Pain Management: Expanding the Pharmacological Options

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Foreword

Medicine has made great strides in the 21st century included among which has been the development of new analgesics and novel routes of administration. However, despite these great advances as well as the prospect of future treatment strategies (such as viral vectors and gene therapy), we still cannot guarantee our patients that we can relieve their pain or avoid drug-related side effects. There is still an ongoing need to carefully weigh the risk/benefit ratios of each potential treatment option and it is not difficult to appreciate why treatment strategies associated with few adverse effects may be attractive to patients as well as health care providers. One can see, therefore, that if an analgesic potential is attributed to a medicine that has been available for sometime, previously with a non-pain indication, physicians may have less reluctance to use that medication than an entirely new agent with which there is little patient experience.

The concept of using medication on an "off-label" fashion often causes those who treat patients concern particularly in this era of intense medico-legal scrutiny. Therefore not only are judgments regarding efficacy and risk of adverse effects required when a "novel" pharmacological agent is considered, but also thought needs to be given regarding the confidence with which the practitioner can stand over their decision to prescribe that drug. Fortunately many of the options outlined in this book fall into a "low risk" category in terms of potential side effects and their use for other indications has been extensive. Furthermore, there are bodies of evidence that supports their use and this must give reassurance to those who choose to use them as pain relievers.

The problem of pain and suffering remains an enormous issue in many respects. On one hand there are still too many patients with inadequate analgesia and on the other hand there are too many adverse effects from treatment efforts to achieve adequate analgesia. The use of unconventional pain treatments, unconventional routes of administration, and the use of drugs outside their license indication is an area of increasing interest to many and currently there is no text which covers all of this

information in one source. This text will likely appeal to a wide variety of practitioners from many disciplines.

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CHAPTER 1
Introduction

One cannot fail to be impressed by the enormous increase in the knowledge of pain mechanisms that have occurred over the last few decades. We now have a much clearer understanding about the processes that convert a noxious stimulus into one that is appreciated as pain. And yet the drugs that would allow us to intervene therapeutically on the basis of this knowledge are often not available and indeed seem some way off. Granted there is a steady stream of products released by the pharmaceutical industry, but when examined in more detail these are often old compounds reformulated or imitations of currently available drugs.

When one thinks of "conventional" pain treatment, one thinks of opioids which have been used historically for millennia, nonsteroidal anti-inflammatories and local anesthetics which have their genesis over one hundred years ago and even the tricyclic antidepressants which are now over 40 years old. It is true, however, that while the basic pain-relieving drugs that are currently used could be recognized by practitioners from a previous generation, our thoughts about how they are used have been, and keep, changing. There is, for example, less reluctance to use strong opioids for chronic pain, and tricyclic antidepressants and anti-epileptic are often initiated by General Practitioners, which were previously used in the realm of specialist practice. In addition, patient expectation has changed from a stoical acceptance of pain to an expectation that pain is not acceptable and that there must be a remedy for it. With an aging population and patients recovering from previously irrecoverable illness, but with pain sequelae, the need for effective pain treatment has never been greater and yet the fundamental question remains as to whether we have the ability to effectively treat all pain. It is beyond contention that the answer to that question is no. Even if currently available drugs were effective in all cases, which they are not, the side effects produced by these drugs are not infrequently unacceptable to the patient. And

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these are only the immediate and obvious side effects of those preparations. The majority of pain drug studies examine the effect and side effect profiles of these medications over just a few weeks. We have few long-term studies of the effects of sustained use of opioids, anti-epileptics, or other drugs used in pain management.

If one went further and proposed that only drugs with a licensed indication could be considered for the treatment of pain in a particular condition then the choice, and indeed chances, of successful treatment are further reduced. The issue of drug use outside its specific licence is one which exorcizes practitioners and leaves them feeling vulnerable if they use a medication for the very best of reasons but when its use is complicated by adverse effect.

On the other hand, it would be unrealistic to expect the pharmaceutical industry to invest the many millions needed to obtain a product licence unless they can recoup their initial investment. This is only possible if they own the Intellectual Property rights to that preparation, or combination of preparations, and can therefore gain patent protection for their developments. One is therefore left with a relatively small number of pharmacological entities with proven analgesic effect which possess an indication for use in a particular pain condition. Everyday practice confirms that choice from such a small group is not always rewarded with pain relief. So what does one do? Explain to the patients that there are no further alternatives or try other low-risk pharmacological strategies that may bring relief?

It is staggering to see the number of scientific papers published month in, month out, on the genesis, transmission, control, and non-clinical treatment of pain. Although not all this work sheds new light on our understanding, the knowledge presented pushes us closer to the goal of complete understanding. This wisdom is only of real use if it helps us to reduce suffering. In some cases it will indicate how an entirely new pharmacological approach can be taken to pain treatment. In other, and probably more, cases it indicates receptors and pathways which we can interact with currently available medication. Such opportunities may allow us to interfere with pain transmission and regulation with drugs which we are familiar with, but for whom there is an entirely different indication. We often have vast experience in using these drugs for other non-pain indications and this means that their use may be inside the "comfort zone" of many more practitioners. It is less likely that negative information will emerge about long-term use since their pre-pain use will have already been long term.

Some will argue that the use of such "unconventional" treatments represent the use of medication for pain in which there is no evidence base. This is rarely the case. Indeed, for many of the treatments to be described, a substantial body of preclinical evidence rationalizes their use and this

evidence is confirmed by human clinical trials. Granted there may be fewer human pain trials on these currently unlicensed drugs but this is hardly surprising as these studies are usually unfunded by the pharmaceutical industry (in direct contrast to those studies on licensed preparations) and so the ability of investigators to assess the pain-relieving effects of these medications is lessened. It cannot be contended that the presence of a pain licence for a particular medication confirms or even suggests that it is the best agent for that type of pain. Rather it tells us that the company who hold the licence have assessed that the financial investment needed to obtain a licence will be offset by sufficient profit from its sale.

Even if evidence of analgesic effect were weaker for some of the medications to be discussed, absence of evidence of effect may only indicate that appropriate studies have not yet been undertaken to prove the effect. To ignore these older drugs which have current non-pain indications would be to ignore the results of basic science investigation that now suggest that they may have useful pain-relieving properties. Given that these older agents often have modes of action which are entirely different to that of currently licensed pain drugs, the use of these older drugs gives new opportunity for pain relief, as previously inaccessible receptors or pathways can be influenced by their use. Is there more logic in trying to assault the same receptor or pathway repeatedly with currently available medication and the copycat forms of it, or to try to access previously inaccessible receptors or pathways? Surely the logic is that faced with therapeutic failure with one type of agent the use of another agent with a different mode of action entirely would be more appropriate.

As anybody dealing with patients will know, it is not unusual to be faced with a patient who fails to respond to the normal pain relief provided, cannot take it because of side effects, or cannot use it because of contraindications. One thinks of the patient with renal impairment in whom the use of non-steroidal anti-inflammatories would be contraindicated and yet has a pain in which tissue inflammation is prominent or the patient with postherpetic neuralgia who cannot afford sleepiness and cognitive impairment associated with tricyclic antidepressant or anti-epileptic use. What do you then do? Or think of the patient with a terminal illness in whom the last days of life risk being ruined by pain, or by the side effects of currently accepted pain medication. Would it not be better if there was a simple, low-risk treatment that would give pain relief without the side effects which, for example, are found with opioid use? It is to suggest options for scenarios such as these that this book exists. The alternatives suggested are not guaranteed to work and are not guaranteed to be free of side effects, but then neither is more conventional treatment. No one analgesic option is universally effective or acceptable for the patient. With a wider range of options whose use is based on logic, then the chances of therapeutic success must be increased.

The focus of this book, therefore, is on widening the available choice of drugs which the practitioner has to choose from when trying to optimalize pain management for the patient should they have acute pain, chronic pain, or the pain associated with a terminal illness. The intention is that by having a wider armamentarium the practitioner can tailor the patient's treatment to provide that patient with the most effective pain treatment with the fewest number of side effects resulting from treatment. By reducing the number of drugs to just those with the licensed indication, the chances of success must be significantly reduced. Furthermore, the evidence base which supports the use of these seemingly novel alternatives will be indicated so that the reader can either accept that there is evidence or explore that evidence to see if it backs up the claims made for these drugs. The ethos of the book is intended to be that the choice of pain-relieving medication should be guided by the published scientific evidence and not by what the drug industry feels able to invest in. There is a difference between these philosophies. By at least considering the former there must be some chance that we can enhance the pain relief provided to the patient.

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.

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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