CHAPTER 2
Conventional Pain Treatment

In the past pain treatment revolved around the use of a small number of drugs. Mild pain was treated with paracetamol/acetaminophen with or without a non-steroidal anti-inflammatory (NSAID), whereas pain of a more severe nature was treated with codeine-based preparations, often in combination with paracetamol/acetaminophen. When postoperative pain was being managed, strong opioids were and are still utilized.

Perhaps one of the most major advances in recent decades has not been the advent of new analgesic agents, but rather an understanding that not all pain is the same with the implication that not all pain treatment can be standardized. We now appreciate that postoperative pain differs from the pain experienced with chronic conditions such as osteoarthritis (OA) while neuropathic pain differs yet again. The management of pain in each of these scenarios is now reasonably standardized and often governed by recommendations from professional organizations, colleges, and other interested parties. A greater proportion of the drugs utilized have a specific indication for the use to which they are put. However, some do not, and yet, because of a sufficient body of trial evidence and clinical experience are widely accepted and used. For example, the tricyclic antidepressants (TCAs) are universally accepted to have a pain-reducing effect in a variety of neuropathic pain conditions and in patients with fibromyalgia, are extensively used in these conditions and yet do not have a licensed indication for pain in these conditions. The whole issue of "off-label" use will be examined in more depth in the next chapter.

An up-to-date selection of guidelines can be accessed at the website of the *National Guideline Clearinghouse*, a US-based site but which contains guidelines from around the world. It can be found at: www.guideline.gov.

There is clearly much merit in benefiting from the considered opinions of consensus panels that formulate these guidelines. However, four issues arise when the guidelines are consulted:

1 They contain the first-line treatment options rather than the options utilized in specialist practice.

Pain Management: Expanding the Pharmacological Options, Gary J. McCleane. © 2008 Blackwell Publishing, ISBN: 978-1-4051-7823-5.

2 The therapeutic options presented, which include labeled and off-labeled drug use, are included because of the weight of evidence of their pain-relieving effects. However, that does not necessarily mean that these are the best options, merely that they have been more rigorously investigated. We lack good studies of comparative effect.
3 The process of drug discovery, investigation, release, and the interval between release and acceptance by practitioners and ultimately by the consensus panels that formulate guidelines imposes a time delay that may make the subsequent guideline dated.
4 The guidelines concentrate on specific diseases and causes of pain such as postherpetic neuralgia and OA. For many conditions no guidelines exist.

Neuropathic pain

Pain arising from injury or irritation of neural tissue may result in neuropathic pain. This pain has characteristic features which distinguish it from pain arising from noxious stimulation of other non-neural structures.

Accepted treatment for neuropathic pain involves the use of three distinct classes of medication:

1 Opioids
2 Antidepressants – Tricyclic antidepressants (TCAs) and serotonin norepinephrine reuptake inhibitors (SNRIs)
3 Antiepileptic drugs (AEDs)

While other types of medication are used, these three groups form the mainstay of treatment.

There is clear advantage on forming treatment around these groups. However, few would contend that therapeutic success is guaranteed when these types of drugs are used either because they prove ineffective or because their use is complicated by unacceptable side effects.

The causes of neuropathic pain are legion: while postherpetic neuralgia and painful diabetic neuropathy are perhaps the most well known, an extensive list of other types could easily be formulated. And yet, no TCA has a specific indication or licence for use in neuropathic pain but their use in these conditions is extensive. In the USA, two AEDs have neuropathic pain-related indications. These are gabapentin which has an indication for postherpetic neuralgia and pregabalin which has an indication for postherpetic neuralgia and painful diabetic neuropathy. No AED has an indication for ilioinguinal neuritis, intercostal neuritis or genitofemoral neuralgia, for example.

It can clearly be seen, therefore, that there would be severe limitations in our ability to provide effective treatment if we were to utilize medication only according to its labeled use.

Two current guidelines advise on the management of neuropathic pain in general. In the first of these, Dworkin and colleagues (2003) suggest:

> *First line-medications*. The efficacy of gabapentin, the 5% lidocaine patch, opioid analgesics, tramadol hydrochloride, and tricyclic antidepressants has been consistently demonstrated in multiple randomized trials.
>
> *Second line-medications*. When patients do not have a satisfactory response to treatment with the five first-line medications alone or in combination, several medications can be considered second-line. The list of second-line medications include:
>
> - lamotrigine
> - carbamazepine
> - bupropion
> - citalopram
> - paroxetine
> - venlafaxine.
>
> *Beyond second-line medications*: Other medications sometimes used for the treatment of patients with neuropathic pain include capsaicin, clonidine, dextromethorophan, and mexiletine.

In a more recent guideline representing the views of the *Canadian Pain Society* (2007) the suggestions are:

> *First-line treatments*
>
> - Tricyclic antidepressants
> - Gabapentin & pregabalin
>
> *Second-line treatments*
>
> - Serotonin noradrenaline reuptake inhibitors.
> - Topical lidocaine
>
> *Third-line treatments*
>
> - Tramadol
> - Controlled release opioids
>
> *Fourth-line treatments*
>
> - Cannabinoids
> - Methadone
> - Lamotrigine
> - Topiramate
> - Valproic acid.

A guideline specific to postherpetic neuralgia has been formulated by the *American Academy of Neurology* (2004). Its major recommendations are:

> **1** Tricyclic antidepressants, gabapentin, pregabalin, opioids, and topical lidocaine patches are effective and should be used in the treatment of postherpetic neuralgia.

2 Aspirin in cream is possibly effective in the relief of pain in patients with postherpetic neuralgia, but the magnitude of benefit is low, as is seen with capsaicin.
3 In countries where preservative-free intrathecal methylprednisolone is available, it may be considered in the treatment of postherpetic neuralgia.
4 Acupuncture, benzydamine cream, dextromethorphan, indomethacin, epidural methylprednisolone, epidural morphine sulphate, iontophoresis of vincristine, lorazepam, vitamin E, and zimelidine are not of benefit.
5 The effectiveness of carbamazepine, nicardipine, biperiden, chlorprothixene, ketamine, helium, neon laser irradiation, intralesional triamcinolone, cryocautery, topical piroxicam, extract of Ganoderma lucidum, dorsal root entry zone lesions, and stellate ganglion block are unproven in the treatment of postherpetic neuralgia.

The only other neuropathic pain condition that currently has a guideline is complex regional pain syndrome. This guideline has been produced by the *Reflex Sympathetic Dystrophy Association* (2006). It suggests:

- Mild to moderate pain: Simple analgesics and/or blocks
- Excruciating, intractable pain: Opioids and/or blocks
- Inflammation/swelling and edema: Steroids, systemic or targeted or NSAIDs; immunomodulators
- Depression, anxiety, insomnia: Sedative, analgesic antidepressant/anxiolytics
- Significant allodynia/hyperalgesia: Anticonvulsants and/or other sodium channel blockers and or *N*-methyl-D-aspartate receptor antagonists

A single drug rather than disease guideline concentrates on the use of AEDs in pain management. It comes from the *Washington State Department of Labor and Industries*. It gives guidance into which AEDs can be used by physicians and attract reimbursement from the department. It states:

> Currently, there is a lack of evidence to demonstrate that AEDs significantly reduce the level of acute pain, myofascial pain, low back pain, or other sources of somatic pain. The evidence of efficacy and safety on AEDs in the treatment of neuropathic pain varies and depends on the specific agent in this drug class.
>
> Gabapentin, along with older antiepileptic drugs, may be used as a first-line therapy in the treatment of chronic neuropathic pain. Because evidence of efficacy with lamotrigine has been inconsistent and there is no evidence of efficacy and safety for levetiracetam, oxcarbazepine, tiagabine, topiramate, and zonisamide, these drugs will not routinely be covered by the department for the treatment of neuropathic pain.

If one takes the messages from these guidelines and extends them into clinical practice there is still a very real chance that pain relief will not be apparent. One is again left with the dilemma of whether to explain to the patient that no other therapeutic intervention is available for them or to try drugs not considered "conventional" and yet which are suggested by

a careful reading of the literature. It is around this latter concept that this book is formed.

Postoperative pain

The management of postoperative pain is perhaps the most regimented of all the types of pain that we treat. At the basis of all postoperative pain treatment is the use of a small number of therapeutic classes of drugs. Local anesthetics, NSAIDs, acetaminophen/paracetamol, and opioids are the mainstays of treatment. Sophisticated postoperative pain management involves the logical use of these drugs delivered by differing varying routes:

Acetaminophen/paracetamol

- Rectal
- Oral
- Intravenous

Local anesthetics

- Skin infiltration
- Nerve blocks
- Epidural
- Intrathecal

Opioids

- Rectal
- Oral
- Transdermal
- Intravenous
- Intramuscular
- Epidural
- Intrathecal

Non-steroidal anti-inflammatory drugs

- Rectal
- Oral
- Intramuscular
- Intravenous

Combination therapy is the cornerstone of postoperative pain management. Problems arise when it is not possible to use one of the constituents of our combinations. For example, NSAIDs may have to be withheld in the patient with severe dyspepsia, previous NSAID allergy, those on anticoagulants, or when there is significant renal impairment. While the worst excesses of pain can be reduced or removed by regional anesthetic techniques, when these are discontinued acetaminophen/paracetamol and opioid combinations may not be sufficient to provide good quality relief.

The primacy of multimodal postoperative pain management is emphasized by the *American Society of Anesthesiologists* Task Force on Acute Pain Management (2004):

> Whenever possible, anesthesiologists should employ multimodal pain management therapy. Unless contraindicated, all patients should receive an around-the-clock regimen of non-steroidal anti-inflammatory drugs (NSAIDs), cyclo-oxygenase-2 inhibitors (COXIBs), or acetaminophen. In addition, regional blockade with local anesthetics should be considered. Dosing regimens should be administered to optimize efficacy while minimizing the risk of adverse events. The choice of medication, dose, route, and duration of therapy should be individualized.

Musculoskeletal pain

Relatively few general guidelines exist for musculoskeletal pain management. As with neuropathic pain, they tend to concentrate on one particular type and source of pain. One example is a guideline formulated by the *American Academy of Orthopedic Surgeons* (2003). In terms of pharmacological therapy they suggest a trial of an analgesic, non-steroidal anti-inflammatory or acetaminophen. If this fails a further option is that of joint aspiration and injection of cortisone, although they rate the strength of evidence for this recommendation as "little or no systematic empirical evidence." They go on to state that the role of "chondroprotective" agents such as glucosamine and chondroitin sulfate in the treatment of OA is not yet clear.

A European perspective is given by the *European League Against Rheumatism* (EULAR) guidelines for the management of OA of the hip (2005). Their suggestions for the pharmacological treatment of OA hip are:

- Paracetamol/acetaminophen as the oral analgesic of first choice for mild to moderate pain.
- NSAIDs at the lowest effective dose for those who fail to respond satisfactorily to paracetamol/acetaminophen.
- Opioids with or without paracetamol/acetaminophen as alternatives to NSAIDs when they are ineffective, poorly tolerated or contraindicated.
- Glucosamine, chondroitin, diacerhein, avocado soybean, and hyaluronic acid may be used although their effects are not well established.
- Intra-articular steroid injections during a flare up when NSAIDs or analgesics are ineffective.

In a further EULAR guideline (2007), this time for the management of hand OA, of the 17 treatment modalities considered, only 6 were supported by research evidence. These were education plus exercise, NSAIDs, COX-2 inhibitors, topical NSAIDs, topical capsaicin, and chondroitin sulfate.

Cancer pain

Perhaps in no other field of pain management is a systematic approach more important than in the field of cancer pain management. Provision of analgesia represents only one strand of management with thought needing to be given to the full panoply of physical and emotional aspects of the individual patient's condition. One of the revolutions in pain management was the institution of the *World Health Organization* analgesic ladder. This concentrated attention on a graded approach to provision of pain relief and emphasized the need to institute strong opioid therapy when pain becomes resistant to simpler analgesic options.

A wide variety of treatment guidelines now exist for cancer pain management and that of the *American Pain Society* (2005) suggests in terms of pharmacological management:

- Provide cancer patients with a prescription for an analgesic medication (e.g., hydrocodone and acetaminophen, oxycodone with acetaminophen) and instruct patients to have the prescription filled, to take the medication if unexpected pain occurs, and to call their healthcare provider for an appointment to evaluate the pain problem.
- Base the initial treatment of cancer pain on the severity of the pain the patient reports.
- Begin a bowel regimen to prevent constipation when the patient is started on an opioid analgesic.
- Administer a long-acting opioid on an around-the-clock basis, along with an immediate-release opioid to be used on an as-needed basis, for breakthrough pain once the patient's pain intensity and dose are stabilized.
- Do not use meperidine in the management of chronic cancer pain.
- Adjust opioid doses for each patient to achieve pain relief with an acceptable level of side effects.
- Avoid intramuscular administration because it is painful and absorption is not reliable.
- Use optimally titrated doses of opioids and maximal safe and tolerable doses of co-analgesics through other routes of administration before considering spinal analgesics.
- Monitor for and prophylactically treat opioid-induced side effects.
- Titrate naloxone, when in the rare instances it is indicated for the reversal of opioid-induced respiratory depression, by giving incremental doses that improve respiratory function but do not reverse analgesia.
- Provide patients and family caregivers with accurate and understandable information about effective cancer pain management, the use of analgesic medications, other methods of pain control, and how to communicate effectively with clinicians about unrelieved cancer pain.

- Provide patients with a written pain management plan.
- Use cognitive and behavioral strategies as part of a multimodal approach to cancer pain management, not as a replacement for analgesic medication.

Fibromyalgia

Those with an interest in rheumatological conditions will know all too well the significant burden of patients with pain associated with fibromyalgia.

The American Pain Society suggest in their *Clinical Practice Guideline* of 2005 the following rules when treating fibromyalgia syndrome (FMS) pharmacologically while pointing out that treatment should also be non-pharmacological as well:

1. For initial treatment of FMS prescribe a TCA for sleep.
2. Use selective serotonin reuptake inhibitors (SSRIs) alone, or in combination with tricyclics, for pain relief.
3. Do not use NSAIDs as the primary pain medication for people with FMS. There is no evidence that NSAIDs are effective when used alone to treat FMS patients.
4. Use tramadol for pain relief in patients with FMS.
5. Use opioids for management of FMS pain only after all other pharmacologic and non-pharmacologic therapies have been exhausted.
6. Use sleep and anti-anxiety medications if sleep disturbances such as restless leg syndrome are prominent.
7. Do not use corticosteroids in the treatment of FMS unless there is concurrent joint, bursa, or tendon inflammation.

A different guideline for the management of FMS has been formulated by Goldenberg and colleagues (2004). They classify drug treatment into those according to the evidence of efficacy:

Strong evidence for efficacy

- Amitriptyline
- Cyclobenzaprine

Modest evidence for efficacy

- Tramadol
- Serotonin reuptake inhibitors (SSRIs)
- Dual-reuptake inhibitors (SNRIs)
- Pregabalin

Weak evidence for efficacy

- Growth hormone
- 5-hydroxytryptamine
- Tropisetron
- *S*-adenosyl-methionine

No evidence for efficacy

- Opioids
- Corticosteroids

- NSAIDs
- Benzodiazepine and non-benzodiazepine hypnotics
- Melatonin
- Calcitonin
- Thyroid hormone
- Guaifenesin
- Dehydroepiandrosterone
- Magnesium

Conclusions

There is no doubt that the guidelines that cover a relatively small number of the conditions that cause pain offer a sound basis for pain treatment and their message can be extended to many other pain conditions. However, those involved in patient treatment will know that the therapeutic modalities suggested in these guidelines are not universally effective in all patients, nor are they universally well tolerated. In this age of resource shortage, the failure to respond to guideline treatment can lead to a discharge from the care of the treating physician with the message being conveyed that all has been tried and nothing more can be done. It could be argued that such a discharge from care equates to a discharge of responsibility. From a humanitarian perspective this is not acceptable. In some fields such as in the care of the dying patient the discharge approach would be entirely unacceptable. And yet what does one do? It is suggested that one approach may be to be mindful of the available pain literature and use the scientific validation contained in it to try other pharmacological strategies that often come with a real chance of providing pain relief along with a low chance of adverse effects.

Bibliography

American Academy of Orthopedic Surgeons. AAOS clinical practice guideline on osteoarthritis of the knee. *American Academy of Orthopedic Surgeons.* Rosemont, Illinois, 2003, p. 17.

American Society of Anesthesiologists Task Force on Acute Pain Management. Practice guidelines for acute pain management in the postoperative setting: an updated report by the American Society of Anesthesiologists Task Force on Acute Pain Management. *Anesthesiology* 2004; 100: 1573–81.

Burckhardt CS, Goldenberg D, Crofford L et al. Guideline for the management of fibromyalgia syndrome pain in adults and children. *American Pain Society.* Glenview, Illinois, 2005, p. 109 (Clinical Practice Guideline No. 4).

Dubinsky RM, Kabbani H, El-Chami Z et al. Practice parameter: treatment of postherpetic neuralgia: an evidence-based report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2004; 63: 959–65.

Dworkin RH, Backonja M, Rowbotham MC et al. Advances in neuropathic pain: diagnosis, mechanisms, and treatment recommendations. *Arch Neurol* 2003; 60: 1524–34.

European League Against Rheumatism. EULAR evidence based recommendations for the management of hip osteoarthritis. *Ann Rheum Dis* 2007; 64: 669–81.

Goldenberg DL, Burckhardt C, Crofford L. Management of fibromyalgia syndrome. *JAMA* 2004; 292: 2388–95.

Miaskowski C, Cleary J, Burney R et al. Guideline for the management of cancer pain in adults and children. *American Pain Society.* Glenview, Illinois 2005; p. 166.

Moulin DE, Clark AJ, Gilron I et al. Pharmacological management of chronic neuropathic pain – consensus statement and guidelines from the Canadian Pain Society. *Pain Res Manage* 2007; 12: 13–21.

Reflex Sympathetic Dystrophy Syndrome Association (RSDSA). Complex regional pain syndrome: treatment guidelines. Reflex Sympathetic Dystrophy Syndrome Association, Milford, Connecticut, 2006, p. 67.

Washington State Department of Labor and Industries. Antiepileptic drugs guideline for chronic pain. *Provider Bull* 2005; 05–10: 1–3.

Zhang W, Doherty M, Leeb BF et al. EULAR evidence based recommendations for the management of hand osteoarthritis: report of a Task Force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). *Ann Rheum Dis* 2007; 66: 377–88.