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Recent Advances in the Pharmacological Management of Pain

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Abstract

Pain is an unpleasant sensation that originates from ongoing or impending tissue damage. Management of different types of pain (acute, postoperative, inflammatory, neuropathic or cancer) is the most frequent issue encountered by clinicians and pharmacological therapy is the first line of approach for the treatment of pain. This review presents and discusses recent clinical advances regarding both the improvements in delivery of analgesic drugs and improvements in the design of analgesic molecules. The new modalities of administration of analgesics used in the clinic are reviewed, including skin patches, oral and mucosal sprays, transdermal delivery systems and intranasal administration. New insights are then presented on standard drugs used to relieve pain, such as opioids (including tramadol), NSAIDs including selective cyclo-oxygenase-2 inhibitors, paracetamol (acetaminophen), local anaesthetics and adjuvant analgesics such as antidepressants, anticonvulsants (gabapentin and pregabalin), cannabinoids, ketamine and others (e.g. nefopam). Although the understanding of pain mechanisms has improved significantly recently, much more is yet to be discovered and awaited. Broadening of our knowledge is needed to improve basic and clinical research in this field in order to better alleviate pain in millions of people.

Pain is an unpleasant sensation, ranging in intensity from slight through severe to indescribable. The word 'pain' comes from the Latin word *peona* meaning punishment or penalty. The two most common forms of pain reported in the US are headaches, affecting 45 million people, and back pain, involving 6 million each year. Cancer-related pain affects 9 million people each year. Management of pain for the treatment of moderate, chronic or severe pain in inflammatory, neuropathic, postoperative and cancer conditions is the burden of clinicians dealing with these patients; trying to improve their quality of life and to diminish their pain states.

Different pharmacological approaches exist for the treatment of pain such as the use of paracetamol (acetaminophen), NSAIDs, opioids, anticonvulsants, antidepressants, local anaesthetics, cannabinoids, ketamine and others (table I). Furthermore, along with standard methods of administration, novel modalities have become available in the last few years, including transdermal patches, oral sprays, intranasal instillation and many others. Despite the discovery of multiple mechanisms involved and a better understanding of the pain pathways, our handling of pain in patients is still inadequate and thus needs rethinking. In particular, the prescription of drugs for the management of pain is not adequate and should take into consideration multiple factors (table II) to optimise the efficacy of the treatment.

This review focuses on the new pharmacological approaches in the treatment and management of pain, notwithstanding the type of pain involved.

Table I. Drugs commonly used in the treatment of pain: classical analgesics and new adjuvants

Opioids: alfentanil, buprenorphine, butorphanol, fentanyl, hydromorphone, pethidine (meperidine), methadone, morphine, nalbuphine, oxycodone, remifentanil, sufentanil, tramadol
NSAIDs: diclofenac, ibuprofen, ketoprofen, ketorolac, naproxen
Coxibs[a]: celecoxib, etoricoxib, lumiracoxib, parecoxib
Antidepressants: bupropion, duloxetine, imipramine, venlafaxine
Antiepileptic drugs: gabapentin, lamotrigine, pregabalin
Cannabinoids: ajulemic acid, cannabis, Δ^9-tetrahydrocannabinol/ cannabidiol, dronabinol, nabilone
Local anaesthetics: bupivacaine, levobupivacaine, lidocaine 5%, ropivacaine
Others: clonidine, ketamine, nefopam, neostigmine, paracetamol (acetaminophen)

a Selective cyclo-oxygenase type 2 inhibitors.

1. New Modalities of Drug Administration

Although patients may be able to control their pain by self-administration of intravenous opioids using patient-controlled analgesia (PCA) devices, which provide better pain control and greater patient satisfaction compared with conventional parenteral analgesic regimens,[1] over the years new approaches have been developed (figure 1).

Firstly, transdermal administration of fentanyl and buprenorphine was reported some years ago.[2,3] This concept of transdermal application of lipophilic opioids in the form of patches has been evolving for several years. Its initial use was proposed for chronic pain and more specifically for cancer pain.[4-6] Currently, it is widely used in different pain conditions,[7,8] but not in acute postoperative pain conditions because the therapeutic concentrations are obtained between 12 and 32 hours after the patch is applied[9,10] for drugs such as fentanyl. As an accumulation of fentanyl can be observed with the patches, the administration of low doses of fentanyl hydrochloride by iontophoresis was developed.[11-13] This technique uses a low intensity electrical current that allows fentanyl to diffuse from a reservoir to the skin to rapidly obtain an effective site concentration, as explained by the favourable pharmacokinetic properties of fentanyl. This patient-controlled transdermal system is a compact self-contained system that is easily applied to the upper outer arm or chest and provides postoperative pain control equivalent to intravenous morphine PCA.[12,13] Furthermore, there is no subcutaneous accumulation of fentanyl with this approach, and therefore no risk of residual analgesia is observed following its withdrawal.[14]

Another approach is the administration of opioids by intranasal spray. This technique has been investigated for fentanyl, alfentanil, sufentanil, pethidine (meperidine), diamorphine and butorphanol tartrate. It can provide analgesia in different pain conditions and can be as effective as intravenous administration.[15-20] This new method of opioid delivery provides good bioavailability, since it avoids hepatic first-pass metabolism because it is absorbed directly by the mucous nasal membrane. Other advantages of this technique are its effectiveness, its noninvasive method of administration and ease of use.[21]

The delivery of opioids by sublingual spray has only been developed for oxycodone hydrochloride and was demonstrated to provide fast pain relief in an acute animal model;[22] therefore, further investigations are needed to assess its effectiveness in humans. Furthermore, although the research on cannabis for pain treatment is relatively new compared with that already carried out with opioids, there have been a few studies testing the sublingual spray delivery of Δ^9-tetrahydrocannabinol (THC) combined with cannabidiol (CBD) mixed in a 1 : 1 ratio (Sativex® [1]). It has been demonstrated that cannabinoids given in this form produced analgesia in chronic, neuropathic pain conditions and multiple sclerosis.[23-26] This new formulation is in phase III clinical trials for multiple sclerosis patients in the

Table II. Multiple factors influencing drug treatment of pain

Cultural belief
Personal experience
Medical history
Pain intensity
Reduced work status
Interference with meaningful activity
Other diseases interacting
Drug-drug interactions
Toxicity
Cost
Patient acceptance and compliance
Patient expectations and beliefs about the cause of pain

1 The use of trade names is for product identification purposes only and does not imply endorsement.

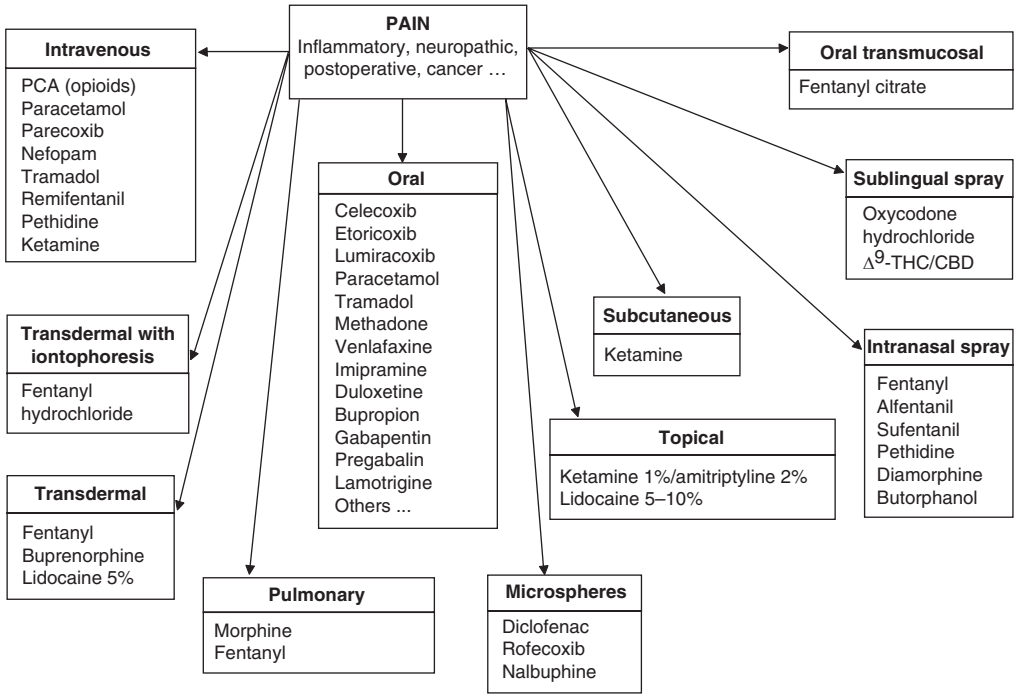

Fig. 1. Overview of recent developments in routes of administration and associated drugs used to treat pain. **PCA** = patient-controlled analgesia; **Δ9-THC/CBD** = Δ9-tetrahydrocannabinol/cannabidiol.

UK and has been granted approval in Canada for the symptomatic relief of neuropathic pain in multiple sclerosis.[27,28]

Another method of drug administration is the use of oral transmucosal analgesia. Fentanyl citrate (Actiq®) is a new opioid formulation that incorporates fentanyl into a lozenge and allows drug delivery through the buccal mucosa as a unique delivery system. This kind of absorption avoids first-pass metabolism, yielding a bioavailability substantially greater than with oral administration. It is used for the treatment of breakthrough pain in cancer patients already stabilised with their pain medications.[29-31]

Morphine can be rapidly and extensively absorbed from the respiratory tract, leading to a favourable pharmacokinetic profile for fast pain relief;[32] therefore, the development of the AERx® pain management system consists of an advanced pulmonary delivery system designed to efficiently deliver bolus aerosols of drugs, such as morphine or fentanyl, to the periphery of the lungs, leading to rapid absorption into the systemic circulation.[33,34] Inhaled morphine or fentanyl delivered from this AERx® system produces an analgesic effect in acute pain and breakthrough cancer pain.[35-37] Moreover, the encapsulation of fentanyl in liposomes has the potential to control the uptake of fentanyl by the lungs and thus provide sustained drug release.[38]

Another system of administration is the use of biodegradable microspheres, which have a special importance since it is possible to target drugs and to provide controlled release. It was demonstrated that microspheres loaded with diclofenac, rofecoxib or nalbuphine can prolong drug release,[39-41] which can be particularly useful in treating joint pain, such as in osteoarthritis. For instance, a 10-fold increase in the concentration of rofecoxib in the joints of rats was observed 24 hours after its intra-articular injection when it was encapsulated in microspheres compared with the drug in a standard solution.[41]

2. NSAIDs

Traditional NSAIDs are widely prescribed as analgesics and anti-inflammatory agents because of

their inhibition of prostanoid synthesis through blockade of both cyclo-oxygenases (COX-1 and COX-2). Thus, selective COX-2 inhibitors, named 'coxibs', were developed with the aim of reducing the incidence of serious gastrointestinal adverse effects associated with traditional NSAIDs in long-term anti-inflammatory analgesic therapy.[42] The first coxibs approved for the relief of osteoarthritis, rheumatoid arthritis, acute pain associated with dental surgery and primary dysmenorrhoea were rofecoxib and celecoxib.[43] Novel coxibs with improved biochemical selectivity were also developed – such as etoricoxib,[44,45] valdecoxib,[46] parecoxib (the prodrug of valdecoxib)[47-49] and lumiracoxib[50-53] – for their use in the treatment of osteoarthritis, rheumatoid arthritis, acute pain and postoperative pain in noncardiac surgical patients. However, major concerns regarding the safety profile of these drugs has resulted in considerable debate and subsequent withdrawal of two of them: rofecoxib for cardiovascular issues[48,54,55] and valdecoxib for serious cutaneous adverse reactions.[48,56,57] Nonetheless, coxibs, such as parecoxib and valdecoxib, are useful adjuncts to opioids, corresponding to a multimodal analgesia for the treatment of postoperative pain in noncardiac surgical patients.[49] In the meantime, the use of these drugs remains under scrutiny, particularly in cardiovascular at-risk populations. Their use should be restricted to individuals who do not respond to traditional NSAIDs or who have an increased risk of gastrointestinal complications, and for patients with low cardiovascular risk.[42]

Although it is widely accepted that NSAIDs are less potent than opioids for the treatment of pain, several NSAIDs provide a documented 30–50% morphine-sparing effect and improve analgesia when co-administered with PCA morphine. Furthermore, Marret and colleagues[58] showed in a meta-analysis that NSAIDs decreased postoperative nausea and vomiting by 30% and sedation by 29%, but had no significant effects on pruritus, urinary retention and respiratory depression. Finally, it was demonstrated that pre-emptive NSAIDs were of no analgesic benefit when compared with post-incisional administration of these drugs.[59] Clinical studies have confirmed that coxibs can produce analgesia similar to NSAIDs for moderate to severe acute pain.[60]

However, there are well recognised gastrointestinal, cardiac, renal and other adverse effects associated with the use of these drugs. Large outcome and epidemiological studies, and postmarketing surveillance data suggest that while coxibs do confer improved gastrointestinal safety, they are not devoid of gastrointestinal effects during long-term use.[52] The cardiovascular effects (leading to myocardial infarction and stroke) of coxibs have emerged as a major concern in recent years.[45,61] Indeed, due to their reversible inhibition of COX activity, NSAIDs can inhibit platelet aggregation. However, this may not be the case with new coxibs. COX-2 inhibition alone may increase the risk of vascular thrombus formation by upsetting the balance of pro- and anti-platelet aggregation effects: thromboxane $(TX)A_2$ synthesis is primarily a COX-1-induced effect and prostaglandin $(PG)I_2$ synthesis a COX-2 effect. These thrombotic properties have been reported after various long-term use of coxibs (rofecoxib and celecoxib) and also with valdecoxib and parecoxib in acute pain management following cardiac revascularisation surgery.[62]

In susceptible patients, NSAIDs cause acute renal failure due to the inhibition of the biosynthesis of prostaglandins involved in the maintenance of renal blood flow. Both isoforms of COX are expressed in the kidney, therefore coxibs can cause sodium retention and decrease glomerular filtration rate to a similar extent as nonselective NSAIDs in patients at risk for adverse renal effects.[63]

Therefore, NSAIDs should be part of a multimodal analgesia approach (see section 11) and should be prescribed when possible. The risks associated with traditional NSAIDs are well known and should be anticipated. The long-term use of coxibs is associated with thrombotic events that need further investigation.[61]

Finally, the use of topical NSAIDs has been investigated recently to reduce pain associated with osteoarthritis. The application of topical diclofenac solution on the knee is able to produce significant pain relief in patients.[64-66] This topical diclofenac solution can provide efficacious, well tolerated and site-specific treatment for osteoarthritic pain, with

minimal systemic adverse effects and only minor local skin irritation.

3. Paracetamol (Acetaminophen)

Paracetamol is commonly used for postoperative or cancer pain in combination with more potent analgesics.[67-70] It is well established as an effective and very well tolerated agent in the management of mild to moderate pain. As paracetamol has none of the renal or cardiovascular adverse effects that characterise anti-inflammatory drugs, it can be used in both NSAID- and opioid-sparing roles. A systematic review by Romsing et al.[71] examined the effects of rectal and parenteral paracetamol, and paracetamol in combination with NSAIDs for postoperative analgesia. Evidence was found of a clinically relevant analgesic effect of rectal and parenteral paracetamol. Furthermore, the concurrent use of paracetamol and an NSAID was superior to paracetamol alone, although no evidence was found of superior analgesic effect of the combination compared with the NSAID alone. Another review of postoperative pain studies comparing paracetamol (minimum 1g) with NSAIDs showed that paracetamol has analgesic efficacy comparable to that of NSAIDs in many of the studies reviewed, but overall, NSAIDs seem to be superior for postoperative pain management, although there seem to be differences in the efficacies of paracetamol and NSAIDs depending on the type of surgery performed.[72] Finally, paracetamol combined with PCA morphine induced a significant morphine-sparing effect, but did not change the incidence of morphine-related adverse effects in the postoperative period.[73]

Recently, an intravenous formulation of paracetamol has been introduced and its pharmacokinetic properties have been characterised,[74] providing multimodal analgesia (see section 11) for pain management when they are combined with opioids.[75] This multimodal approach decreases the amount of opioids needed and reduces their adverse effects, while improving the quality of cancer or postoperative analgesia.[76] The intravenous formulation of a prodrug of paracetamol, propacetamol, was administered to adults as an alternative to ketorolac in the perioperative period. Propacetamol reduced PCA morphine consumption by 22–46% in patients undergoing major orthopaedic surgery.[73] A new intravenous formulation of paracetamol, Perfalgan™, which is equivalent to propacetamol but with better injection-site tolerance, has recently been developed.[59]

Finally, despite widespread use of paracetamol in medical everyday life, the mechanism of its analgesic action still remains poorly understood.[77] However, there is now human evidence suggesting that the mechanism of its analgesic action involves the serotoninergic system.[78]

Therefore, the very low cost and apparent risks of paracetamol therapy (following maximum dosage recommendations) suggest a highly favourable risk/benefit ratio that might justify a role for paracetamol as a near-routine background analgesic.

4. Nefopam

Nefopam is a potent central non-opioid analgesic used clinically to improve postoperative opioid analgesia in patients by significantly reducing the amount of morphine needed, by 20–50%.[79-82] Interestingly, it has been shown that the early administration of nefopam during the perioperative phase significantly improves postoperative analgesia.[79,80] Furthermore, an analgesic synergistic effect between nefopam and ketoprofen has been described.[83] Moreover, this compound does not have any effects on respiratory and haemostasis functions, but is devoid of antipyretic properties.[84-86] It is centrally acting at the supraspinal and spinal levels,[87,88] and has been identified as a monoamine uptake inhibitor.[89-91] The antinociceptive effect of nefopam could be explained by its activation of serotoninergic descending inhibitory pathways[92] and its antihyperalgesic activity by the modulation of glutamatergic transmission.[93,94]

5. Recent Advances with Opioids

Tramadol, although not a new opioid but recently rediscovered, is a weak opioid agonist that has been shown to be effective in the treatment of neuropathic pain,[95] producing equivalent analgesia when compared with pethidine in postoperative pain conditions.[96] Indeed, tramadol is an alternative option for postoperative pain relief after tonsillectomy in children, as it is associated with less nausea than morphine.[97] Tramadol alone or in combination with

paracetamol produces a comparable relief in low back pain patients,[98] and the combination of tramadol and paracetamol is as effective as the combination of hydrocodone and paracetamol in relieving acute musculoskeletal pain.[99] Tramadol can be administered orally or intravenously, and is an interesting alternative to other opioids for pain management.

The role of methadone has been stigmatised by its longstanding use in maintenance programmes for opioid addiction. However, methadone is being increasingly recognised as a valuable second-line opioid analgesic for chronic noncancer pain, especially neuropathic pain.[100-102] It is also used in the treatment of cancer pain.[103-105] Methadone has undergone a renaissance because it has high oral bioavailability, a long duration of action, a lack of active metabolites, antagonist properties at *N*-methyl-D-aspartate receptors and blocks the reuptake of monoamines,[106] making it useful in the treatment of neuropathic and cancer pain.

Remifentanil, an opioid agonist characterised by a rapid onset and a short duration of action, is an analogue of fentanyl and can be used to decrease postoperative pain after surgical procedures.[107,108] This short-acting opioid is administered intravenously and is commonly used to provide adequate analgesia following cardiac surgery.[109,110] Remifentanil can also be used in a PCA mode in patients in labour when regional techniques are not possible.[111,112] Indeed, the satisfaction of the analgesia with remifentanil given as a PCA was higher than the values obtained with pethidine analgesia for women in labour.[113]

Opioid-related constipation is one of the most frequent adverse effects of chronic pain treatment. Enteral administration of naloxone or naltrexone blocks opioid action at the intestinal receptor level, but has low systemic bioavailability as a result of marked hepatic first-pass metabolism.[114] Methylnaltrexone is a peripheral opioid receptor antagonist undergoing phase III clinical trials for the treatment of opioid-induced constipation in patients with advanced medical illness who are being treated with opioids for pain. It does not cross the blood-brain barrier in humans and reverses the opioid effects without interfering with pain relief.[115] Some opioid-induced adverse events that this kind of drug may potentially target include constipation, nausea/vomiting, cough suppression and urinary retention.

6. Ketamine

Ketamine is an analogue of phencyclidine with a mechanism of action that is associated with antagonism of *N*-methyl-D-aspartate receptors. This dissociative anaesthetic has a role to play in the treatment of pathological pain conditions such as neuropathic pain.[116] Indeed, the administration of low-dose ketamine either intravenously or subcutaneously decreases pain in nonresponsive neuropathic pain patients from the start of the infusion treatment to the end.[117] A cream made of 1% ketamine combined with 2% amitriptyline also demonstrated analgesic effectiveness in the treatment of peripheral neuropathic pain.[118] Meanwhile, ketamine has also been used successfully for the treatment of intractable cancer pain.[119,120]

For perioperative pain management, preoperative epidural administration of a low dose of ketamine combined with midazolam has been found more effective in relieving postoperative pain than the use of ketamine alone.[121] Furthermore, a qualitative systematic review of the role of *N*-methyl-D-aspartate receptor antagonists in preventive analgesia reported nine positive and seven negative studies about intravenous ketamine administration.[122] Furthermore, a recent meta-analysis reported that when administered intravenously during anaesthesia in adults, ketamine decreased postoperative pain intensity for up to 48 hours, decreased cumulative 24-hour morphine consumption and delayed the time to first request of rescue analgesic. However, when assessing the clinical relevance of these potentially beneficial effects, several issues needed to be considered and the authors concluded that despite many published randomised trials, the role of ketamine, as a component of perioperative analgesia, remains unclear.[123]

In conclusion, the place of ketamine in the treatment of various pain conditions and its effects in long-term medicinal use still need further investigation.

7. Antidepressants

The standard and first-line treatment for different kinds of neuropathic pain is generally antidepressant drugs, and more specifically, tricyclic antidepressants, where the main effect is to non-selectively inhibit the uptake of noradrenaline (norepinephrine) and serotonin.[124-126] There is also new evidence suggesting that some tricyclic antidepressants can block sodium channels, which may contribute to their antihyperalgesic efficacy.[127] Although the effectiveness of amitriptyline in relieving neuropathic pain has been shown in different studies,[128-130] its adverse effects (sedation, confusion, blurred vision, postural hypotension and many others) are the main constraint to its use and reason for withdrawal of patients who experience those adverse effects.[124] Therefore, new drugs have been developed to address the problem of these adverse effects.

Venlafaxine, which is a serotonin and noradrenergic reuptake inhibitor, has been the most investigated, and it is devoid of action on muscarinic-cholinergic, histaminic and α_1-adrenergic receptors responsible for the common adverse effects seen with tricyclic antidepressants.[124,131] Venlafaxine is efficacious in the treatment of neuropathic pain[131] and considered as effective as imipramine (tricyclic antidepressant) in the treatment of pain related to polyneuropathy.[132] Newer antidepressants, such as selective noradrenaline and serotonin reuptake inhibitors (e.g. duloxetine), have demonstrated obvious benefits, a reduction in toxicity and are effective in the treatment of diabetic neuropathic pain.[133-135] Other studies have also demonstrated that bupropion, a noradrenaline and dopamine uptake inhibitor, is highly efficacious in relieving peripheral neuropathic pain.[136,137]

In summary, antidepressants represent useful pharmacological tools for clinicians in the treatment of neuropathic pain.

8. Antiepileptic Drugs

Carbamazepine and phenytoin were the first antiepileptic drugs (AEDs) to be used in controlled clinical trials to relieve painful diabetic neuropathy and paroxysmal attacks in trigeminal neuralgia.[138] However, since they have significant adverse effects, newer AEDs have been developed.[139] Gabapentin and pregabalin (gabapentin analogue) act at the $\alpha_2\delta$ subunit of the voltage-gated calcium channels to reduce neurotransmitter release.[140,141] Laboratory evidence suggests that they can both inhibit hyperalgesia and allodynia evoked by a variety of neural insults, including peripheral trauma, diabetes mellitus and chemotherapy.[142] Clinical evidence in most studies supports their analgesic efficacy in diabetic neuropathy and postherpetic neuralgia.[133,140,142] Gabapentin has also been shown to reduce chronic neuropathic pain more effectively when combined with morphine, and both were able to be given at lower doses than each drug alone.[126] Lamotrigine is another new AED that blocks voltage-dependent sodium channels and inhibits glutamate release;[143] it is effective in trigeminal neuralgia, painful peripheral neuropathy and for post-stroke pain.[127,138]

Future research efforts are necessary to fully understand the mechanism of action of AEDs, and to clearly characterise their safety and efficacy in the treatment of chronic pain conditions. For acute pain management, results from recent clinical trials demonstrate analgesic efficacy, an opioid-sparing effect, and possible postoperative functional improvement associated with gabapentin.[144] Other trials also suggest the potential analgesic efficacy of other AEDs including pregabalin, lamotrigine and possibly oxcarbazepine.[144] This was also confirmed in a recent meta-analysis showing that gabapentin given preoperatively decreased pain scores and analgesic consumption in the first 24 hours after surgery. However, the clinical significance of this finding has yet to be determined. Furthermore, a significant reduction in the incidence of adverse effects could not be demonstrated.[145]

9. Local Anaesthetics

Continuous nerve blockade is the only available medium- to long-term modality that blocks evoked pain. Decreased nausea and vomiting, and increased patient satisfaction are consequences of continuous peripheral nerve blocks, whereas other interesting concepts, such as improved rehabilitation and decreased incidence of postsurgery chronic pain syndromes, are currently receiving attention.[146] The use of continuous peripheral nerve blocks at home has also been recently reviewed.[147]

The 5% lidocaine patch has been demonstrated to relieve localised pain in postherpetic neuralgia, with no increase in adverse effects.[148] For countries where this patch formulation is not available (e.g. Canada), pharmacists can make up a gel or a cream at a concentration between 5% and 10%.[139,149]

Combinations of local anaesthetics with other adjuvants, such as morphine, clonidine, ketorolac or ketamine, have been reported. Intra-articular morphine (0.5–1mg) with bupivacaine provided long-lasting analgesia after knee arthroscopy,[60] and the bupivacaine/ketamine combination was superior to intra-articular ketamine analgesia following arthroscopic knee surgery.[150]

Finally, wound or intra-articular infiltration with local anaesthetics with or without the use of continuous infusions via subcutaneous catheters is being reassessed.[151,152] For example, Karamanlioglu et al.[152] compared efficacy and patient outcome of wound infiltration with ropivacaine, lornoxicam or their combination, for control of pain following thyroid surgery. These authors showed that wound infiltration with a combination of ropivacaine 0.75% plus lornoxicam 8mg improved postoperative pain control and patient comfort, and decreased the need for opioids compared with the use of either drug alone. In another study, Harvey et al.[151] evaluated the efficacy of a subacromial PCA infusion of ropivacaine 0.2% versus saline for postoperative pain control following arthroscopic shoulder surgery. They showed that the use of subacromial ropivacaine infusion provided effective postoperative pain control.

10. Cannabinoids

The use of cannabinoids for the treatment of acute and chronic pain has a long and well documented history.[153] For chronic pain, the evidence is mounting that cannabinoids may constitute a new class of agents to add to the pharmaceutical toolbox in the management of chronic pain.[23-26,154-159] The effects of cannabinoids on pain (including peripheral and central neuropathic pain states, and spasticity) are measurable and meaningful to patients, and suggest that with appropriate prescribing and monitoring some additional benefit to some patients may be expected with cannabinoid therapy. Short-term adverse effects are well described and are often the main drawbacks to patient compliance with therapy. More specific information is required on the long-term adverse effects of cannabinoid therapy, including drug-drug interactions, tolerance, cognitive impairment and risks of addiction. However, these issues are not unique to cannabinoids and indeed point to the need for pain physicians to exercise diligence in following patients on psychoactive medications.[27]

The role of cannabinoids in postoperative pain management has been recently evaluated. The conclusions from only four studies show that cannabinoids are not ideally suited to manage postoperative pain, being moderately effective,[160,161] no different from placebo[162] or even antianalgesic at high doses.[163]

11. Multimodal Approach

A main concern of clinical health professionals nowadays is to improve the management of pain in their patients. Pain is a multifactorial phenomenon and knowledge of the complexity of pain pathways is growing, as demonstrated by current research. The concept of multimodal analgesia involves the use of different classes of analgesics (table III) and different sites of analgesic administration to provide superior dynamic pain relief with reduced analgesic-related adverse effects.[164] A multimodal approach is associated with an increase in patient satisfaction and a reduction in adverse effects compared with those resulting from single analgesic techniques in pain management.[165-167] The use of nonpharmacological options, such as acupuncture, relaxation and transcutaneous nerve stimulation, as adjuvants to conventional analgesia can also be considered, and incorporated to achieve an effective and successful pain management regimen in some patients.[167]

12. Conclusions

Many treatment modalities are being used to reduce and alleviate pain; however, many clinical questions are still unanswered. This is attributed to the complexity of the process involved. Indeed, the research and treatments concerning the field of pain management are in the early stages of development, with many unmet goals. In the coming years, several advances are expected in the basic and clinical sci-

Table III. Clinical pharmacology of drugs commonly used in the treatment of pain

Drug class[a]	Indications	Route of administration	Adverse effects	Contraindications
Opioids	Treatment of pain such as acute, postoperative, neuropathic, inflammatory, cancer	Oral, intravenous, transdermal (patch), sublingual spray, intranasal spray, oral transmucosal, pulmonary, microspheres	Respiratory depression, sedation, nausea and vomiting, constipation, cognitive dysfunction, pruritus, tolerance/ dependence, euphoria	Screen patients for alcohol/ substance abuse; coadminister pre-emptive stool softeners and antiemetics
NSAIDs (traditional)	Prescribed as analgesics and anti-inflammatory agents	Oral, intravenous, intramuscular, topical	Gastrointestinal disturbances, renal, skin reactions	Patients with gastrointestinal and renal complications
Coxibs[b]	Relief of osteoarthritis, rheumatoid arthritis, acute and postoperative pain	Oral, intravenous	Cardiac (myocardial infarction and stroke), gastrointestinal problems with long-term use, renal (acute renal failure)	Patients with cardiovascular and cerebrovascular disease; care in patients with hypertension, hyperlipidaemia, diabetes mellitus, arterial disease or smoking
Antidepressants	Neuropathic pain	Oral	Sedation, constipation, dry mouth, orthostatic hypotension and weight gain using tricyclic antidepressants; ataxia, nausea and anorexia using newer antidepressants	Patients with glaucoma and/or taking monoamine oxidase inhibitors; duloxetine has been approved by US FDA for use in diabetic neuropathy.
Antiepileptic drugs	Painful diabetic neuropathy, post-herpetic neuralgia and trigeminal neuralgia	Oral	Sedation, ataxia, oedema, weight gain, diplopia	Patients with renal dysfunction need a dose adjustment
Cannabinoids	Chronic pain	Oral, sublingual spray, inhalation	Euphoria, memory impairment, tachycardia, tolerance	Patients with hypertension and ischaemic heart disease
Local anaesthetics	Blocking evoked pain	Local/regional, transdermal (patch), intravenous, neuroaxial (spinal, epidural)	Skin erythema, rash, convulsions, coma, cardiorespiratory depression with increasing doses	Those associated with loco-regional anaesthesia: non-consenting patient, local infection, coagulation disorders, inadequate monitoring

a See table I for lists of drugs within each class that are commonly used.

b Selective cyclo-oxygenase type 2 inhibitors.

ences of pain, which will provide improved new therapies for patients. Since treatment paradigms are shifting from single-drug trials to multiple-drug therapies, research in multiple-drug therapy is needed in order to better alleviate pain in patients. Increased knowledge of the complexity of the pain pathways is responsible for this necessity for new strategies involving combined medication. Therefore, medical education will be necessary to explain and better understand the importance of multiple drug therapy in the near future.

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