ACTIQ Managed Care Dossier

Module 2: Assessment and Management of Chronic Pain

ACTIQ Managed Care Document

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Synopsis

A comprehensive pain assessment is imperative to the effective management of pain. This assessment should elucidate the nature of the pain, the underlying cause of the pain, and the degree to which the pain impairs the patient's quality of life. Because the prevalence of breakthrough pain in patients with chronic pain is high, all patients with chronic pain should be evaluated for the presence of this type of pain. When breakthrough pain is identified, an additional pain assessment specific to the breakthrough pain is warranted.

Effective management of chronic pain requires a multidisciplinary approach that is individualized to meet the specific needs of each patient, and addresses both persistent pain and breakthrough pain. Primary therapies that can be directed at the source of pain should be identified (e.g., radiation to a bone metastases) and non-pharmacologic approaches that may be useful in managing pain should be implemented.

The cornerstone of pain management, however, is the use of drug therapy, especially the use of opioids to treat moderate to severe pain. Persistent pain is best treated with opioids that are administered on a fixed schedule (i.e., around-the-clock) to provide relatively constant blood levels, and breakthrough pain is best treated with a shorter acting opioid that is prescribed "as needed." Unfortunately, traditional oral opioids used to manage breakthrough pain have a relatively slow onset (up to 30-45 minutes), which can be problematic for patients whose breakthrough pain reaches maximal intensity quickly. Intravenous or patient-controlled analgesia (PCA) medications provide rapid onset of action, but they are expensive, invasive, and require technical expertise.

The opioids used to manage chronic pain are chosen based on the intensity of the pain and not on the extent of the underlying disease. As a general rule, less invasive routes are

preferable to more invasive ones because of their ease of use, convenience, reduced risk of infection or complications, and lower cost. Opioids are often started at a low dose to minimize initial side effects and to enhance compliance. From there, opioid doses are rapidly titrated upwards until a safe and effective dose is identified. Because almost all patients receiving chronic opioid therapy experience side effects, these effects should be anticipated and must be successfully managed to optimize the analgesic regimen. In some cases, side effects of an initial opioid medication cannot be adequately managed, or a patient does not attain adequate analgesia from one opioid. Switching to another opioid may result in a favorable balance between analgesia and side effects.

The use of opioids for the management of cancer pain is well accepted, and the use of opioids for the management of nonmalignant pain is gaining wider acceptance among pain care specialists. Several professional societies have advocated use of the same pain management practices that have been promulgated for cancer patients with the caveat that vigilance and rigorous monitoring for opioid abuse occur.

A widespread misunderstanding about patients becoming tolerant to, dependent on, or addicted to opioids has been an important barrier to the effective management of pain in both patients with cancer-related pain and nonmalignant pain. Tolerance and physical dependence are expected physiological effects that are not usually problematic for patients who are on chronic opioid therapy. Addiction, a disease characterized by behaviors such as compulsion, harm to the user or continued use despite harm, is uncommon in patients using opioids for a medical condition. Therefore, good medical practice should guide the physician in prescribing opioids. Physicians should integrate published opioid pain management guidelines into their practice to minimize the risk of abuse of these drugs.

1.0 Pain Assessment: The First Step in Effective Management of Chronic Pain

A comprehensive pain assessment is the cornerstone of effective pain management. An assessment that is both compassionate and objective facilitates an interactive and trusting relationship between the healthcare provider and the patient, and enables the clinician to develop a pain management regimen that maximizes the patient's overall comfort and function. Without an accurate pain assessment, analgesic therapy cannot be optimized. Moreover, because pain may be indicative of disease progression or because pain may result from medical treatments, an accurate and ongoing pain assessment is necessary to guide therapeutic decisions (McCaffery 1992).

1.1 Assessment of Chronic Pain

A comprehensive pain assessment defines the nature of the pain, the underlying cause of the pain, and the degree to which the pain impairs the patient's quality of life. This assessment typically includes a thorough medical history, a physical examination, a psychosocial examination, and diagnostic tests such as laboratory or radiographic tests, if appropriate. Clinicians should use the patient self-report as the primary source of assessment, should document pain intensity and relief via at least one easily administered scale (see Figures 1 and 2), and should make pain intensity records available to all clinicians involved in treatment. Following the initial pain assessment, pain should be assessed at regular intervals, after the development of new pain, and following modification of the treatment plan.

The pain assessment focuses not only on the severity of the pain, but also on the location of the pain, the quality of the pain (e.g., dull, sharp, or lancinating), the temporal patterns of pain (e.g., onset of pain, and course of pain throughout the day), the impact of pain on the quality of life, and the factors that contribute to the pain or relieve the pain. In addition, the success or failure of previous analgesic treatments should be ascertained. Defining each of these characteristics is useful for defining an optimal therapeutic strategy.

1.2 Assessment of Breakthrough Pain

As described in Module 1, chronic pain is generally comprised of two distinct components—persistent pain and breakthrough pain. Because of the prevalence of breakthrough pain in patients with chronic pain, especially patients with cancer, all patients with chronic pain should be evaluated for the presence of breakthrough pain. Patients with breakthrough pain should undergo an additional pain assessment specific to their breakthrough pain. This assessment should focus on the speed of onset, severity, location, and quality of the pain. In addition, temporal characteristics such as frequency of breakthrough pain episodes and duration of the episodes are particularly important characteristics to assess. The relationship of the breakthrough pain to the timing of the analgesic doses used to manage persistent pain should be assessed to determine whether pain occurs or worsens at the end of a dosing interval (end-of-dose failure). Because breakthrough pain can be either spontaneous (occurring without an identifiable cause) or precipitated, any events that precipitate a breakthrough pain episode should be identified. Finally, any factors that exacerbate or relieve the breakthrough pain should be identified.

1.3 Pain Assessment Tools

As noted, a patient's self-report of pain is the most important component of the pain assessment. The American Pain Society encourages clinicians to chart and display the patient's self-report of pain in a "highly visible" way that "facilitates regular review by the healthcare team" (APS 1995). Further, the APS suggests incorporating pain assessments, including patient satisfaction with pain relief, into vital signs charts, as a reminder to consider pain status regularly, just as they would body temperature or blood pressure.

Four pain scales commonly used for eliciting patient self-report of pain are shown in Figure 1: a simple descriptive pain intensity scale, a numeric pain intensity scale, a visual analog scale, and a "faces" scale, which is used primarily with children. Patients with pain also are frequently asked to document the long-term safety and efficacy of analgesia provided by their medications (Figure 2). These scales can be used to assess both persistent pain and breakthrough pain.

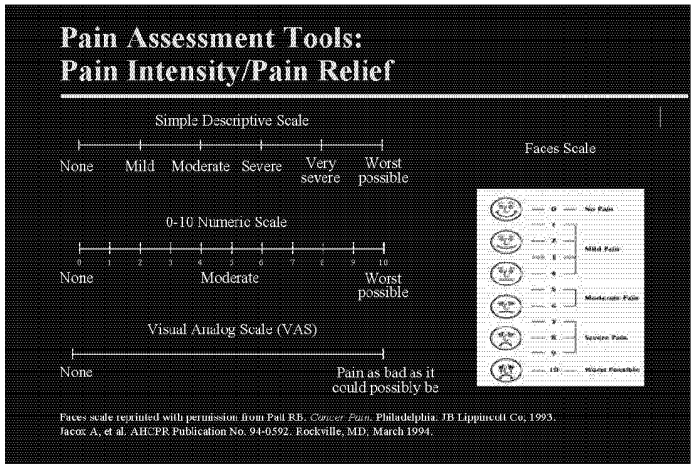


Figure 1. Pain Intensity and Pain Relief Tools

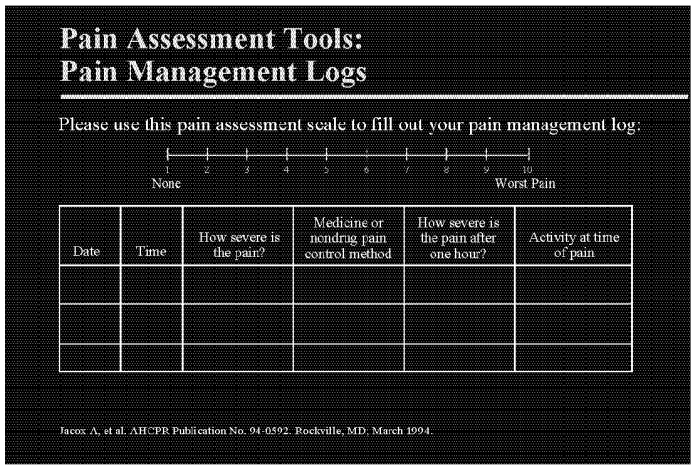


Figure 2. Sample Pain Management Log

2.0 Overview of Chronic Pain Management

In recognition of the widespread undertreatment of pain, especially in patients with cancer, several organizations have published guidelines for pain management in patients with chronic pain (WHO 1990, Jacox et al. 1994, APS 2003, Levy 1996, ASA 1997, Kalso et al. 2003, AAPM and APS 1997, FSMB 2004). Effectively managing chronic pain requires a multidisciplinary approach that includes both pharmacological and non-pharmacological options. The approach must be individualized to meet the specific needs of each patient, and must address both the persistent pain and breakthrough pain (Levy 1996).

2.1 Primary Therapy Directed at the Source of Pain

The first step in the management of pain is to identify any primary therapies that can be directed at the source of pain. For example, pain in cancer patients may be related to tumor infiltration, cancer treatment, or to other non-cancer related disorders (e.g., arthritis). Primary therapies might include such treatments as surgery for a fractured bone, radiation for bone metastases, or laxatives to manage constipation that is causing pain. Primary therapies should also be considered specifically for breakthrough pain. For example, a patient who experiences breakthrough pain as a result of coughing should receive an antitussive. A patient with breakthrough pain related to movement (i.e., incident pain) may benefit from the use of an assistive device.

2.2 Non-Pharmacologic Interventions to Reduce Pain

Several non-pharmacologic approaches are used to manage pain. Non-pharmacologic interventions such as physical therapy, relaxation therapy, and cognitive-behavioral therapy may help reduce pain and the stress associated with it (Levy 1996; APS 2003). These approaches are rarely effective alone for the management of pain, but are routinely used in conjunction with pharmacologic approaches to pain.

Other less common pain management techniques include anesthesiologic approaches (e.g., chemical neurolysis), neurostimulatory approaches (e.g., transcutaneous electrical nerve stimulation [TENS]), and surgical approaches (e.g., cordotomy). These approaches can reduce or eliminate pain in patients with pain that is refractory to pharmacologic management. The majority of these procedures must be undertaken only by clincians specially trained in the management of pain.

2.3 Pharmacologic Management of Pain

For most patients with chronic pain, particularly those patients with pain related to serious illnesses such as cancer and AIDS, drug therapy is the cornerstone of pain management. The "analgesic ladder" approach (Figure 3) developed by the World Health Organization (WHO) in 1990 continues to be widely used in the practice of pain management today (Portenoy, 2006). WHO recommends choosing the analgesic agent based on a patient's self report of pain severity. Patients with mild pain are treated initially with acetaminophen or a nonsteroidal anit-inflammatory drug (NSAID) provided there are no contraindications (e.g., peptic ulcer disease, bleeding diatheses, liver failure). These agents have a ceiling effect to the analgesia they produce. If patients have moderate to severe pain or if they have mild pain that persists or increases while they are receiving the maximum dosage of nonopioid analgesic agents, opioid analgesics are administered. Importantly, the steps in the analgesic ladder need not be followed in order. Patients presenting with severe pain, for example, may be appropriately started on potent opioids and need not undergo a therapeutic trial of typical Step 1 opioids. Because opioids are the mainstay of treatment of pain that is moderate to severe in intensity, opioid pharmacotherapy is discussed in detail in Sections 3.0 through 5.0 of this module.

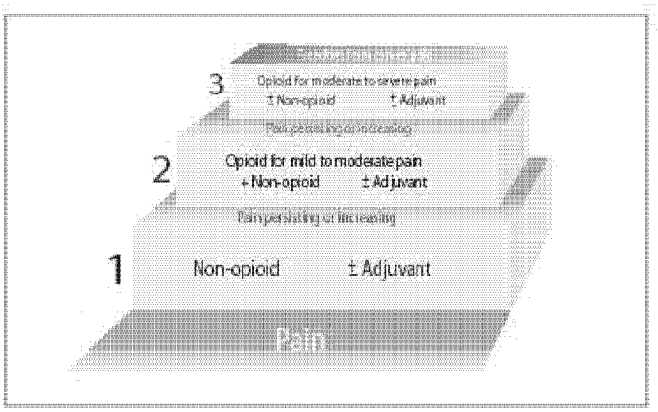


Figure 3. WHO Analgesic Ladder

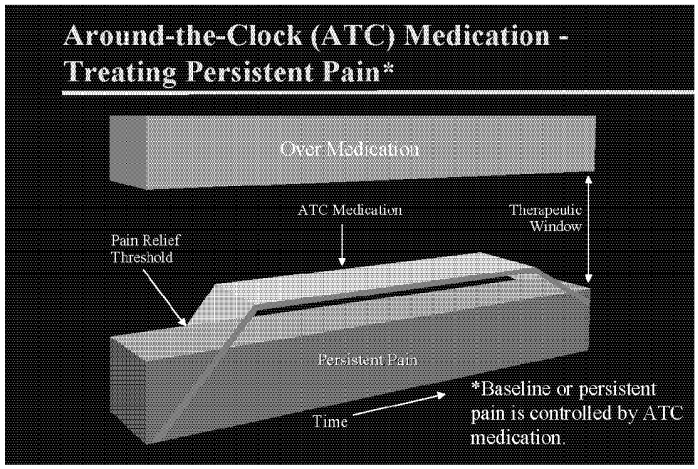
Adjuvant drugs are also an essential component of the management of chronic pain. Adjuvant drugs are drugs that can enhance the therapeutic effects of analgesics, produce independent analgesia, or counteract side effects of analgesics (Levy 1996). Such drugs include non-opioid analgesics (e.g., acetaminophen, NSAIDs) and coanalgesics (e.g., tricyclic antidepressants, anticonvulsant drugs, glucocorticoids). NSAIDs enhance the efficacy of opioid analgesia in inflammation-based pain occurring in such conditions as bone metastases, soft-tissue infiltration and recent surgery (Levy 1996). Two classes of coanalgesic drugs (tricyclic antidepressants and anticonvulsants) may be particularly helpful in managing neuropathic pain, which occurs in 30-40% of cancer patients as an overlay to coexisting nociceptive pain (APS 2003).

3.0 Opioid Pharmacotherapy for the Management of Cancer Pain

Opioids are the standard treatment for treating moderate to severe pain. Commonly used opioids include morphine, hydromorphone, hydrocodone, oxycodone, and fentanyl. An extensive body of clinical experience exists for the use of opioids for cancer pain management, and as noted previously, several guidelines exist to guide practitioners in the effective management of this type of pain.

3.1 Managing the Two Components of Cancer Pain—Persistent Pain and Breakthrough Pain

Optimal cancer pain management involves the treatment of both persistent pain and breakthrough pain. Persistent pain is best treated with medications that are administered on a fixed schedule (i.e., around-the-clock) to provide relatively constant blood levels (Figure 4). Analgesia for persistent pain is usually achieved with an opioid that has prolonged absorption, such as controlled-release oral medications or transdermal medications. Dosing intervals are adjusted to ensure that blood concentrations do not fall significantly at the end of the dosing interval. The goal is to remain above the analgesic threshold and to cover the persistent pain constantly, without overmedicating the patient.



F igure 4. Managing Persistent Pain

Breakthrough pain occurs on a background of controlled persistent pain (Figure 5). A common approach to managing breakthrough pain is to increase the around-the-clock medication to cover these episodes of breakthrough pain. However, if the around-the-clock analgesic is raised high enough to cover the episodes of breakthrough pain, patients become overmedicated and experience more side effects (Figure 6). Patients typically complain of excessive sedation when they are overmedicated. By raising the around-the-clock dosage excessively, the optimal balance between analgesia and side effects may be lost. To address the issue of overmedication, most dosing guidelines for cancer and noncancer pain recommend that whenever a longer acting opioid is prescribed for chronic pain, a shorter acting opioid should also be prescribed to treat episodes of breakthrough pain (i.e., the supplemental dose).

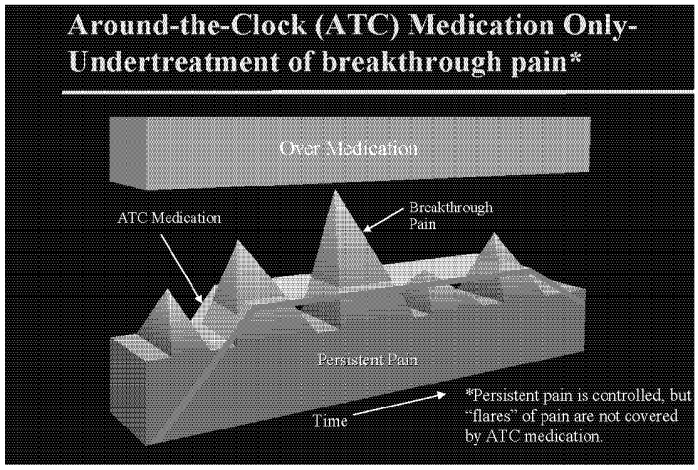


Figure 5. Breakthrough Cancer Pain

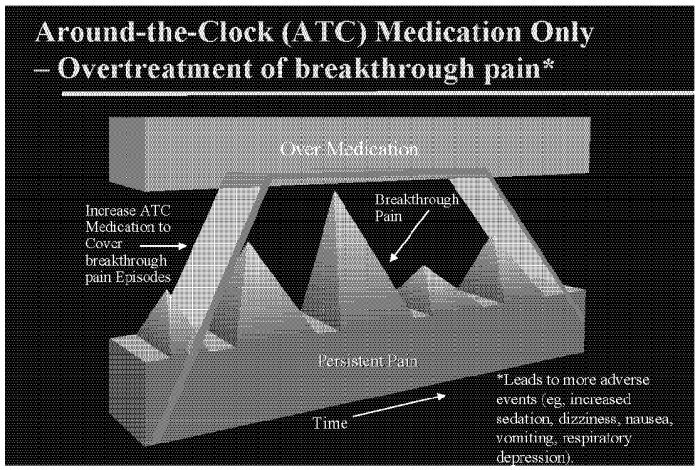


Figure 6. Overmedication from Raising Dose of Around-the-Clock Medication for Breatkthrough Pain

The goal for using a supplemental opioid dose to treat breakthrough pain is to provide rapid and effective pain relief, without overmedicating the patient. Unfortunately, the onset of effect with typical tablet and liquid formulation opioids, on the order of 30-45 minutes, sometimes does not compare with the rapid onset of a typical breakthrough pain episode. This results in a "pain gap" — the length of time between the occurrence of significant breakthrough pain and the time of meaningful pain relief (Figure 7). This time delay can be very problematic for patients whose breakthrough pain reaches maximal intensity quickly.

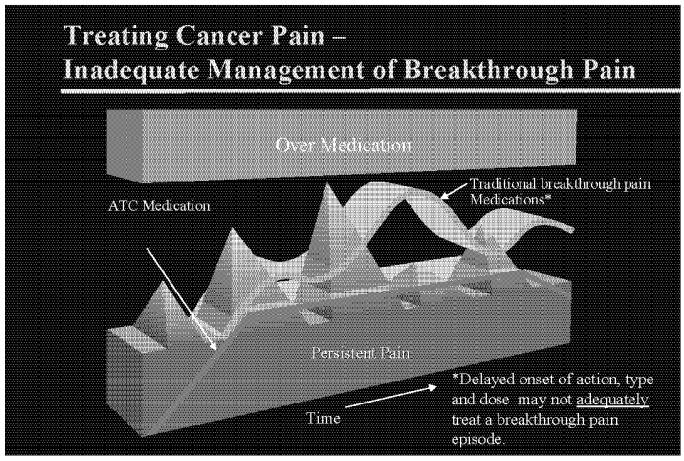


Figure 7. Inadequate Management of Breakghrough Pain with Traditional Oral Breakthrough Pain Medications

The "ideal" supplemental medication for breakthrough pain would have pharmacodynamic qualities that match the unique characteristics of breakthrough pain, e.g., rapid onset, short duration, and sufficient potency to relieve pain of moderate or severe intensity (Figure 8). Intravenous or patient-controlled analgesia (PCA) medications, which are frequently used for hospitalized patients, come close to this ideal and often provide a rapid onset of action that is sufficient to relieve the most severe breakthrough pains. Moreover, PCA medications are easy for patients to use, and have actually been shown to produce better pain control and to reduce the overall opioid requirement in patients. Unfortunately, the use of PCA medications is not practical for outpatients because they are expensive and invasive and require technical expertise.

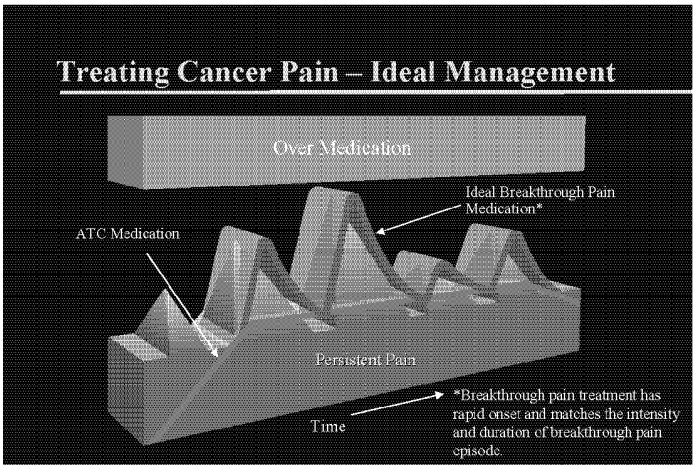


Figure 8. Effective Management of Breakthrough Pain

3.2 Selecting the Opioid

As discussed previously, analgesic medications are typically selected in accordance with the WHO analgesic ladder. Agents are chosen based on the intensity of the pain and not on the extent of the underlying disease. For example, a patient who is recently diagnosed with cancer and is experiencing severe pain should be started on a potent opioid. A fixed schedule medication (around-the-clock) is selected for the treatment of persistent pain. These drugs should have a prolonged absorption, such as with oral controlled-release medications or transdermal medications.

A supplemental medication that is given on an "as needed" basis should be selected to manage breakthrough pain. This medication should have a rapid onset of effect as breakthrough pain occurs rapidly, and should have a relatively short duration of action that overlaps the typical duration of breakthrough cancer pain episodes. In one study in cancer patients, 43% of breakthrough pain episodes reached maximal intensity within 3 minutes (Portenoy and Hagan 1990). Similarly, in another study in noncancer patients, 46% of breakthrough episodes reached maximal intensity within 5 minutes (Portenoy et al 2005). The duration of breakthrough pain episodes ranged from 1 to 240 minutes (median duration: 30 minutes) in cancer patients (Portenoy and Hagen 1990) and from 1-720 minutes (median duration: 60 minutes) in noncancer patients (Portenoy et al 2005). The breakthrough pain medication should work long enough to treat the pain, but not longer than needed to avoid overmedication. Finally, the breakthrough pain medication must be potent enough to adequately manage moderate to severe episodes of breakthrough pain.

3.3 Selecting the Route of Administration

Several routes of opioid administration are currently utilized, including oral, transdermal, transmucosal, intraspinal, rectal, intravenous or subcutaneous, and sublingual routes. As a general rule, less invasive routes are preferable to more invasive ones because of their ease of use, convenience, reduced risk of infection or complications, and lower cost.

Oral Route. The oral route is the most convenient and cost-effective, making it the route of choice when it can be used effectively. The oral route is unreliable in the setting of persistent nausea and vomiting, bowel obstruction, dysphagia, and malabsorption. This route is also problematic for patients who need rapid pain relief because stomach acid and first-pass metabolism markedly reduce the bioavailability of oral opioids and lead to slow absorption. Therefore, the onset of action of an oral opioid pill may be too slow to effectively treat breakthrough pain. The onset time of breakthrough pain (approximately 3 minutes) is much shorter than the time it takes for the supplemental opioid to begin working (30 minutes or more). Therefore, the medication may not reach its peak effect until after breakthrough pain has begun to subside.

Transdermal Route. The transdermal route is an alternative for patients who cannot use oral medications, but it is more expensive than most oral formulations. As noted previously, the transdermal route of administration (i.e., transdermal fentanyl) is used frequently for the around-the-clock medication used to treat persistent pain.

Invasive Routes. Subcutaneous or intravenous infusions may be beneficial for patients with severe pain who are unable to take oral medications or who require rapid analgesia. Subcutaneous or intravenous infusions may be particularly useful in patients with severe or rapidly occurring breakthrough pain. Patients receiving subcutaneous or intravenous infusions can receive both fixed schedule doses to manage their persistent pain as well as supplemental doses for breakthrough pain by the same route for quick pain relief. However, this route requires painful injections or drug infusion pumps that are expensive and require extra physician and or nursing time and expertise. Intraspinal opioid administration has been used to control cancer pain in hospitalized patients and implantable pumps have been used in outpatients with and without cancer, but they require a skilled team of healthcare professionals and supervision by a pain specialist. Intramuscular opioid therapy is not recommended because it is painful, difficult to administer, and does not produce consistent analgesis effects.

Transmucosal Route. The oral transmucosal route of drug delivery is desirable for several reasons. The oral cavity has a relatively uniform temperature and a large surface area. The oral mucosa is highly permeable—20 times more permeable than the skin. Additionally, the oral mucosa is highly vascularized. Because of these characteristics, certain drugs are able to cross the oral mucosa and enter the bloodstream rapidly and directly, without hepatic and intestinal first-pass metabolism. Drug bioavailability is thus increased, and rapid onset of action is achieved without invasive methods. For drugs that can be rapidly absorbed through the oral mucosa, transmucosal administration is an effective and convenient method of drug administration.

Sublingual Route. While sublingual formulations of opioids would appear to provide an ideal route for rapid absorption, only a few drugs are suitable for sublingual administration. Although morphine is sometimes administered sublingually, a clinical study has demonstrated that sublingual morphine actually is poorly absorbed (Osborne et al. 1990). The time to maximum concentration was significantly delayed due to poor lipophilicity. Moreover, due to the extremely bitter taste, all of the patients in the study found the sublingual route an unpleasant way to receive their opioid treatment.

Rectal Route. The rectal route may be useful is some patients who cannot use oral medications. However, rectally administered drugs are relatively slow in onset of effect, unpredictable, and the method is inconvenient for frequent use. The rectal route of opioid administration is particularly unsuitable for breakthrough pain because of the slow absorption.

3.4 Selecting the Starting Dose and Dosing Interval

Opioids are often started at a low dose to minimize initial side effects and to enhance compliance. From there, opioid doses are rapidly titrated upwards until a safe and effective dose is identified.

For persistent pain, the dosing interval depends on the pharmacologic properties of the selected drug. Most opioids require a dosing interval of 3 to 4 hours; controlled release formulations of opioids have a dosing interval of 8 to 12 hours; and the transdermal fentanyl system has a dosing interval of 48 to 72 hours. Whichever agent is used, the time between doses must be long enough to prevent overmedication but short enough to avoid end-of-dose pain. The controlled release oral opioids and transdermal opioid patches are useful for persistent pain because their extended duration of action appears to lessen end-of-dose pain and allow patients to sleep through the night (APS 2003). However, the onset of action of these medications is considerably longer than immediate-release opioid medications, and therefore should never be used on an as-needed basis.

Breakthrough pain medication should be taken as needed, usually up to several times per day. In some cases, the starting dose of the breakthrough pain medication is estimated to be approximately 15% of the opioid dose used for persistent pain. However, this guideline is based on empirical evidence and has not been formally studied. Some studies have demonstrated that the effective dose of the breakthrough pain medication is not related to the opioid dose for persistent pain (Portenoy et al. 1999, Christie et al. 1998).

3.5 Titrating the Opioid

Opioid doses should be rapidly titrated to achieve an optimal balance between analgesia and side effects. Because opioids have no ceiling effect to analgesia and no maximum dosage, dosages may be increased until the desired effect is achieved or intolerable side effects are experienced. The dosage may be increased either by increasing the individual dose size or by increasing the dosing frequency. Patients with disease progression commonly experience pain at the end of a dosing time period; this typically indicates that the regularly scheduled analgesic dosage should be increased.

In some cases, downward titration is necessary because pain has been lessened, the cause of pain was effectively treated, or the pain was blocked via neurolysis or neurosurgery (Levy 1996). Signs that the opioid used for persistent pain should be titrated downward include a patient's report that pain has subsided, the need for less medication for breakthrough pain, or the occurrence of intolerable side effects.

3.6 Managing Opioid-Related Side Effects

Almost all patients receiving chronic opioid therapy will experience drug side effects (Levy 1996; APS 2003). Common opioid side effects include sedation, constipation, nausea, vomiting, and itching. Respiratory depression, a more serious side effect of opioids that is common in opioid-naïve patients, occurs infrequently in patients who have been chronically exposed to opioids and are termed "opioid-tolerant." Successful management of pain requires that the benefits of analgesia be balanced against opioid side effects.

Intolerable side effects can be managed in several ways. For example, the dosing regimen or route of administration may be changed to reduce high peak serum levels that frequently cause side effects. Multimodal therapy that includes non-opioids and non-pharmacological interventions may allow a reduction in total opioid dose, limiting opioid side effects. Prescibing a medication to treat the side effect is also an option—laxative therapy for consitpation or caffiene for chronic sedation, for example.

3.7 Managing Pain That Is Less Responsive to Opioids

Overall, most opioids produce similar efficacy and have similar side effect profiles at equianalgesic doses (APS 2003). However, some patients do not attain a favorable balance between analgesia and side effects with gradual escalation of the opioid dose. Indeed, there is a growing body of evidence indicating that there is great intra-individual variability in the response to different opioids, likely resulting from genetically determined differences in subtypes of opioid receptors or peptide genes (Snyder & Pasternak 2003, Mayer & Höllt 2001, Galer et al. 1992). Therefore, if the side effects of an initial opioid medication cannot be adequately managed, or if a patient does not attain adequate analgesia from one opioid, switching to another opioid may result in a favorable balance between analgesia and side effects (Mercadante & Portenoy 2001; Levy 1996; APS 2003). Sequential opioid trials (i.e., opioid rotation) may be necessary to identify the drug that yields the most favorable balance between analgesia and side effects. When switching opioids, a lower dose of the new drug is generally used initially because of incomplete cross tolerance (Levy 1996).

4.0 Opioid Pharmacotherapy for the Management of Nonmalignant Pain

Dosing guidelines for opioid therapy are based on extensive clinical experience in the cancer population, and they can be easily adapted to the management of nonmalignant pain. The use of opioids for the management of cancer pain is well accepted, and the use of opioids for the management of nonmalignant pain is gaining wider acceptance among pain care specialists. Indeed, the president-elect of the American Pain Society has recently argued that:

> "Greater efforts need to be directed toward classifying pain according to relevant mechanisms. There seems no advantage and a number of disadvantages to continuing to differentiate between cancer- and noncancer-related pain, let alone attempting to distinguish between malignant and benign pain."
>
> --Dennis C. Turk, PhD, president-elect of the American Pain Society, 2002 (Turk 2002)

Several guidelines that strongly support opioids for nonmalignant pain have been proposed by key medical organizations, including the American Pain Society, the American Academy of Pain Medicine, the American Society of Anesthesiologists and others (Haddox et al. 1997, ASA 1997, Kalso et al. 2003, FSMB 2004, AAPM/APS 1997, AGS 2002). In general, these guidelines advocate using the same pain management practices that have been promulgated for cancer patients with the caveat that vigilance and rigorous monitoring for opioid abuse occur (Ballantyne and Mao 2003).

Overall, the medical community recognizes that there are personal and societal costs of chronic non-cancer pain and that the use of opioids may be warranted as part of an overall multidisciplinary pain management program for some patients. Good medical

practice should guide prescribing of opioids and treatment should be tailored to the individual.

5.0 Risk of Opioid Abuse by Patients with Chronic Pain

5.1 Terminology of Substance Abuse

An important barrier to the effective management of pain has been the widespread misunderstanding about patients becoming addicted to, tolerant to, or dependent on opioids. These misunderstandings are common not only in patients and their families, but in many healthcare providers as well. A distinction between the terms "addiction," "tolerance," and "physical dependence" must be made so as not to stigmatize patients, or to alarm patients, caregivers or medical staff. These terms have recently been defined in a joint statement of the American Academy of Pain Medicine, the American Pain Society, and the American Society of Addiction Medicine (Table 2).

Table 2 Terminology of Substance Abuse

Term	Definition
Addiction	A primary, chronic, neurobiologic disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving. Drug addiction is a treatable disease, utilizing a multidisciplinary approach, but relapse is common.
Tolerance	A state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more of the drug's effects over time. Analgesic tolerance differs from tolerance to adverse effects. Tolerance to analgesia and adverse effects is variable in occurrence but is never absolute; it may develop at different rates for different effects.
Physical Dependence	A state of adaptation that is manifested by a drug class specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist. Opioid analgesics may cause physical dependence which usually does not occur to a clinically significant degree until after several weeks of continued opioid use.

Addiction. Medical use of a pharmacologic agent uncommonly results in behaviors characteristic of addiction such as compulsion, harm to the user, or continued use despite harm. Clinical experience and research suggest that there are several differences between most cancer patients and most people who become addicted. Those who become addicted generally receive psychic effects such as euphoria from the drugs, while few

patients in pain describe such feelings. People who become addicted to various substances may also have genetic predisposition or complex environmental and situational factors that reinforrce abusive behavior.

Psuedoaddiction. Addiction should be distinguished from pseudoaddiction, which is characterized by drug-seeking behaviors caused by unrelieved pain. Some patients with unrelieved or undertreated pain may be aggressive in requesting additional analgesics. When such requests are not related to psychological beliefs nor to psychic effects but rather to unrelieved pain, the appropriate response is improved pain management.

Tolerance. Tolerance refers to a condition in which the patient requires larger doses of a drug over time to achieve the same pharmacologic effect. Once patients have been titrated to an appropriate opioid dosage, they generally remain on the same dosage for weeks to months. When dosage escalations are required, the overriding factor is generally disease progression (Foley 1995). Pateints with disease progression often find analgesic efficacy declining before the next scheduled dose. In this case, the opioid dosage should be titrated upward to an effective level, unless side effects preclude a higher dosage. Patients often become tolerant to opioid side effects, including nausea, vomiting, and sedation, but the development of tolerance to side effects should not be construed to mean that analgesic efficacy has been lost at a given dosage (Foley 1995).

Physical Dependence. Physical dependence on opioids should not be confused with addiction. Physical dependence is a common and natural result of a body becoming accustomed to a medication. It is characterized by the development of an abstinence or withdrawal syndrome after a reduction or sudden cessation of dosing. Patients with progressive diseases such as cancer rarely require withdrawal of opioids. In patients whose need for opioids has diminished, weaning patients from the drug can be managed through a gradual reduction of dosage. Such a regimen may eliminate withdrawal symptoms.

In summary, a precise understanding of the terminology of substance abuse is a crucial prerequisite for the proper use of opioids in patients with chronic pain. Extensive clinical experience with the use of opioids for patients with cancer pain indicates that the risk of addiction in this population is very low. Similarly, the risk of abuse is low in patients with nonmalignant pain, though there is less experience in this patient population.

5.2 Managing the Risk of Opioid Abuse

Although it is uncommon for chronic pain patients to abuse opioid medications, there is a potential risk associated with the use of all opioids. Addictive behavior occurs in a minority of the US population. According to the 2005 National Household Survey on Drug Abuse, 8.1% of the population use illicit drugs, 1.7% are dependent on or abuse illicit drugs, 7.7% abuse or are dependent on alcohol, and 29.4% use tobacco products (2005 National Household Survey on Drug Abuse). These estimates have remained stable since 2002. Regardless, patients with a history of substance abuse are at higher risk of addiction to opioids prescribed for pain and should be managed accordingly.

Physicians should routinely assess patients for the risk of opioid misuse and abuse and integrate published opioid pain management guidelines into their practice to minimize the risk of abuse of these drugs (e.g., ASA 1997, FSMB 2004, AAPM/APS 1997, AGS 2002, Emerging Solutions in Pain, 2006). Patients who receive opioids for long-term use of nonmalignant pain should have a documented treatment plan that outlines goals for pain relief and improvement in physical and psychological functioning. They must also be monitored for development of aberrant drug-related behaviors and proper controls such as the use of an opioid agreement (Fishman and Kreis 2002, FSMB 2004) must be in place throughout therapy (Savage 1996). Urine drug testing contributes to the management of the patient's treatment plan, aids in early diagnosis of relapse or drug abuse, and verifies compliance of the prescribed opioid (Heit and Gourlay 2004). Other appropriate measures that can help physicians to minimize the risk of abuse and diversion include careful assessment of patients, proper prescribing practices, periodic re-evaluation of therapy, documentation in patient records, and restriction of access and accounting procedures.

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