The traditional three-step approach

Up to 70% of patients with cancer experience moderate to severe pain during their illness. In an effort to better manage malignancy-related pain, the World Health Organization (WHO) in 1986 developed a stepwise approach to analgesic dosing [1–3]. The WHO three-step “ladder” correlated analgesic selection and dosing in relation to the intensity of the pain complaint (Figure 12.1). The ladder classified cancer pain into three levels of severity: mild, moderate, and severe [1,2]. Patients with mild pain were assigned to the lowest step or rung of the ladder (step 1) and were to be treated with non-opioid analgesics. If pain persisted and progressed to moderate intensity, the patient was advanced to step 2 and treated with “weak” opioid analgesics such as codeine, propoxyphene, tramadol, oxycodone, and hydrocodone. Advancement to step 2 was often problematic since weak opioids are associated with the same risks of adverse effects, tolerance, and diversion/abuse as more potent agents. For this reason, many clinicians consider step 2 to be a “large” step when compared to those that precede and follow it (Figure 12.2).

Patients may be advanced to step 3 of the ladder in situations where pain has progressed to severe or very severe intensity, and is inadequately controlled with weak opioids. At this step, potent opioids including morphine, hydromorphone, oxymorphone, and transdermal delivered (TDS) fentanyl are commonly prescribed. In general, sustained-release opioids are provided daily or twice daily for baseline pain control with immediate-release opioids taken as needed for breakthrough pain. Total daily opioid dose is increased as required, thereby allowing patients to gain freedom from pain.

While simplistic in nature, the WHO analgesic ladder was considered to be a successful therapeutic advance as it provided an organized approach to pain assessment and management on a global scale [3]. The major drawback associated with the WHO stepwise approach was the fact that approximately 20–25% of patients did not respond to morphine or other potent opioids, and continued to suffer severe pain [3–5].

A stepwise analgesic care plan would be expected to be even less effective for long-term chronic pain management, and controversy exists as to whether opioids should be prescribed to patients with musculoskeletal pain or benign disease-related pain [4,5]. Some caregivers argue that prescription of step 2 and 3 opioids may be the only way to provide effective pain relief, while others worry that such therapy may lead to lifelong dependencies, which can be particularly problematic in younger patients. Despite acceptance of a stepwise approach to chronic pain, many primary care physicians and surgeons remain uncomfortable prescribing opioids, while at the same time they lack a clear understanding of pain processing and the benefits of multimodal analgesia. Other educational deficits, including patient assessment, determination of need, initiation of opioid therapy, and how to treat adverse effects, often lead to undermedication, intolerability, and inadequate management of chronic pain. Comorbid conditions, including obesity, sleep apnea, and chronic obstructive pulmonary disease, and mental health issues such as anxiety, depression, and post-traumatic stress, further complicate pain management and reduce caregiver comfort in prescribing opioids [4,5].

Rationale for a four-step approach

With the advent of anaesthesiology and multi-specialty-based pain clinics and caregiver specialization in interventional pain management, a four-step analgesic approach was developed to more effectively treat patients with benign and malignancy-related chronic pain (Figure 12.3). The first three steps of this care plan are similar to the WHO analgesic ladder; however, a new fourth step, termed the interventional step, utilizes invasive techniques that are placed and managed by pain specialists. Interventional therapy
includes implantable analgesic pumps, peripheral and epidural stimulators, regional and neuraxial steroids, and neurolysis. Such therapy may provide measurable reductions in pain intensity and opioid sparing effects that are particularly beneficial to highly tolerant patients, the elderly, and those suffering intolerable dose-related adverse events.

The current four-step approach for chronic pain management is initiated and maintained in a manner that is the exact opposite to analgesic treatment plans employed for post-operative pain (Figure 12.4). In acute settings, the intensity of pain is most severe during the first 24–72 h following surgery or traumatic injury. During this period pain is optimally controlled using step–4 interventional techniques including neuraxial analgesia and continuous peripheral neural blockade. Analgesic benefits are greatest in high-risk patients and those recovering from the most painful of procedures, and must be balanced by the fact that these techniques are more invasive, require skill and specialization for placement, are associated with risk of bleeding/infection, and are more expensive than treatment with oral/IV opioids. As the patient recovers, interventional therapy is discontinued and the patient is advanced downward to step 3, and treated with intravenous PCA or strong parenteral opioids. As bowel function returns, the patient may be advanced downward to step 2 and treated with oral opioid plus acetaminophen compounds for several days to weeks depending upon the surgical procedure. Thereafter, residual discomfort may be treated with step-1 non-opioid analgesics, until complaints of pain resolve entirely.

In chronic pain settings, patients follow the opposite clinical course characterized by progressive increases in pain intensity. Progression of disease and associated discomfort is best controlled by upward steps in analgesic dose, and potency, as well as increasing complexity and invasiveness of analgesic delivery. The major difference between the WHO three-step ladder and the four-step approach is that the latter care plan recognizes that not all patients can gain adequate pain relief with opioids, despite proportionate increases in dose. The WHO ladder was designed for malignancy-related chronic pain and palliation in patients not expected to survive beyond several months to a year [1,2,5,6]. This care plan is often unacceptable and inappropriate for individuals suffering intractable benign pain that may last for many years. For these patients, interventional techniques offer an analgesic alternative that can often minimize risks of excessive sedation and cognitive deficits while improving functionality and quality of life.

The four-step approach to chronic pain management: common sense guidelines

Optimal pain management is initiated following a thorough screening of the patient. In addition to history and diagnostic imaging, a focused yet detailed physical examination is necessary to evaluate the pain complaint [7]. The caregiver must not only localize the site(s) involved and the intensity of discomfort but should also characterize associated symptoms as being either somatic, visceral, inflammatory neuropathic, myelopathic or mixed pain. Pain complaints are rarely the same and these clinical findings are key to formulating analgesic prescriptions and developing a treatment plan.

Whenever possible chronic pain management should begin on step 1 with non-opioid analgesics.
Caregivers should always use the lowest effective analgesic dose administered by the simplest route and consider a multimodal approach rather than relying on high-dose monotherapy. The caregiver should maintain patients on step 1 as long as is possible by adding pharmacological adjuvants, physical therapy, emotional and psychological support, and non-pharmacological and non-traditional analgesic techniques.

When opioids are deemed necessary to establish or maintain effective pain control, caregivers often face a controversial dilemma regarding whether “weak” or “potent” agonists should be employed. Conventional stepwise care plans recommend that caregivers prescribe weaker agents including tramadol, buprenorphine, hydrocodone, and oxycodone, while maximizing their effectiveness with non-opioid analgesics and adjuvants. New thinking suggests that step-2 opioids should not be prescribed at all for malignancy-related pain, as these agents are associated with less uniform pain control, adverse events and rapid dose escalation [5,6,8]. Instead, caregivers should consider prescribing more potent step-3 agents in low dose, and preferably as extended-duration tabs or transdermal patches. The correct solution is to adjust opioid potency and dose according to the current severity of pain complaint. For example, patients initially presenting with excruciating or rapidly progressing pain should be given the option to bypass step 2 and take an “analgesic elevator” to step 3 [8]. In contrast, patients requiring minimal analgesic supplementation may gain effective relief for an extended period of time, with occasional “as needed” doses of step-2 agonists. If, or when, pain intensity increases
and step-2 opioid dosing is either ineffectual or excessive, advance to step 3 is appropriate.

Whether short-acting or sustained-release/extended-duration preparations, or their combination, are most useful for step-3 analgesia is generally based on patient need. Patients who complain of occasional episodes of severe breakthrough pain are best treated with rapid-acting short-duration opioids, while those with constant discomfort or frequent episodes of pain appreciate the convenience and uniformity of relief provided by extended-duration opioids. The fact that extended-duration formulations produce steady-state concentration with fewer peak-and-trough levels may also reduce the incidence of annoying AEs such as nausea or somnolence.

Patients treated with extended-duration opioids may experience breakthrough pain which can be controlled with immediate-release, short-acting opioids; however, if three or more PRN doses are used daily, the dose of extended-duration opioid should be increased by 10–25%. With regard to ongoing dose escalation and total opioid dose, the caregiver should think long term, and consider a daily maximum dose that should not be exceed. This is a very controversial aspect of chronic pain management and there are few guidelines. In general, the maximum allowable dose is determined by caregiver experience and level of comfort, as well as other variables including adverse effects and intolerability, patient age, expected duration of need (weeks, months, years, decades), and risk of abuse and diversion.

Patients treated with potent opioids often experience reductions in analgesic efficacy related to tolerance development. As dosing escalates, many patients experience intolerable adverse effects that limit the overall analgesic effectiveness of the agent originally prescribed. In these individuals, opioid rotation to a different agonist may be useful. The success of rotation has been related to differences in opioid receptor subtypes, greater mu receptor affinity and differences in metabolism, that may allow a new opioid to re-establish analgesic efficacy with greater tolerability.

Patients exceeding the maximum opioid daily dose and those exhibiting intolerability and increased adverse events despite rotation are candidates for step-4 interventional therapy [9,10]. Techniques that may be offered include spinal and peripheral neural stimulation, which provides effective non-pharmacological modulation of pain transmission. Intrathecal infusions of morphine or hydromorphone either alone or in combination with local anesthetics offer powerful pain control as well as significant reductions in total opioid dose. Intrathecal dosing is particularly useful for patients suffering benign and malignancy-related thoracic, abdominal, and pelvic pain. Other techniques, including neurolysis, intrajoint and epidural steroids, and blockade or destruction of sympathetic ganglia or celiac plexus, can dramatically reduce opioid dose requirements while restoring functionality and quality of life [10]. Following successful intervention, pain scores may decline dramatically; however, opioids employed at step 3 should in most cases be continued to further improve overall analgesic effectiveness, although significant dose reductions may be achievable.

To further optimize analgesic effectiveness and reduce opioid burden, non-opioid analgesics employed at step 1 should be continued whenever possible, as patients are advanced to steps 2, 3 and 4. In addition, analgesic adjuvants including central noradrenaline reuptake inhibitors, gabapentinoids, and NMDA receptor inhibitors should be prescribed particularly for patients with high-grade opioid tolerance and neuropathic pain. Finally, pharmacological, nonpharmaceutical, and non-traditional therapeutic techniques including use of anxiotylitics and antidepressants, heat/cold applications, topical analgesics, transcutaneous electrical neural stimulation (TENS), acupuncture, and massage could be included at every step of the ladder.

Moving toward a flexible approach to pain management

The previously described three- and four-step ladders are widely employed for managing malignancy-related and other terminal pain states, however, the time has come to rethink and possibly discard these traditional stepwise approaches [6,8,9]. Application of flexible and more individualized treatment plans would be particularly beneficial for patients suffering benign chronic pain. For these individuals, care plans that include non-opioid-based multimodal analgesia and early application of interventional pain management may be superior to progressive increases in opioid dosing [10,11]. For example, an elderly female with pain related to spinal stenosis can often gain superior pain relief with greater safety and analgesic tolerability by avoiding steps 2 and 3 and moving directly to an interventional step-4 technique such as
epidural steroid injections. For patients with chronic low back pain and chronic pelvic pain, early use of spinal stimulation, neurolysis, and intrathecal analgesic techniques may improve functionality and quality of life while avoiding the sedative effects of step-3 opioids. Even in patients with malignancy-related pain, evidence suggests that substituting interventional procedures for high doses of potent opioids offers more effective analgesia and possibly a more prolonged survival rate [11].

Patients entering a flexible pain management care plan can be treated with a mixture of peripheral and central-acting non-opioid analgesics as well as psychological support, physical therapy, and non-traditional analgesic techniques. Entry-level analgesics would include NSAIDs and COX-2 inhibitors for patients suffering inflammatory pain, as well as acetaminophen, lidocaine transdermal patch and clonidine for patients complaining of somatic pain. Muscle relaxants should always be prescribed for skeletal muscle spasm and associated discomfort. Norepinephrine reuptake inhibitors including tricyclic antidepressants, SNRIs ( duloxetine), alpha-2 delta subunit ion channel blockers ( gabapentin, pregabalin), and transdermal local anesthetic patches may be prescribed for patients presenting with neuropathic pain (Figure 12.5).

Instead of being considered as a “last resort”, interventional pain management can be employed at an early stage of care. Patients are carefully assessed and, if deemed to be clinically appropriate, offered interventional procedures including neurolysis, spinal stimulation, and intrathecal infusions. Such therapy, while invasive and expensive, would be encouraged in settings where patients might benefit from improved pain relief and significant opioid-sparing effects.

If, and when, additional opioid mediated analgesia is required, supplementation with dual-acting analgesics such as tramadol and tapentadol can be provided. Although the clinical usefulness of “weaker” opioids in the management of cancer pain has been challenged, these agents offer dosing versatility for either moderate or severe discomfort and should be considered as entry-level supplements for patients with benign chronic pain. Tramadol is a relatively weak unscheduled analgesic that can provide useful supplementation of multimodal analgesic regimens and can help control moderate breakthrough pain. In

Figure 12.5.

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contrast, tapentadol is a more powerful schedule II agent that binds mu opioid receptors and blocks noradrenaline reuptake. Tapentadol 50–100 mg provides analgesic efficacy comparable to oxycodone 10–15 mg with an unexpectedly lower incidence of adverse events [12]. Currently tapentadol has approval for acute pain or acute breakthrough pain in patients with chronic pain. A sustained-release tapentadol preparation is being developed for around the clock treatment of chronic pain. Tapentadol's improved tolerability profile may overcome an important barrier to optimal chronic pain management; that being the fact that patients are often unwilling to take effective medications because they don't like how they make them feel. Nevertheless, the added cost of tapentadol may restrict its use as a first-line opioid analgesic. In that case, judicious use of hydrocodone and oxycodone plus acetaminophen compounds may also be considered.

In opioid-naive patients, supplemental opioids should be prescribed for control of breakthrough incident pain and pain during sleep, not for constant pain. A potential advantage of flexible pain management plans that employ combinations of multimodal and interventional analgesia is that many patients may require only minimal to moderate amounts of opioid supplementation in order to maintain effective relief [10,13].

For patients presenting with excruciating pain or those experiencing progressive increases in discomfort despite receiving multimodal and interventional therapy, supplementation with potent sustained- and immediate-release opioids may be indicated. Dosing should not be restricted, but instead titrated according to the individual patient's needs. There are many options, including oral administration of sustained-release morphine, oxycodone, and oxymorphone as well as fentanyl transdermal patch [14]. Extended-release oxymorphone has been well tested in patients with chronic low back pain where it provides uniform and durable pain relief. Methadone in low dose has also been advocated as a method of reducing dose escalation of the primary opioid being administered. In palliative care settings and for individuals suffering intractable pain, parenteral opioids and infusions of ketamine may also be provided [15].

Flexible chronic pain management care plans would best be initiated at earlier stages of complaint rather than after progression of symptoms and development of disability. Individuals suffering longstanding poorly controlled pain develop central sensitization and neural plasticity changes that may be difficult to overcome. These alterations facilitate noxious transmission and are associated with development of pain behaviors, sleep deprivation, de-conditioning, fatigue, and weight gain, which negatively influence the patient's ability to return to work or resume a normal quality of life. The early application of analgesic adjuvants and interventional pain management may restore CNS homeostasis and hopefully break the cycle of sensitization, plasticity, and intractable noxious transmission and perception. Other clinical benefits that may be achieved include a significant reduction and possibly elimination of opioids and their associated adverse events, and improvements in functionality and rehabilitation.

This is an exciting time for both primary caregivers and pain specialists as a number of new analgesics are emerging that will complement existing non-opioid regimens and further ensure the success of opioid-avoidance care plans. While there is no analgesic "silver bullet" on the horizon, peripherally acting agents in development, including anti-nerve growth factor, TRPV-1 inhibitors, and peripherally selective mu and kappa agonists, promise not only high analgesic efficacy but also improved patient safety and greater tolerability than opioids and other central-acting agents.

The ultimate goal of flexible chronic pain management is to achieve a balance of patient safety and meaningful pain relief, not a stepwise plan to eliminate all pain at the cost of therapeutic intolerability. The patient must not be led to believe that “you take this pill and you will feel much better.” Instead, the patient agrees to, and actively participates in, a multi-disciplined flexible care plan that includes interventional therapy, vigorous physical therapy, and psychological support. The therapeutic goals are to limit chronic pain disability and restore physical and psychological functionality, while avoiding excessive opioid dependency.

In summary, a stepwise approach to pain management, while useful for many patients, may not be appropriate for all. The application of a flexible multimodal care plan and appropriate opioid supplementation can, in most settings, offer patients freedom from severe chronic pain and return to baseline quality of life. Therapy should always be individualized and provided in a logical order based on potential benefits, associated risks, adverse events, and overall cost.
References