (10 mg cc^{-1}), make it particularly suitable for subcutaneous infusion [33]. In some countries a sustained-release formulation of oral hydromorphone is available [35]. The equianalgesic ratio of parenteral morphine to hydromorphone has become a matter of controversy: recent data suggests that it is less than the traditionally quoted ratio 7:1 and that it is probably closer to 4:1 [36,37].

Fentanyl

Fentanyl is a semisynthetic opioid characterized by high potency, lipophilicity, and a short half-life after bolus administration. In its transdermal formulations, it is widely used in the management of cancer pain [38–40]. An oral transmucosal formulation may be particularly useful in the management of "breakthrough" pain in the cancer population [41,42]. Fentanyl is also used parenterally as a premedication for painful procedures and in continual infusion either intravenously [43,44] or by the subcutaneous route [45].

Methadone

Methadone is a synthetic opioid with a very long plasma half-life, which averages approximately 24 hr (range from 13 to over 100 hours) [46,47]. Despite this long half-life, many patients require dosing at a 4–8 hr interval to maintain analgesic effects [48]. After treatment is initiated or the dose is increased, plasma concentration rises for a prolonged period, and this may be associated with delayed onset of side effects. Serious adverse effects can be avoided if the initial period of dosing is accomplished with "as needed" administration [49,50]. When steady state has been achieved, scheduled dose frequency should be determined by the duration of analgesia following each dose. Oral and parenteral preparations of methadone are available. Subcutaneous infusion has been reported to cause local skin toxicity and is not generally recommended [51].

The equianalgesic dose ratio of morphine to methadone has been a matter of confusion and controversy. Recent data from crossover studies indicate that methadone is much more potent than previously described in literature, and that the ratio correlates with total opioid dose administered before switching to methadone [52]. Among patients receiving low doses of morphine the ratio is 4:1; in contrast, for patients receiving more than 300 mg of oral morphine (or parenteral equivalent) the ratio is approximately 10:1 [52].

Pethedine

Pethedine is a short half-life opioid agonist with a profile of potential adverse effects that limits its utility. Pethedine is N-demethylated to norpethedine, which is an active metabolite that is twice as potent as a convulsant and one-half as potent as an analgesic than its parent compound. The half-life of norpethedine is 12–16 hr, approximately 4–5 times the half-life of pethedine. Accumulation of norpethedine after repetitive dosing of pethedine can result in CNS toxicity characterized by subtle adverse mood effects, tremulousness, multifocal myoclonus and, occasionally, seizures [53,54]. The most serious toxicity associated with pethedine is norpethedine-induced seizures. Naloxone does not reverse this effect, and indeed, could theoretically precipitate seizures in patients receiving pethedine by blocking the depressant action of pethedine and allowing the convulsant activity of norpethedine to become manifest [55,56]. If naloxone must be administered to a patient receiving pethedine, it should be diluted and slowly titrated while appropriate seizure precautions are taken. Selective toxicity of pethedine can also occur following administration to patients receiving monoamine oxidase inhibitors. This combination may produce a syndrome characterized by hyperpyrexia, muscle rigidity and seizures which may occasionally be fatal [57]. The pathophysiology of this syndrome is related to excess availability of serotonin at the 5-HT1A-receptor in the CNS.

Selecting an appropriate opioid

The factors that influence opioid selection in chronic pain states include pain intensity, pharmacokinetic and formulatory considerations, previous adverse effects and the presence of co-existing disease.

Traditionally, patients with moderate pain have been treated with a combination product containing acetaminophen or aspirin plus codeine, dihydrocodeine, hydrocodone, oxycodone and propoxyphene. The doses of these combination products can be increased until the maximum dose of the non-opioid co-analgesic is attained (e.g. 4000 mg acetaminophen). Recent years have witnessed the proliferation of new opioid formulations that may improve the convenience of drug administration for patients with moderate pain. These include controlled-release formulations of codeine, dihydrocodeine, oxycodone, morphine and tramadol in dosages appropriate for moderate pain.

Patients who present with strong pain are usually treated with morphine, hydromorphone, oxycodone, oxymorphone, fentanyl or methadone. Of these, the short half-life opioid agonists (morphine, hydromorphone, fentanyl, oxycodone or oxymorphone) are generally favoured because they are easier to titrate than the long half-life drugs which require a longer period to approach steady-state plasma concentrations. Morphine is generally preferred since it has a short half-life and is easy to titrate in its immediate release form, and it is also available as a controlled-release preparation that allows an 8–12 hr dosing interval.

If the patient is currently using an opioid that is well tolerated, it is usually continued unless difficulties in dose titration occur or the required dose cannot be administered conveniently. A switch to an alternative opioid is considered if the patient develops dose-limiting toxicity which precludes adequate relief of pain without excessive side effects or if a specific formulation, not available with the current drug, is either needed or may substantially improve the convenience of opioid administration.

Some patients will require sequential trials of several different opioids before a drug which is effective and well tolerated is identified. This strategy has been variably labelled opioid rotation or opioid switching. The existence of incomplete cross-tolerance to various opioid effects (analgesia and side effects) may explain the utility of these sequential trials. It is strongly recommended that clinicians be familiar with at least 3 opioid drugs used in the management of severe pain and have the ability to calculate appropriate starting doses using equianalgesic dosing data when switching between drugs.

Selecting the appropriate route of systemic opioid administration

Opioids should be administered by the least invasive and safest route capable of providing adequate analgesia. Usually, the oral route is preferred. Alternative

routes are necessary for patients who have impaired swallowing or gastrointestinal dysfunction, those who require a very rapid onset of analgesia and those who are unable to manage either the logistics or side effects associated with the oral route.

The development of transdermal fentanyl has provided a convenient and non-invasive alternative to oral administration. Transdermal patches capable of delivering 25, 50, 75 and 100 $\mu g\,hr^{-1}$ are available. The dosing interval for each patch is usually 72 hr but some patients require a 48 hr schedule [58]. Data from controlled studies indicate that the transdermal administration of fentanyl is associated with a lesser incidence of constipation than oral morphine and is often preferred [59–61].

Other non-invasive routes are less commonly used. Rectal suppositories containing oxycodone, hydromorphone, oxymorphone and morphine have been formulated and controlled-release morphine tablets can also be administered per rectum [62,63]. The potency of opioids administered rectally is approximately equivalent to that achieved by the oral route [32].

The sublingual route has limited value due to the lack of formulations, poor absorption of most drugs and the inability to deliver high doses or prevent swallowing of the dose. An oral transmucosal formulation of fentanyl that is absorbed across the buccal mucosa, is approved for the management of breakthrough pain. This formulation is rapidly absorbed and achieves blood levels and time to peak effect that are comparable to parenterally administered fentanyl. Indeed, the time to onset of effect is 5–10 min [42,64]. Studies in cancer patients suggested that it is useful and that it can provide rapid and very effective relief of breakthrough pain [41]. Formulations incorporating 200, 400, 600 and 800 μg are available. The most common adverse effects associated with this formulation are somnolence, nausea and dizziness.

Parenteral routes

A parenteral route may be considered when the oral route is precluded or there is need for rapid onset of analgesia, or a more convenient regimen. Repeated parenteral bolus injections, which may be administered by the intravenous (IV), intramuscular (IM) or subcutaneous (SC) routes, provides the most rapid onset and shortest duration of action. Parenteral boluses are most commonly used to treat very severe pain, in which case doses can be repeated at an interval as brief as that determined by the time to peak effect, until adequate relief is achieved. Repeated bolus doses without frequent skin punctures can be accomplished through the use of an indwelling IV or SC infusion device such as a 25–27 gauge infusion device (a butterfly) which can be left under the skin for up to a week [65].

Continuous parenteral infusions are useful for many patients who cannot be maintained on oral opioids. Long-term infusions may be administered IV or SC. In practice, the major indication for continuous infusion occurs among patients who are unable to swallow or absorb opioids. Continuous infusion is also used in some patients whose high opioid requirement renders oral treatment impractical. Ambulatory patients can easily use continuous SC infusion. A range of pumps are available varying in complexity, cost and ability to provide patient-controlled "rescue doses" as an adjunct to a continuous basal infusion [66]. Opioids suitable for continuous SC infusion must be soluble, well absorbed and non-irritant. Extensive experience has been reported with heroin, hydromorphone, oxymorphone, morphine and fentanyl [66]. Methadone appears to be relatively irritating and is not generally recommended. To maintain the comfort of an infusion site, the SC infusion rate should not usually exceed 3–5 $cc\,hr^{-1}$. Patients who require high doses may benefit from the use of concentrated solutions or hypodermoclysis. For patients needing very high doses of opioids, a high-concentration hydromorphone (10 $mg\,cc^{-1}$) is available commercially and the organic salt of morphine, morphine tartrate, is available in some countries as an 80 $mg\,cc^{-1}$ solution.

Changing routes of administration

The switch between oral and parenteral routes should be guided by knowledge of relative potency (Table 2) to avoid subsequent over-dosing or under-dosing. In calculating the equianalgesic dose, the potencies of the IV, SC and IM routes are considered equivalent. In recognition of the imprecision in the accepted equianalgesic doses and the risk of toxicity from potential overdose, a modest reduction in the equianalgesic dose is prudent.

Scheduling of opioid administration

The schedule of opioid administration should be individualised to optimise the balance between patient comfort and convenience. "Around the clock" dosing and "as needed" dosing both have a place in clinical practice.

"Around the clock" dosing with "rescue doses"

"Around the clock" dosing provides the chronic pain patient with continuous relief by preventing the

pain from recurring. Controlled-release preparations of opioids can lessen the inconvenience associated with the use of "around the clock" administration of drugs with a short duration of action. Patients should also be provided a so-called "rescue dose", which is a supplemental dose offered on an "as needed" basis to treat pain that breaks through the regular schedule [67].

The frequency with which the rescue dose can be offered depends on the route of administration and the time to peak effect for the particular drug. Oral rescue doses are usually offered up to every 1–2 hr and parenteral doses can be offered as frequently as every 15–30 min. Clinical experience suggests that the initial size of the rescue dose should be equivalent to approximately 50–100% of the dose administered every 4 hr for oral or parenteral bolus medications, or 50–100% of the hourly infusion rate for patients receiving continuous infusions. Alternatively, this may be calculated as 5–15% of the 24-hr baseline dose. The magnitude of the rescue dose should be individualised and some patients with low baseline pain but severe exacerbations may require rescue doses that are substantially higher [68]. The drug used for the rescue dose is usually identical to that administered on a scheduled basis.

This approach provides a method for safe and rational stepwise dose escalation, which is applicable to all routes of opioid administration. Patients who are requiring more than 4–6 rescue doses per day should generally undergo escalation of the baseline dose. The quantity of the rescue medication consumed can be used to guide the dose increment. Alternatively, each dose increment can be set at 33–50% of the pre-existing dose. In all cases, escalation of the baseline dose should be accompanied by a proportionate increase in the rescue dose, so that the size of the supplemental dose remains a constant percentage of the fixed dose.

"As-needed" (PRN) dosing

Opioid administration on an "as needed" basis, without an "around the clock" dosing regimen, may provide additional safety during the initiation of opioid therapy, particularly when rapid dose escalation is needed or therapy with a long half-life opioid such as methadone or levorphanol is begun. "As needed" dosing may also be appropriate for patients who have rapidly decreasing analgesic requirement or intermittent pains separated by pain-free intervals.

Patient Controlled Analgesia (PCA)

PCA generally refers to a technique of parenteral drug administration in which the patient controls an infusion device that delivers a bolus of analgesic drug "on demand" according to parameters set by the physician. Long-term PCA in cancer patients is most commonly accomplished via the subcutaneous route using an ambulatory infusion device [69]. In most cases, PCA is added to a basal infusion rate and acts essentially as a rescue dose [69]. In rare cases patients may benefit from PCA alone to manage episodic pains characterised by an onset so rapid that an oral dose could not provide sufficient prompt relief.

Dose selection and titration

Selecting a starting dose

A patient who is relatively non-tolerant, having had only some exposure to an opioid typically used on the second rung of the "analgesic ladder" for moderate pain, should generally begin one of the opioids typically used for severe pain at a dose equivalent to 5–10 morphine IM every 4 hr [32]. If morphine is used, a PO:IM relative potency ratio of 2:1–3:1 is conventional [32].

Dose adjustment

Inadequate relief should be addressed through gradual escalation of dose until adequate analgesia is reported or excessive side effects supervene. Because opioid response increases linearly with the log of the dose, a dose increment of less than 30–50% is not likely to significantly improve analgesia. The absolute dose is immaterial as long as administration is not compromised by excessive side effects, inconvenience, discomfort or cost.

Rate of dose titration

The rate of dose titration depends on the severity of the pain, the medical condition of the patient and the goals of care. Patients who present with very severe pain are sometimes best managed by repeated parenteral administration of a dose every 15–30 min until pain is partially relieved. Patients with moderate pain may not require a loading dose of the opioid, but rather the initiation of a regular dose with provision for rescue doses and gradual dose titration. In this situation dose increments of 30–50% can be administered at intervals greater than that required to reach steady state following each change. The dose of morphine

(tablets or elixir), hydromorphone or oxycodone can be increased on a twice-daily basis, and the dose of controlled-release opioids or transdermal fentanyl can be increased every 24–48 hr.

The problem of tolerance

When the need for dose escalation arises, disease progression [70,71], increasing psychological distress or changes in the pharmacokinetics of an analgesic drug are much more common than true analgesic tolerance. True analgesic tolerance, which could compromise the utility of treatment, can only be said to occur if a patient manifests the need for increasing opioid doses in the absence of other factors (e.g. progressive disease) that would be capable of explaining the increase in pain.

Management of opioid 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 summarised in Table 3.

Among adverse effects there is substantial variability in their dose response. A dose–response relationship is most commonly evident with regards to the central nervous system adverse effects of sedation: cognitive impairment, hallucinations, myoclonus and respiratory depression. Even among these, however, there is 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 central nervous system effects become the neuroexcitatory ones of delirium and myoclonus. 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.

Table 3
Common opioid-induced adverse effects

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

Factors predictive of opioid adverse effects

Drug related

Overall, there is very little reproducible evidence suggesting that any one pure opioid agonist has a substantially better adverse effect profile than any other. Pethedine is not recommended in the management of chronic cancer pain because of concerns regarding its side effect profile. Recent data from controlled studies indicate that the transdermal administration of fentanyl is associated with a lesser incidence of constipation than oral morphine [59–61].

Route related

There is very limited evidence to suggest differences in adverse effects associated with specific routes of systemic administration. Compared to the oral morphine administration, small studies have demonstrated less nausea and vomiting with rectal [72] and subcutaneous administration [73]. 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 [59–61].

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 in preclinical studies clearly affects the sensitivity to opioids and it is reasonable to assume that the genetic background plays a similar important role clinically.

Some of this variability is related to co-morbidity. Aging is associated with altered pharmakokinetics particularly characterised by diminished clearance and volume of distribution. This has been well evaluated for morphine [74] and fentanyl [75,76]. In a study of morphine use in the management of chronic cancer pain in the elderly, overall elderly patients required lower doses than their younger counterparts without exhibiting an enhanced risk for opioid induced adverse effects [77]. In patients with impaired renal function there is delayed clearance of an active metabolite of morphine, morphine-6-glucuronide [28]. Anecdotally, high concentrations of M6G have been associated with toxicity [29–31], however, in a prospective study of patients with opioid-induced delirium or myoclonus no relationship with renal function was observed [78].

Other patient-related factors that may enhance the risk of adverse effects include the co-administration of drugs which may have cumulative toxicity or other concurrent co-morbidity.

Opioid initiation and dose escalation

Some adverse effects appear transiently and spontaneously abate after the initiation of an opioid or after dose escalation. This phenomenon has been well demonstrated in a prospective study on the effect of morphine dose escalation on cognitive performance [79]. This study demonstrated that cognitive impairment commonly improved after 7 days. This phenomenon, though often described, has not been formally studied in regards to other adverse effects.

Differential diagnosis

Adverse changes in patient well-being among patients taking opioids are not always caused by the opioid. Adverse effects must be differentiated from other causes of co-morbitity that may develop in the treated patient and from drug interections. Common causes of co-morbidity that may mimic opioid-induced adverse effects are presented in Table 4.

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, 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 medication administration to evaluate for possible drug interactions or some other drug-related explanation for the reported symptoms.

Table 4
Co-morbidity that may mimic opioid-induced adverse effects

Cause	Adverse effects
Central nervous system	
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
Steroids	Agitated delirium
Non-steroidal anti-inflammatory drugs	Nausea, drowsiness
Chemotherapy	Nausea, vomiting, drowsiness, cognitive impairment
Radiotherapy	Nausea, vomiting, drowsiness

Overview of the 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) Specific therapy to reduce the adverse effect.
(3) Opioid rotation.
(4) Change route of 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 whilst preserving adequate pain relief [80]. When opioid doses cannot be reduced without the loss of pain control, reduction in dose must be accompanied by the addition of an accompanying synergist approach. Extensive experience has been reported with four accompanying approaches:

(1) The addition of a non-opioid co-analgesic. The analgesia achieved with non-opioid co-analgesics from the non-steroidal anti-inflammatory class of agents is additive and often synergistic with that achieved by opioids. This is supported by a number of prospective studies [81–84] and one retrospective drug utilisation survey [85].

(2) The addition of an adjuvant analgesic that is appropriate to the pain syndrome and mechanism. Adjuvant analgesics (see below) may be combined with primary analgesics to improve the outcome for patients who cannot otherwise attain an acceptable balance between relief and side effects [86]. 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 which 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 anti-tumor 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 favourable clinical experience in the treatment of painful bone metastases, epidural neoplasm and headache due to cerebral metastases. 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 there is a strong clinical impression that tumor shrinkage is generally associated with relief of pain [87]. Although there are some reports of analgesic value even in the absence of significant tumour shrinkage [88], the likelihood of a favourable effect on pain is generally related to the likelihood of tumour response. Surgery may have a role in the relief of symptoms caused by specific problems, such as obstruction of a hollow viscus, unstable bony structures and compression of neural tissues [89,90]. In cases of otherwise uncontrollable extremity pain due to unresponsive locally advanced disease, amputation of the effected limb may have a dramatic impact on pain control [91]. Endoprosthetic treatments with stents may be very helpful in some situations of pain related to esophageal, biliary, colonic and ureteral obstructions [92,93].

(4) The application of a regional anesthetic or neuroablative intervention. The results of the WHO "analgesic ladder" validation studies suggest that 10–30% of patients with cancer pain do not achieve a satisfactory balance between relief and side effects using systemic pharmacotherapy alone without unacceptable drug toxicity [94–99]. 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 neurological 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 favourable enough risk:benefit ratio that early treatment is warranted.

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 long-term toxicity of these approaches. In general, this approach involves the addition of a new medication, adding to medication burden and with the associated risks of adverse effects or drug interaction.

Opioid rotation

Over the past 10 years numerous clinicians and cancer pain services have reported successful reduction in opioid side effects by switching to an alternative opioid [37,45,100–112]. Improvements in cognitive impairment, sedation, hallucinations, nausea, vomiting and myoclonus have been commonly reported. This approach requires familiarity with a range of opioid agonists and with the use of equianalgesic tables to convert doses when switching between opioids. While this approach has the practical advantage of minimising polypharmacy, outcomes are variable and unpredictable. When switching between opioids, even with prudent use of equianalgesic tables, patients are at risk for under or over dosing by virtue of individual sensitivities.

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 [103,113–115] 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 [4,5,8,116–119] and similar phenomena may contribute to variability in adverse effect sensitivity.

Switching route of systemic administration

Limited data indicates that some adverse side 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 [73], in another there was less constipation, drowsiness and nausea [120].

Initial management of the patient receiving opioids who presents with adverse effects

Among patients receiving opioid analgesic therapy there are two key steps in the initial management of adverse effects. Firstly, the clinician must distinguish between morphine adverse effects from co-morbidity or drug interactions. This step requires careful evaluation of the patient for factors outlined in Table 5. If present, these factors should be redressed. Metabolic disorders, dehydration or sepsis should be treated. Non-essential drugs that may be producing an adverse interaction should be discontinued. Symptomatic measures may be required until a positive effect is observed.

Secondly, if indeed it seems that there is a true adverse effect of opioid, consideration should be given to reducing the opioid dose. If the patient has good pain control, reduce morphine dose by 25%.

Adverse drug interactions

In patients with advanced cancer side effects due to drug combinations are common. The potential for additive side effects and serious toxicity from drug combinations must be recognised. The sedative effect of an opioid may add to that produced by numerous other centrally acting drugs, such as anxiolytics, neuroleptics and antidepressants [121]. Likewise, drugs with anticholinergic effects probably worsen the constipatory effects of opioids. As noted previously, a severe adverse reaction, including excitation, hyperpyrexia, convulsions and death, has been reported after the administration of pethedine to patients treated with a monoamine oxidase inhibitor [122].

Gastrointestinal side effects

The gastrointestinal adverse effects of opioids are common. In general they are characterised by having a weak dose–response relationship.

Constipation

Constipation is the most common adverse effect of chronic opioid therapy [123]. The likelihood of opioid-induced constipation is so great that laxative medications should be prescribed prophylactically to most patients.

Nausea and vomiting

Opioids may produce nausea and vomiting through both central and peripheral mechanisms. These drugs stimulate the medullary chemoreceptor trigger zone, increase vestibular sensitivity and have effects on the gastrointestinal tract (including increased gastric antral tone, diminished motility and delayed gastric emptying). With the initiation of opioid therapy, patients should be informed that nausea can occur and that it is usually transitory and controllable. Routine prophylactic administration of an antiemetic is not necessary, except in patients with a history of severe opioid-induced nausea and vomiting, but patients should have access to an antiemetic at the start of therapy if the need for one arises. Anecdotally, the use of prochlorperazine and metoclopromide has usually been sufficient.

Central nervous system side effects

The CNS side effects of opioids are generally dose related. The specific pattern of CNS adverse effects is influenced by individual patient factors, duration of opioid exposure and dose.

Sedation

Initiation of opioid therapy or significant dose escalation commonly induces sedation that persists until tolerance to this effect develops, usually in days to weeks. It is useful to forewarn patients of this potential, and thereby reduce anxiety and to encourage avoidance of activities, such as driving, that may be dangerous if sedation occurs [124]. Some patients have a persistent problem with sedation, particularly if other confounding factors exist. These factors include the use of other sedating drugs or coexistent diseases such as dementia, metabolic encephalopathy or brain metastases. Both dextroamphetamine and methylphenidate have been widely used in the treatment of opioid-induced sedation [125]. Treatment with methylphenidate or dextroamphetamine is typically begun with 2.5 mg to 5 mg in the morning, which is repeated at midday if necessary to maintain effects until evening. Doses are then increased gradually if needed. Few patients require more than 40 mg per day in divided doses. This approach is relatively contraindicated among patients with cardiac arrhythmias, agitated delirium, paranoid personality and past amphetamine abuse.

Confusion and delirium

Mild cognitive impairment is common following the initiation of opioid therapy or dose. Similar to sedation, however, pure opioid-induced encephalopathy appears to be transient in most patients, persisting from days to a week or two. Although persistent confusion attributable to opioid alone occurs, the etiology of persistent delirium is usually related to the combined effect of the opioid and other contributing factors, including electrolyte disorders, neoplastic involvement of CNS, sepsis, vital organ failure and hypoxemia [125]. A stepwise approach to management often culminates in a trial of a neuroleptic drug. Haloperidol in low doses (0.5–1.0 mg PO or 0.25–0.5 mg IV or IM) is most commonly recommended because of its efficacy and low incidence of cardiovascular and anticholinergic effects.

Respiratory depression

When sedation is used as a clinical indicator of CNS toxicity and appropriate steps are taken, respiratory depression is rare. When, however, it does occur it is always accompanied by other signs of CNS depression, including sedation and mental clouding. Respiratory compromise accompanied by tachypnea and anxiety is never a primary opioid event.

With repeated opioid administration, tolerance appears to develop rapidly to the respiratory depressant effects of the opioid drugs, consequently clinically important respiratory depression is a very rare event in the cancer patient whose opioid dose has been titrated against pain.

The ability to tolerate high doses of opioids is also related to the stimulus-related effect of pain on respiration in a manner that is balanced against the depressant opioid effect. Opioid-induced respiratory depression can occur, however, if pain is suddenly eliminated (such as may occur following neurolytic procedures) and the opioid dose is not reduced [126].

When respiratory depression occurs in patients on chronic opioid therapy, administration of the specific opioid antagonist, naloxone, usually improves ventilation. This is true even if the primary cause of the respiratory event was not the opioid itself, but rather, an intercurrent cardiac or pulmonary process. A response to naloxone, therefore, should not be taken as proof that the event was due to the opioid alone and an evaluation for these other processes should ensue.

Naloxone can precipitate a severe abstinence syndrome and should be administered only if strongly indicated. If the patient is bradypneic but readily arousable, and the peak plasma level of the last opioid dose has already been reached, the opioid should be withheld and the patient monitored until improved. If severe hypoventilation occurs (regardless of the associated factors that may be contributing to respiratory compromise), or the patient is bradypneic and unarousable, naloxone should be administered. To reduce the risk of severe withdrawal following a period of opioid administration, dilute naloxone (1:10) should be used in doses titrated to respiratory rate and level of consciousness. In the comatose patient, it may be prudent to place an endotracheal tube to prevent aspiration following administration of naloxone.

Multifocal myoclonus

All opioid analgesics can produce myoclonus. Mild and infrequent myoclonus is common. In occasional patients, however, myoclonus can be distressing or contribute to breakthrough pain that occurs with

involuntary movement. If the dose cannot be reduced due to persistent pain, consideration should be given to either switching to an alternative opioid [102] or to symptomatic treatment with a benzodiazepine (particularly clonazepam or midazolam), dantrolene or an anticonvulsant [125].

Other effects

Urinary retention

Opioid analgesics increase smooth muscle tone and can occasionally cause bladder spasm or urinary retention (due to an increase in sphincter tone). This is an infrequent problem that is usually observed in elderly male patients. Tolerance can develop rapidly but catheterisation may be necessary to manage transient problems.

Conclusion

Opioid analgesics are an essential element in the oncologist' s therapeutic repertoire. In the management of patients with advanced cancer the pharmacologic management of pain is a core clinical task. It is incumbent upon oncologists to have a deep understanding of these medications, their application and administration including indications, dosing and the management of adverse effects.

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