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Abstract:

Pain is an unpleasant sensory and emotional experience for patients. Management of pain is the most frequent issue encountered by clinicians and treatment is usually with pharmacological therapy. This review discusses recent pharmaceutical advances in pain management with respect to new modes of analgesic delivery, as well as new analgesic agents and adjuvants that are currently being investigated for their analgesic properties. New modes of administration include transdermal delivery in the form of skin patches, transmucosal delivery, inhalational administration, various patient-controlled devices and extended-release analgesic formulations. Up-to-date research is presented on classical analgesics, such as opioids, anti-inflammatory agents, including cyclo-oxygenase-2 inhibitors and paracetamol (acetaminophen), local anesthetics and ketamine. In addition, newer agents such as antidepressants and antiepileptic drugs as well as medicinal cannabinoids are discussed. As our understanding of the multiple pain pathways involved in the pathogenesis of pain expands, further compounds with analgesic properties will be developed.

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The International Association for the Study of Pain (IASP) defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage" [1] . Despite progress in both pharmaceutical and physical treatments for pain, it is still a burden for patients, their carers, employers and society as a whole. In the most in-depth and largest-ever survey of 46,000 Europeans, chronic pain was found to affect one in five people, lasting an average of 7 years and accounting for nearly 500 million lost working days every year - costing the European economy at least â¬34 billion. Over 40% of chronic pain sufferers said their pain impacts on everyday activities, from lifting and carrying to taking exercise and sleeping [2] . Pain is a complex, subjective, perceptual phenomenon with a number of contributing factors that are uniquely experienced by each individual. It includes acute pain, such as headaches, postoperative pain, chronic nonmalignant pain, such as back pain, and cancer-related pain. It has been recognized in recent years that there is a direct correlation between severe acute pain and the subsequent development of chronic pain states [3,4] , and therefore, it is essential that we continue to make improvements in the management of both acute and chronic pain in order to improve quality of life for pain sufferers and thus reduce its economic burden.

Pharmaceuticals have been the mainstay of management for both acute and chronic pain states and they have developed in conjunction with our understanding of the multiple pain pathways involved in the pathogenesis of pain (Box 1). In addition, contemporary methods of administration have been developed for analgesics and analgesic adjuvants (defined as drugs with a primary indication other than pain that have analgesic properties in some painful conditions) that alter pharmacokinetics, thus, changing the ease of administration, time of onset, bioavailability and the duration of action of these drugs. This review focuses on recent advances in

pharmaceutical management of both acute and chronic pain, including new modes of administration and new medicines.

New modes of administration

Analgesics and analgesic adjuvants can be administered by the enteral route when administered via the digestive tract or parenteral route when given by routes other than the digestive tract (Figure 1). The US FDA recognizes a total of 111 distinct routes of drug administration. In acutely painful conditions, the intravenous route of analgesic administration is favored because of the rapid onset of effect, easy titrability and 100% bioavailability. Intravenous patient-controlled analgesia (PCA) was developed more than 20 years ago to take advantage of this and provide a method for safe self-administration of a small bolus of intravenous opioid. PCA provides better pain control and greater patient satisfaction, and has become the accepted standard of acute postoperative pain management compared with conventional intermittent intramuscular or intravenous analgesic regimens [5] , which may involve delay in pain treatment. Patient-controlled analgesia modalities have now expanded to include epidural analgesia (PCEA), regional analgesia (PCRA), intranasal analgesia (PCINA) and transdermal analgesia, as will be discussed. The latter two methods of drug administration have been developed because intravenous PCA, PCEA and PCRA are all invasive, can restrict patient mobility, can lead to needle-related injury and require substantial hospital staff time and resources.

Transdermal administration of analgesics was developed in the 1990s for drugs with high potency, lipophilicity, low molecular weight and good skin flux properties, for example, fentanyl. Initially, this method of delivery was proposed for chronic pain and more specifically cancer pain because there is a lag period of 24 h (range: 8-66 h) before blood concentrations reach steady state with the Fentanyl Transdermal Therapeutic System [6,7] . Reservoir skin patches were introduced at the outset, but more recently matrix delivery systems (e.g., Duragesic® /Fen Tek® /Osmophen®) have superseded these because they provide more reliable and consistent delivery of fentanyl, are smaller, thinner, translucent and flexible, and are more comfortable to wear and also reduce the risk of drug leakage and abuse [7,8] . Transdermal buprenorphine matrix patches can deliver the agent over 96 h (Transtec®) or over 1 week (BuTrans®), and are similarly indicated for the treatment of severe cancer and noncancer pain not responding to nonopioid analgesics.

Iontophoretic transdermal systems (ITS) significantly enhance the rate and speed of fentanyl delivery, making these suitable for acute pain treatment; IONSYS® was approved by the European Medicines Agency (EMEA) in 2006 for the management of acute, moderate-to-severe postoperative pain [9-12] . It utilizes the process of iontophoresis to deliver ionized fentanyl molecules across intact skin and directly into the systemic circulation within minutes of application of an imperceptible electric current. The self-contained ITS is patient controlled and is applied to the patient's upper outer arm or chest via a self-adhesive backing. Approximately 41% of the nominal 40-µg fentanyl dose is absorbed into the bloodstream in the first hour of treatment, and increases to nearly 100% after 10 h of treatment, indicating good bioavailability [13] . It has been shown to be equivalent to morphine PCA in a large study of adult patients undergoing major abdominal, orthopedic or thoracic surgery [11] , and avoids the need for needles, pumps, catheters or pump stands making it less intrusive to patients. However, despite these advantages, the marketing authority was suspended by EMEA in November 2008, after corrosion of a component of the system in one batch was detected [201] . This fault carries the risk of triggering the self-activation of the system, which could lead to fentanyl overdose. As this problem could not yet be resolved, the system is currently not available.

Apart from approval of nasal butorphanol in the USA, few regulatory authorities have licensed opioids for intranasal administration, and much of the clinical investigation of intranasal opioid analgesia in the acute pain setting has been limited to investigator-sponsored sites. However, this technique has been investigated for alfentanil, diamorphine, fentanyl, morphine (Rylomine®), pethidine and sufentanil. The clinical use of

nasal opioids, including fentanyl, has expanded into a number of settings other than postoperative pain. These include acute pain control in adult and pediatric emergency departments, in retrieval medicine, in burns pain management and for the control of breakthrough pain in oncology and palliative care patients [14-16] . This novel method of delivery avoids first-pass metabolism because it is absorbed directly by the mucous membrane and is noninvasive, easy to use and has a rapid onset of analgesic effect. A single-center, crossover pilot study compared the efficacy and safety of an intranasal, patient-controlled, spray bottle to that of intravenous fentanyl administration for the treatment of acute pain following gynecological surgery [17] . Pain-intensity scores were similar in both groups, however, more patients preferred intravenous to intranasal administration, possibly because of side effects, such as mild stinging in the nose and bitter taste following intranasal administration. Further studies are awaited on PCINA with fentanyl. Another development in this area is intranasal ketamine for the treatment of acute moderate-to-severe pain. The first trial published showed it to be effective without serious adverse effects for the treatment of breakthrough pain in chronic pain patients [18] . Subsequently, the intranasal administration of ketamine 50 mg in patients after dental surgery provided postoperative analgesia superior to placebo within 15 min after administration [19] . The spray (Ereska®) is currently in Phase III trials in the USA.

Other forms of transmucosal analgesic administration include oral transmucosal (in the form of lozenges or sticks) and sublingual sprays. Oral transmucosal fentanyl citrate (OTFC) is a solid formulation of fentanyl on a stick (Actiq®) and was developed for breakthrough pain in cancer patients [20] . There is also a new rapidly-dissolving fentanyl lozenge (Effentora® /Fentora®). The effervescence obtained from citric acid, sodium bicarbonate and pH-adjusting ingredients optimizes solubility of the fentanyl lozenge by initially creating a pH value of approximately 6.1 through the chemical reaction of water and carbon dioxide to form carbonic acid [21] . Later, this unstable molecule disintegrates leaving carbon dioxide in the air and tissue, which causes the pH to rise to 8.4 and thereby creates optimum conditions for the unionized fentanyl molecule to be transmucosally absorbed. Absolute bioavailability is 65% of the total dose administered compared with 50% in Actiq® [21] . Rapinyl® /Abstral® , another sublingual form of fentanyl, has gained approval from the EMEA for breakthrough pain in cancer patients and is already marketed in a number of European countries.

Buprenorphine can also be administered sublingually; in addition to previous low-dose preparations for analgesia (Temgesic®) it is now available in much higher doses as Subutex® or Suboxone® . The latter of these has naloxone added in order to prevent patients from injecting the drug. These formulations were initially indicated as substitution therapy in drug addiction, but are now also being used for pain treatment [22] . A sublingual spray of oxycodone has been developed and was demonstrated to provide fast pain relief in an acute animal model [23] . Further studies are required to assess its efficacy in humans. Finally, a sublingual spray of tetrahydrocannabinol combined with cannabidiol mixed in a 1'1 ratio (Sativex®) has demonstrated analgesic properties when used for chronic, neuropathic pain conditions and multiple sclerosis [24-26] .

The AERx® pulmonary delivery system combines precise control of aerosol particle size with regulation of the patient's inhalation flow rate to achieve maximal efficiency of drug delivery to the lungs. It has been used to deliver analgesics, such as morphine [27] and fentanyl, to the periphery of the lungs, leading to rapid absorption into the systemic circulation similar to intravenous administration. It has been advanced to a palm-sized, light-weight, inexpensive device (AERx® Essence) and the bioavailability after fentanyl administration is 67% [28] . Further studies are required to determine its clinical applicability.

Last, manufacturers are working on products that extend the release of the analgesic contained within them to increase the time between doses. Extended-release polymer-coated morphine (KADIAN® [29] , Avinza® [30]

) provide systemic opioid analgesia for 24 h. The use of multivesicular liposomes of morphine (DepoDur®) can prolong the duration of action when administered epidurally. The compound has now been approved for single epidural injection in the treatment of postoperative pain and can provide pain relief for up to 48 h after surgery [31] . Clinical studies suggest that the use of DepoDur® decreases the amount of systemically administered analgesics needed for adequate postoperative pain control [32] . It may also provide superior pain control during the first 1-2 postoperative days compared with epidural administration of unencapsulated morphine [32] or intravenous administration of an opioid [33] . The discussion on safety, in particular with higher doses causing delayed respiratory depression continues. A possible solution here is to use lower doses during the multimodal analgesia regimen [34] .

Recent advances in pharmaceuticals

Opioids

Tapentadol immediate release (IR) is a new centrally acting μ-opioid receptor agonist and norepinephrine reuptake inhibitor that has recently been approved by the FDA in the USA, and is awaiting Drug Enforcement Administration (DEA) scheduling. This is the first new drug in its class in 25 years. It underwent Phase III clinical trials assessing the efficacy, safety and tolerability in 603 patients undergoing bunionectomy, 659 patients with end-stage joint disease and 878 with either low back pain or osteoarthritic pain of the hip or knee [35-37] . Treatment with tapentadol IR 100 mg resulted in 79% of patients experiencing at least a 30% improvement in pain intensity at 48 h. This is comparable with the 78% of patients who experienced the same percentage of improvement with oxycodone IR 15 mg. In addition, tapentadol had a reduced incidence of gastrointestinal side effects (76 vs 83% with oxycodone) [37] .

Tramadol is an atypical opioid with partial μ agonist activity in addition to central catecholamine and serotonergic effects. It has gained new interest because of its effect on neuropathic pain [38] with a number needed to treat (NNT) of 3.5. As a combination preparation with paracetamol (Ultracet® , Zaldiar®) for the treatment of subacute back pain, it showed similar efficacy, but fewer adverse events and better tolerability than tramadol on its own [39] . Pharmacokinetic data show a high oral bioavailability (75%) and new prolonged-release formulations (UltramER® , TradorecXL®) assure constant blood levels over 24 h with once-daily dosing, which is convenient for chronic pain treatment [40] . It is included into the most recent guidelines on the management of chronic pain states, such as fibromyalgia and musculoskeletal pain [41,42] .

Methadone has been stigmatized because of its longstanding use in the maintenance programs for opioid addiction. However, it is being increasingly recognized as a valuable second-line opioid analgesic for chronic nonmalignant pain [43] and malignant pain [44] when previous opioid treatment is either ineffective or has intolerable side effects [45] . Opioid rotation to methadone has become a widely used therapeutic concept [45] . Advantages are possibly due to high oral bioavailability, long duration of action, absence of active metabolites, monoaminergic effects and NMDA receptor antagonism. Sandoval *et al.* performed a systematic review of methadone involving 21 papers and 545 patients with multiple noncancer pain conditions [43] . The methadone starting dose ranged from 0.2 to 80 mg/day with maximum doses of 20-930 mg/day. They reported a statistical improvement in pain for methadone 20 mg/day compared with placebo in 59% of the cases, side effects in 225 patients (41%) with nausea and/or vomiting in 23%, sedation in 18%, itching and/or rash in 13%, and constipation in 11%. They noted that the oral dose had a poor correlation with serum blood levels, confirming a large interindividual variability of metabolism. This wide variability, in particular of the half-life of methadone, and the unpredictability of converting equi-analgesic doses of other opioids to methadone requires care and experience from prescribers. Measures must also be instituted to ensure that patients receiving methadone for pain are not considered opioid addicts owing to its common use as maintenance here.

Last, but not least, methadone can cause a small but statistically significant increase in QTc time and has occasionally precipitated torsades de pointes ventricular arrythmias [46] .

Clinical experience and a few controlled trials suggest that available stimulant and osmotic laxatives have limited usefulness for managing opioid-induced constipation, particularly in palliative care settings. Consistent with a peripheral mechanism of action, methylnaltrexone, a quaternary amine μ-opioid antagonist, improved bowel habits but did not increase pain [47] . Response to treatment, defined as laxation within 4 h after each dose, was higher with methylnaltrexone (48%) than with placebo (15%) throughout the 2-week study. Methylnaltrexone (Relistor®) was approved by the EMEA in 2008 for patients with opioid-induced constipation refractory to other laxatives. In theory, methylnaltrexone may also reduce nausea by gaining access to and preventing the opioid effects on the brainstem chemoreceptor trigger zone although this has not been proven. It is unclear whether the drug's beneficial effects are attributable to antagonism of pharmacological and/or physiological effects; endogenous opioids act as inhibitory neurotransmitters in the gut, and opioid antagonists can accelerate colonic transit even in people not receiving opioids.

Similar results have been achieved with the peripherally acting opioid antagonist alvimopan (Entereg®) [48] , which has its indication in the short-term treatment of postoperative ileus [49] . A fixed combination preparation of slow-release oxycodone and slow-release naloxone (Targin®) has been registered in Europe recently. The preparation is aimed at the treatment of chronic pain patients and reduces oxycodone-induced constipation [50,51] .

Remifentanil is a potent ultra-short acting μ-opioid receptor agonist. It is administered to patients during surgery to relieve pain and as an adjunct to anesthesia. More recently it has been used as intravenous PCA both postoperatively [52,53] and for labor analgesia where it was superior to pethidine [54] , but was associated with worse pain scores relative to epidural analgesia [55] . In a trial of 60 patients who underwent coronary artery bypass surgery, remifentanil PCA provided superior analgesia to morphine PCA [53] . Remifentanil is also being used for painful procedures requiring sedoanalgesia, such as in the emergency department [56,57] or pacemaker insertion [58] .

NSAIDs & coxibs

The NSAIDs are widely prescribed to reduce primary hyperalgesia following tissue injury by inhibiting prostanoid synthesis through blockade of cyclooxygenases (COX)-1 and -2. They may also have an effect centrally on dorsal horn cells. However, some prostanoids have a cytoprotective effect within areas such as the gastric mucosa, therefore, COX-2 inhibitors (known as 'coxibs') were developed to selectively block the 'inducible' COX-2 and leave the 'constitutive' COX-1 to have its protective effect. The first coxibs approved for the relief of pain caused by osteoarthritis and rheumatoid arthritis were rofecoxib (Vioxx®) [59] and celecoxib (Celebrex®) [60] . Both publications concluded that coxibs were associated with significantly fewer adverse gastrointestinal (GI) effects than nonselective NSAIDs. However, the study comparing rofecoxib with naproxen (VIGOR) identified an increase of serious cardiovascular thrombotic events with rofecoxib, which was initially explained as a difference between the 'coronary protective' naproxen and the lack of such an effect for rofecoxib [59] . The subsequent APPROVE study [61] , however, found an increased incidence of adverse cardiovascular events for rofecoxib in comparison with the placebo, which resulted in the immediate withdrawal of this compound.

The initial explanation for this phenomenon was that coxibs may increase the risk of vascular thrombosis formation by upsetting the balance of pro- and anti-platelet aggregation effects reducing prostacyclin, and allowing thromboxane to act unopposed (FitzGerald hypothesis) [62] . However, in a number of studies of

other coxibs and in more recent systematic reviews and meta-analyses, it appears that traditional NSAIDs as well as coxibs increase cardiovascular adverse events, rather than just coxibs alone [63-66] . In an attempt to quantify these risks, Moore *et al*. used meta-analyses and randomized controlled trials (RCTs) and determined that in an overall comparison, for every 1000 patients treated for a year with a coxib rather than a NSAID, there would be eight fewer complicated upper GI events, but one more heart attack or stroke [67] . Celecoxib and valdecoxib appeared to have a lower risk of not only GI events, but also cardiovascular events than nonselective NSAIDs. The authors concluded that for all coxibs, the reduction in complicated upper GI events is greater than any increase in risk owing to thrombotic events and, therefore, they should be favored over traditional NSAIDs. Similarly, after initial studies described increased cardiac events in patients undergoing CABG surgery after the use of parecoxib and valdecoxib [68,69] , a recent meta-analysis on postoperative pain showed that parecoxib and valdecoxib do not significantly increase the risk of cardiovascular thrombotic events compared with placebo in patients undergoing noncardiac surgery [70] .

These findings are in particular reassuring in the perioperative setting, where coxibs provide a 30-50% opioid-sparing effect and improve analgesia when coadministered with opioids via PCA [71] . Here they are an important component of multimodal analgesia without the risk of increasing blood loss which nonselective NSAIDs carry [72] . The opioid-sparing effect has a secondary effect of reducing opioid-related symptoms, including postoperative nausea, vomiting and sedation [71,73] . Parecoxib, as a parenteral formulation of a coxib, has a specific role in the setting of acute pain after surgery and trauma, when the oral route is not available [74] . However, both coxibs and nonspecific NSAIDs can have harmful effects on the kidney including precipitatation of acute renal failure because both isoforms of COX are expressed here and are involved in the prostanoid-mediated control of renal blood flow [75] .

The most probable explanation for the increased rate of cardiovascular adverse effects with rofecoxib is its propensity to increase blood pressure more than other compounds, such as naproxen or celecoxib [76] . Explanations on the basis of the chemical structure of rofecoxib are also discussed [77] .

After the withdrawal of valdecoxib owing to rare, but serious, cutaneous adverse events [78] , and the removal of lumiracoxib from the market in a number of countries, including Australia after a number of fatal cases of liver failure [202] , celecoxib remains the only oral coxib available in most markets.

Paracetamol (acetaminophen)

An intravenous form of paracetamol (Perfalgan®) is now available in adult and pediatric formulations. It superseded a previous intravenous form of propacetamol, a prodrug of paracetamol, that had a high incidence of pain and thrombophlebitis on injection [79,80] . It can be used alone [81] or in combination with other analgesics [82] to provide multimodal analgesia (using different classes and sites of analgesic administration to provide superior dynamic pain relief with reduced analgesic-related adverse effects). The parenteral form offers the opportunity to use paracetamol perioperatively; previously used rectal preparations showed poor and unreliable absorption.

Paracetamol is a widely used analgesic and antipyretic agent with good clinical efficacy and adverse effects similar to placebo [83,84] . It lacks the adverse cardiovascular and renal effects that characterize anti-inflammatory drugs. Its efficacy is surgical procedure-dependent but similar to NSAIDs except in dental surgery [85] . The combination of NSAIDs and paracetamol appears to be more effective than either drug alone [85] . Although paracetamol has a morphine-sparing effect of approximately 20%, unfortunately this is not translated into a decrease in the incidence of morphine-related adverse effects or an increase in patient

satisfaction at commonly used doses [86] .

Despite its widespread use for over 100 years, its mechanism of action remains elusive. One theory regarding paracetamol's mechanism of action is that it reduces the oxidized (active) form of the COX enzyme, thus preventing it from forming proinflammatory chemicals [87] . Therefore, in an inflammatory environment where the concentration of peroxides is high, paracetamol's activity may be impaired. This means that it may not have a direct effect on the site of inflammation but instead acts on the CNS to produce analgesia and antipyresis where the environment is not oxidative. Allied to this theory is the fact that paracetamol works by inhibiting the COX-3 isoform of the COX family of enzymes. When expressed in dogs, this enzyme shares a strong similarity to the other COX enzymes, produces proinflammatory chemicals and is selectively inhibited by paracetamol [88] . However, research has suggested that in humans and mice, the COX-3 enzyme does not possess inflammatory action [89] . Further research has shown that paracetamol also modulates the endogenous cannabinoid system [90,91] . Paracetamol is metabolised to AM404, a compound with several actions; most importantly, it inhibits the reuptake of the endogenous cannabinoid/vanilloid anandamide by neurons. Anandamide has an analgesic effect. It has been demonstrated that, after blocking cannabinoid receptors and, hence, making any action on cannabinoid reuptake irrelevant, paracetamol no longer has any analgesic effect. Furthermore, AM404 inhibits sodium channels similarly to the local anesthetics lidocaine and procaine. Either of these actions alone have been shown to reduce pain, and are possible targets for paracetamol. More recently, Pickering *et al*. have suggested the serotonergic system as a site for paracetamol's action [92] . They hypothesize that paracetamol reinforces descending inhibitory pain pathways; which may have practical implications, as coadministration of the 5-HT_3 -antagonist antiemetics tropisetron and granisetron inhibits the analgesic effects of paracetamol [93] .

Ketamine

Ketamine is an old substance that was introduced into clinical practice in 1963 as a dissociative anesthetic. More recently, if has been increasingly used in very low doses to provide analgesic effects in a wide range of acute and chronic pain settings. This concept is based on the antagonistic effect of ketamine on the NMDA receptor, a ligand-gated calcium channel with glutamate as its major endogenous agonist. As the activation of this calcium channel leads to central sensitization, it was postulated that ketamine would be particularly effective in so called 'pathological' pain states caused by this process [94] . The administration of low-dose ketamine either intravenously or subcutaneously has been shown to decrease pain in nonresponsive neuropathic pain patients [95] , and it has been successfully used for treating intractable cancer pain [96] . However, there are insufficient data to support the routine or long-term use of ketamine in the treatment of chronic pain or refractory cancer pain. A Cochrane review stated that "the benefits and harms of adding ketamine to strong painkillers, such as morphine, for relief of cancer pain are not yet established" owing to a lack of suitable RCTs [97] .

The role of ketamine in the treatment of postoperative pain is also unclear. When added to opioid-based analgesia, either as a low-dose bolus or parenteral infusion, pain scores were reduced by less than 1 cm on a 10 cm visual analogue scale, and delayed time to first request for analgesia by 16 min [98] . Both results were statistically but not clinically significant. Opioid consumption is reduced by approximately 30% without a reduction in opioid-related adverse effects except nausea and vomiting [99] . Ketamine is most effective as a continuous low-dose intravenous infusion and there appears to be no benefits from adding ketamine to an opioid in a PCA device [100] . Ketamine can provide safe and effective sedation and analgesia for painful procedures, such as fracture reduction [101] and burns dressings. It is also a good 'rescue' analgesic in patients poorly responsive to morphine [102] or who have opioid-induced hyperalgesia following remifentanil infusions

[103] . It can also reduce secondary hyperalgesia and allodynia surrounding an incision. Therefore, ketamine appears to be more effective as a central sensitization modulator (antiallodynic, antihyperalgesic) by inhibiting 'wind-up' in the acute postoperative period rather than as an analgesic *per se* ; it also improves analgesia in opioid tolerance [94] .

Local anesthetics

Local anesthetics are the only medication for providing medium to long-term analgesia in evoked pain in the form of continuous nerve blockade [104] . Postoperative analgesia is generally limited to 12-16 h or less after single-injection regional nerve blocks, but can be prolonged by using a local anesthetic infusion via a perineural catheter. This technique may now be used in the outpatient setting with the relatively recent introduction of reliable, portable infusion pumps [105] . This has resulted in faster and improved rehabilitation, better analgesia, greater patient satisfaction and reduced nausea and vomiting because of an opioid-sparing effect [106] .

Lidoderm® /Versatis® , a lidocaine 5% medicated plaster ('patch'), is indicated for the treatment of postherpetic neuralgia (PHN) with effects on pain and allodynia [107] . Other models of neuropathic pain, such as sensory polyneuropathy [108] , have also been studied; in PHN, the plaster was superior to pregabalin, and comparable to pregabalin in diabetic polyneuropathy [109] . Investigations in healthy human volunteers have shown that only 3% of the plaster's drug contents are systemically absorbed with negligible plasma concentrations of lidocaine [107] . Up to three plasters can be applied for up to 12 h per day on intact, dry, nonirritated skin. Approximately 16% of patients can be expected to experience adverse reactions, mostly localized reactions, and the incidence of systemic toxicity is rare. The discontinuation rate owing to adverse events was much lower for the plaster than for pregabalin (1.3 vs 20.3%) [109] . The efficacy and in particular the lack of systemic adverse effects, have made the lidocaine medicated plaster the recommended first-line treatment in localized neuropathic pain [110,111] . It has also been recently studied in a number of chronic settings, such as lower back pain [112] , osteoarthritis [113] , and in postoperative pain following laparoscopic hernia repair [114] .

In addition to topical and perineural administration, wound or intra-articular infiltration with local anesthetics as single doses or infusions are currently being investigated. These can be used alone or in combination with other analgesics, such as morphine and ketorolac, to provide greater patient satisfaction, less sleep disturbance owing to pain, and an earlier return to employment after knee arthroscopy [115] with similar effects after shoulder surgery [116] . Patient-controlled subacromial infusion with ropivacaine resulted in a 34% reduction of postoperative pain following arthroscopic sub-acromial decompression [117] . The approach has also been used very successfully after total hip and knee joint replacement [118] enabling fast-track recovery. Forastiere *et al*. evaluated the effectiveness of continuous wound infusion with 0.5% ropivacaine after open nephrectomy [119] . The authors showed that pain scores, morphine consumption, time to bowel recovery and mean length of hospital stay were significantly reduced in the infusion group compared with controls. Cost analysis revealed an overall saving of approximately â¬273 per patient.

Antidepressants

Tricyclic antidepressants (TCAs) are the classical therapeutic compounds for neuropathic pain with a NNT value of 3.6 for the achievement of at least moderate pain relief [120] . The main effect of these drugs is to nonselectively inhibit the uptake of norepinephrine and serotonin and some may also block sodium channels

in a state and use-dependent manner [121] . This may contribute to their antihyperalgesic effects, by preventing central sensitization. Unfortunately, adverse effects including sedation, confusion, blurred vision, postural hypotension and many others limit the usefulness of TCAs and newer drugs have been investigated that circumvent these issues.

Selective serotonin-reuptake inhibitors (SSRIs), such as fluoxetine, investigated in only four studies, were found to be superior to placebo, but evidence was insufficient to calculate a robust NNT value [122] . Two additional studies, which compared SSRIs to TCAs, found SSRIs to be less efficient than TCAs. Therefore, the analgesic effect of SSRIs in neuropathic pain is limited; although beneficial effects on wellbeing have been reported in several chronic pain conditions.

Venlafaxine, a serotonin-norepinephrine reuptake inhibitor (SNRI), is devoid of cholinergic, histaminergic and [alpha]-adrenergic adverse effects. This drug has an NNT value of 3.1 for neuropathic pain [120] , although the number of studies is still low. It is, however, recommended for neuropathic pain, migraines and fibromyalgia [122] .

Another SNRI, duloxetine, is also an effective compound in neuropathic pain and fibromyalgia with an NNT of 5.8 [123] .

Milnacipran, also a SNRI but with an equal effect on serotonin and norepinephrine (compared with venlafaxine which has a much greater effect on serotonin), was approved by the FDA this year for fibromyalgia following the publication of two Phase III trials involving over 2000 patients [124,125] .

In summary, recent evidence-based guidelines confirm that TCAs have established efficacy in neuropathic pain and consider them (in particular amitriptyline) as first-line treatment [126] . It is also proposed that the SNRIs, venlafaxine and duloxetine, should be second-choice treatments in painful neuropathy [126] . In the elderly and in patients with cardiovascular risk factors, it is suggested that SNRIs should be preferred to TCAs given the adverse cardiovascular effects of TCAs. All reviews agree that there are insufficient data on the effectiveness of SSRIs in neuropathic pain.

Antiepileptic drugs

The first antiepileptic drugs (AEDs) to be used to relieve painful diabetic neuropathy and trigeminal neuralgia were carbamazepine and phenytoin [110] . Unfortunately, high incidences of adverse effects have limited their use and newer AEDs were investigated for their analgesic effect. Gabapentin has been studied in several large trials and has a documented effect on pain and quality of life measures, including mood and sleep disturbance in mixed neuropathic pain states, postherpetic neuralgia, painful diabetic neuropathy and spinal cord injury [127] . Pregabalin has a comparable effect to gabapentin in post-herpetic, painful diabetic neuropathy and spinal cord injury pain, but superior pharmacokinetics [128] . Both these drugs are thought to work at the a_2 -d subunit of voltage-gated calcium channels to reduce calcium influx at presynaptic terminals in hyperexcited neurons [129] . This leads to reduced release of excitatory neurotransmitters. Pregabalin has also shown promising effects in fibromyalgia [130] , where it now has an indication by the FDA, and both drugs have been studied in a number of other chronic pain states. Both drugs are now recommended as first-line treatment in peripheral and central neuropathic pain [110,126] .

There is increasing interest in the use of both gabapentin and pregabalin for postoperative analgesia. Oral gabapentin activates spinal cholinergic circuits to reduce hypersensitivity after peripheral nerve injury [131] . Several studies have shown that gabapentin and pregabalin are effective in reducing pain intensity, opioid

consumption and opioid-related adverse effects after surgery [132,133] . Both drugs have very few adverse effects on their own. However, at the present time, no conclusions regarding the optimal dose and duration of treatment can be drawn.

Lamotrigine, another new AED that blocks voltage-dependent sodium channels and inhibits glutamate release, has shown poor efficacy in neuropathic pain states [134] , but may be useful as add-on treatment, in painful diabetic neuropathy and poststroke pain [110] .

Cannabinoids

Cannabis has been used anecdotally for more than 5000 years to treat a variety of conditions, including insomnia, nausea, anorexia, glaucoma and pain. In recent years, there has been renewed interest in the use of cannabis for analgesic purposes because of the favorable safety profile of cannabinoids (a group of terpenophenolic compounds present in *Cannabis sativa* that bind to cannabinoid receptors) [135] . There have been no reported deaths directly attributed to cannabis overdose. The primary active component of marijuana is d-9-tetrahydrocannabinol (THC) and is responsible for most of its common effects. There are another 65 cannabinoids, most of which have not had their activity profiles clarified. The first cannabinoid receptor identified in 1990 was CB1, which has an effect on pain transmission, followed by CB2 in 1993 which is thought to have immunosuppressive and anti-inflammatory activities. There are several endogenous ligands for these receptors called endocannabinoids, of which anandamide is one.

At present, there are three cannabinoids available on the international market: dronabinol, nabilone and cannabis medicinal extract (CME). Dronabinol is synthetically manufactured THC and is available in the USA as a Schedule III controlled substance indicated for use as an appetite stimulant in patients with HIV or for chemotherapy-induced nausea and vomiting. Nabilone is a synthetic THC analogue and is available in the UK, USA, Switzerland and Canada. Nabilone is indicated for chemotherapy-induced nausea and vomiting, but more recently it has been investigated for use in spasticity [136] , chronic pain [137] and fibromyalgia [138] . It was also compared with dihydrocodeine for neuropathic pain and was considered less effective with more adverse effects [139] . CME (Sativex®) was approved in Canada in 2005 with the indication of adjunctive treatment for symptomatic relief of neuropathic pain in adults with multiple sclerosis [26,140] . It is a sublingual whole plant extract that contains a 1:1 ratio of THC and cannabidiol. Although it is not similarly licensed in the UK, it can be imported from Canada for named-patient prescription use. Unfortunately, cannabinoids do not seem to be effective in postoperative pain management being only moderately effective, no different from placebo or even antanalgesic at high doses [135] .

Dexmedetomidine

Dexmedetomidine is an [alpha]-2 adrenoreceptor agonist, similar to clonidine. It has sedative, analgesic, sympatholytic and anxiolytic effects that blunt many of the cardiovascular responses in the perioperative period. Studies have examined its properties for reducing postoperative analgesic requirements. Lin *et al*. showed that the addition of dexmedetomidine to intravenous PCA morphine resulted in superior analgesia, significant morphine sparing, less morphine-induced nausea, and was devoid of additional sedation and untoward hemodynamic changes [141] . A preoperative single dose of dexmedetomidine also reduced postoperative morphine consumption, but had no effect on postoperative recovery time [142] . Dexmedetomidine has been added to lidocaine for intravenous regional anesthesia where it improves the quality of the block and reduces analgesic requirements [143] . In addition, intra-articular administration enhanced postoperative analgesia after arthroscopic knee surgery [144] . It may even reduce ischemia-reperfusion injury and studies are required in humans to confirm this.

Expert commentary

The pharmaceutical management of pain has been the focus of considerable research efforts over the last 10 years. This research effort was driven by a better understanding of the physiology of pain, but also by data on the epidemiology of pain alluded to in the introduction, by consumer demand and by the economic interests of the pharmaceutical industry on discovering a large market. The results of this endeavor have been significant as outlined in this review, although many unmet needs remain.

With regard to new modes of administration, adjusting pharmacokinetics to specific clinical needs has been the main goal. Transdermal delivery systems for long-term management of cancer and chronic pain have been improved by a change from reservoir to matrix patches. These matrix patches offer advantages in particular with regard to patient comfort, but also safety. The availability of buprenorphine by transdermal delivery systems has added an interesting new treatment option. While conventional transdermal delivery systems aim at stable maintenance of steady state concentrations, the development of an iontophoretic transdermal system offers a completely new concept; it enables use of a transdermal system as a replacement for an intravenous PCA device for treatment of postoperative pain. It is regrettable that corrosion problems led to the current suspension of the marketing authority for this innovative and promising device.

The treatment of acute and breakthrough pain is also the indication for a wide range of intranasal, transmucosal and inhalational preparations of opioids, in particular fentanyl, but also other analgesics, such as ketamine. Rapid absorption, avoidance of first-pass metabolism and short duration of action are the ideas behind these preparations.

Advances with regard to pharmaceuticals have been made not only in the development of new compounds, but also in better understanding of established analgesics with regard to their effects and adverse effects. With regard to opioids, the development of the new compound tapentadol, the introduction of peripheral opioid antagonists to reduce opioid-induced constipation with better understanding and, therefore, clinical use of tramadol, methadone and remifentanil remains to be mentioned. The debate on non-opioids has focused, in the wake of rofecoxib withdrawal, primarily on the the cardiovascular risk of NSAIDs and coxibs, where a much better understanding of the risks has been achieved. The debate on the mechanism of action of the old compound paracetamol has intensified and interesting new hypotheses have been developed.

Among the adjuvants the anesthetic agent ketamine has undergone a renaissance in its use as a modulator of central sensitization, in particular in difficult to control pain states. The lidocaine medicated plaster indicated for the treatment of postherpetic neuralgia has proven to be increasingly useful in other neuropathic and, more recently, a number of nociceptive pain states. Newer antidepressants with serotonergic and noradrenergic effects (SNRIs) are getting the indication for neuropathic pain and central sensitization disorders such as fibromyalgia and may become replacements for the classical tricyclic compounds owing to less adverse effects. Gabapentin and, more recently, pregabalin, have not only revolutionized the treatment of neuropathic pain by becoming first-line drugs for this indication in many guidelines, but are proving effective in other chronic and, more recently, acute pain conditions including postoperative pain. Thus, the debate on cannabinoids and their role in pain therapy continues to be as emotive as ever.

Five-year view

Despite considerable recent advances in the development of pharmaceutical compounds to treat pain presented in this review, current therapeutic modalities are still insufficient to provide effective and safe analgesia without adverse effects to many patients. This is not only true for postoperative pain states, but even more for patients with neuropathic pain conditions and chronic pain states, often owing to central sensitization, such as fibromyalgia, interstitial cystitis and nonspecific low back pain. Future treatments need to be more targeted to pain pathways and with fewer adverse effects, otherwise pain relief *per se* will not lead to improvement in function and overall quality of life. Chronic pain states in particular need to be seen as a

biopsychosocial phenomenon; there will possibly never be a 'magic bullet' to treat these states pharmacologically without multidisciplinary management and rehabilitation approaches. However, increasing understanding of pain physiology has offered a number of potential targets for future treatments, in particular for neuropathic and chronic pain [145,146] .

One such target is ligand-gated ion channels, which are an important component of multimodal nociceptors. The best example is the transient receptor potential (TRP) channel TRPV1 (previously called Vanilloid receptor 1), which is responsive to noxious heat, acidity and mediators of inflammation (structurally similar to capsaicin) [147] . One approach here is the use of agonists to achieve desensitization or even degeneration of the receptor; high concentration capsaicin has been shown to have an effect in PHN [148] , here administered as a plaster and instilled into the wound in herniotomy patients [149] . Alternatively, there is interest in TRPV1 antagonists, which would block this rather pain-specific receptor; a number of compounds are currently under clinical investigation with some promising preliminary results [150] .

In neuropathic pain states, voltage-gated sodium channels show increased expression and/or activity. In particular, the channels NaV1.7 (which by mutation can cause erythromelalgia) NaV1.8 and NaV1.3 seem to be specific for pain transmission [151] . While the aforementioned lidocaine plaster, has its effect by a localized nonspecific block of sodium channels, specific blockers of these channels for systemic use are currently being investigated with promising effects not on acute nociceptive, but chronic neuropathic pain [152] .

Calcium channels are further targets for future analgesic drug development. Already currently available compounds act on calcium channels; gabapentin and pregabalin modulate the a2-d subunit of voltage-gated N-type calcium channels [129] and the conotoxin ziconotide available only for intrathecal administration, blocks N-type calcium channels [153] . Thus, the development of compounds modulating N- and T-type calcium channels might provide drugs that are effective in the treatment of chronic and neuropathic pain states [154] .

The excitatory amino acid glutamate is the most important excitatory transmitter in the pain pathway; its binding to AMPA and NMDA receptors as well as a variety of glutamate receptors leads to excitation of the secondary neuron [155] . Therefore, antagonists to these receptors are promising compounds for the treatment of neuropathic and chronic pain in particular; the renaissance of low-dose ketamine described earlier illustrates this, although its adverse effect profile limits its usefulness [94] . A wide range of such antagonists is currently in various stages of preclinical and clinical development.

While the concepts described above are aiming to reduce excitation, the opposite approach of enhancing inhibition of pain pathways also offers promising results. TCAs, SNRIs and tramadol interfere with monaminergic transmission and thereby strengthen inhibitory systems. The recent approval of duloxetine, milnacipran and tapentadol for pain indications illustrates the potential of this approach; further research in this area continues [122] .

Cannabinoids have so far been rather disappointing compounds in clinical practice with limited efficacy in restricted indications as outlined above. However, research continues in the areas of CB1 and CB2 agonists [156] , as well as the areas of inhibition of fatty acid amide hydrolysis, aiming to increase endogenous CB1 and CB2 ligand concentrations (endocannabinoids) [157] .

Looking even further into the future, the recognition of the role of neuroglial cells in maintaining states of central sensitization offers a completely different area of therapeutic interventions [158] . Options under

investigation here are substances which reduce glial activation or antagonize the cytokines produced by activated glia [159] .

The role of neurotrophins, such as NGF, BDNF and GDNF, in the regulation of nerve excitability has lead to research into the modulation of this system. Antagonists to NGF receptors are a possible option; a monoclonal antibody against NGF has been tried clinically with long-lasting pain reduction as an outcome [160] . While neurotophic factors play an important role as mediators and modulators of pain, the therapeutic usage remains poorly defined [161] .

This limited outlook into the future illustrates not only the complexity of the processes involved in the physiology of pain, but also a wide range of promising therapeutic options to come.

Box 1. Pharmaceuticals used in the treatment of pain.

Opioids

• Alfentanil, buprenorphine, butorphanol, codeine, diamorphine, fentanyl, hydromorphone, levorphanol, pethidine, meperidine, methadone, morphine, nalbuphine, oxycodone, remifentanil, sufentanil and tramadol

NSAIDs

• Aspirin, diclofenac, ibuprofen, indomethacin and ketoprofen, ketorolac, mefenamic acid, naproxen and piroxicam

COX-2 inhibitors

• Celecoxib, etoricoxib, lumiracoxib and parecoxib

Cannabinoids

• Ajulemic acid (CT-3), dexanabinol, dronabinol, nabilone and THC/CBD

LAs

• Bupivacaine, levobupivacaine, lidocaine and ropivacaine

Analgesic adjuvants

Antiepileptic drugs

• Carbamazepine, gabapentin, lamotrigine, phenytoin, pregabalin and sodium valproate

Antidepressants

• SNRIs, SSRIs and TCAs

Others

• [beta]-blockers, capsaicin, clonidine, dexmedetomidine, ketamine, magnesium, mexiletine, nicotine, nefopam, neostigmine, paracetamol (acetaminophen)

CBD: Cannabidiol; LA: Local anesthetic; NSAID: Non-steroidal anti-inflammatory drugs; SNRI: Serotonin-norepinephrine reuptake inhibitor; SSRI: Selective serotonin-reuptake inhibitor; TCA: Tricyclic

antidepressant; THC: Δ^{9} -tetrahydrocannabinol.

Key issues

• Pain is a symptom most frequently encountered by clinicians.

• Pharmaceuticals remain the mainstay of treatment for acute and cancer-related pain and are an important component of chronic pain management.

• Recent advances in pharmaceutical pain management include innovative modes of administration for analgesics, as well as further development of compounds in established and new indications.

• Contemporary methods of analgesic administration include the transdermal, iontophoretic, transmucosal and inhalational route, as well as various patient-controlled devices and extended-release preparations.

• Non-opioid analgesics of interest include paracetamol (acetaminophen) in a new parenteral administration and with new data on its mechanism of action, as well as coxibs in view of a better understanding of their cardiovascular effects.

• Among opioids, the new compound tapentadol is promising as are new indications for tramadol, methadone and remifentanil; the opioid antagonists methylnaltrexone, alvimopan and naloxone are aimed at opioid-induced constipation.

• Ketamine has gained a new role for treatment of central sensitization, while indications for medicinal cannabinoids remain limited despite multiple research efforts.

• In the area of analgesic adjuvants (defined as drugs with a primary indication other than pain that have analgesic properties in some painful conditions), such as antidepressants and antiepileptic drugs, new compounds for pain treatment are promising and are effective in new indications, such as fibromyalgia.

• Further research is directed at compounds modulating sodium and calcium channels, glutamate receptors, cannabinoid receptors and neurotrophins involved in glial cell activation.

CAPTION(S):

Figure 1. Methods of analgesic administration and relevant pharmaceuticals.

References

Papers of special note have been highlighted as: • of interest •• of considerable interest

1 Merskey H. The taxonomy of pain. *Med. Clin. North Am.* 91(1), 13-20, vii (2007).

2 Breivik H, Collett B, Ventafridda V, Cohen R, Gallacher D. Survey of chronic pain in Europe: prevalence, impact on daily life, and treatment. *Eur. J. Pain* 10(4), 287-333 (2006).

3 Eisenach JC, Pan PH, Smiley R *et al.* Severity of acute pain after childbirth, but not type of delivery, predicts persistent pain and postpartum depression. *Pain* 140(1), 87-94 (2008).

4 Poleshuck EL, Katz J, Andrus CH *et al.* Risk factors for chronic pain following breast cancer surgery: a prospective study. *J. Pain* 7(9), 626-634 (2006).

5 Hudcova J, McNicol E, Quah C, Lau J, Carr DB. Patient controlled opioid analgesia versus conventional opioid analgesia for postoperative pain. *Cochrane Database Syst. Rev.* 4, CD003348 (2006).

6 Ashburn MA, Ogden LL, Zhang J, Love G, Basta SV. The pharmacokinetics of transdermal fentanyl delivered with and without controlled heat. *J. Pain* 4(6), 291-297 (2003).

7 Sathyan G, Guo C, Sivakumar K, Gidwani S, Gupta S. Evaluation of the bioequivalence of two transdermal fentanyl systems following single and repeat applications. *Curr. Med. Res. Opin.* 21(12), 1961-1968 (2005).

8 Freynhagen R, von Giesen HJ, Busche P *et al.* Switching from reservoir to matrix systems for the transdermal delivery of fentanyl: a prospective, multicenter pilot study in outpatients with chronic pain. *J. Pain Symptom Manage.* 30(3), 289-297 (2005).

9 Chelly JE, Grass J, Houseman TW, Minkowitz H, Pue A. The safety and efficacy of a fentanyl patient-controlled transdermal system for acute postoperative analgesia: a multicenter, placebo-controlled trial. *Anesth. Analg.* 98(2), 427-433 (2004).

10 Koo PJ. Postoperative pain management with a patient-controlled transdermal delivery system for fentanyl. *Am. J. Health Syst. Pharm.* 62(11), 1171-1176 (2005).

11 Viscusi ER, Siccardi M, Damaraju CV, Hewitt DJ, Kershaw P. The safety and efficacy of fentanyl iontophoretic transdermal system compared with morphine intravenous patient-controlled analgesia for postoperative pain management: an analysis of pooled data from three randomized, active-controlled clinical studies. *Anesth. Analg.* 105(5), 1428-1436 (2007).

•• Provides a good overview of the relevant trials of iontophoretic transdermal systems fentanyl.

12 Rawal N, Langford RM. Current practices for postoperative pain management in Europe and the potential role of the fentanyl HCl iontophoretic transdermal system. *Eur. J. Anaesthesiol.* 24(4), 299-308 (2007).

13 Sathyan G, Zomorodi K, Gidwani S, Gupta S. The effect of dosing frequency on the pharmacokinetics of a fentanyl HCl patient-controlled transdermal system (PCTS). *Clin. Pharmacokinet.* 44(Suppl. 1), 17-24 (2005).

14 Shelley K, Paech MJ. The clinical applications of intranasal opioids. *Curr. Drug Deliv.* 5(1), 55-58 (2008).

• Assessment of the intranasal route of administration for opioids.

15 Borland M, Jacobs I, King B, O'Brien D. A randomized controlled trial comparing intranasal fentanyl to intravenous morphine for managing acute pain in children in the emergency department. *Ann. Emerg. Med.* 49(3), 335-340 (2007).

16 Borland ML, Bergesio R, Pascoe EM, Turner S, Woodger S. Intranasal fentanyl is an equivalent analgesic to oral morphine in paediatric burns patients for dressing changes: a randomised double blind crossover study. *Burns* 31(7), 831-837 (2005).

17 Paech MJ, Lim CB, Banks SL, Rucklidge MW, Doherty DA. A new formulation of nasal fentanyl spray for postoperative analgesia: a pilot study. *Anaesthesia* 58(8), 740-744 (2003).

18 Carr DB, Goudas LC, Denman WT *et al.* Safety and efficacy of intranasal ketamine for the treatment of breakthrough pain in patients with chronic pain: a randomized, double-blind, placebo-controlled, crossover study. *Pain* 108(1-2), 17-27 (2004).

19 Christensen K, Rogers E, Green GA *et al.* Safety and efficacy of intranasal ketamine for acute postoperative pain. *Acute Pain* 9(4), 183-192 (2007).

20 Mystakidou K, Katsouda E, Parpa E, Vlahos L, Tsiatas ML. Oral transmucosal fentanyl citrate: overview of pharmacological and clinical characteristics. *Drug Deliv.* 13(4), 269-276 (2006).

21 Darwish M, Kirby M, Robertson P Jr, Tracewell W, Jiang JG. Absolute and relative bioavailability of fentanyl buccal tablet and oral transmucosal fentanyl citrate. *J. Clin. Pharmacol.* 47(3), 343-350 (2007).

22 Heit HA, Gourlay DL. Buprenorphine: new tricks with an old molecule for pain management. *Clin. J. Pain* 24(2), 93-97 (2008).

23 Al-Ghananeem AM, Malkawi AH, Crooks PA. Effect of pH on sublingual absorption of oxycodone hydrochloride. *AAPS PharmSciTech* 7(1), E23 (2006).

24 Perez J, Ribera MV. Managing neuropathic pain with Sativex: a review of its pros and cons. *Expert Opin. Pharmacother.* 9(7), 1189-1195 (2008).

• Critical review of the use of cannabinioids in the setting of neuropathic pain.

25 Nurmikko TJ, Serpell MG, Hoggart B *et al.* Sativex successfully treats neuropathic pain characterised by allodynia: a randomised, double-blind, placebo-controlled clinical trial. *Pain* 133(1-3), 210-220 (2007).

26 Rog DJ, Nurmikko TJ, Young CA. Oromucosal d9-tetrahydrocannabinol/cannabidiol for neuropathic pain associated with multiple sclerosis: an uncontrolled, open-label, 2-year extension trial. *Clin. Ther.* 29(9), 2068-2079 (2007).

27 Thipphawong JB, Babul N, Morishige RJ *et al.* Analgesic efficacy of inhaled morphine in patients after bunionectomy surgery. *Anesthesiology* 99(3), 693-700; discussion 696A (2003).

28 Farr SJ, Otulana BA. Pulmonary delivery of opioids as pain therapeutics. *Adv. Drug Deliv. Rev.* 58(9-10), 1076-1088 (2006).

29 Ross EL, Hahn K. KADIAN (morphine sulfate extended-release) capsules for treatment of chronic, moderate-to-severe, nonmalignant pain. *Int. J. Clin. Pract.* 62(3), 471-479 (2008).

30 Rauck RL, Bookbinder SA, Bunker TR *et al.* The ACTION study: a randomized, open-label, multicenter trial comparing once-a-day extended-release morphine sulfate capsules (AVINZA) to twice-a-day controlled-release oxycodone hydrochloride tablets (OxyContin) for the treatment of chronic, moderate to severe low back pain. *J. Opioid. Manag.* 2(3), 155-166 (2006).

31 Viscusi ER, Martin G, Hartrick CT, Singla N, Manvelian G. Forty-eight hours of postoperative pain relief after total hip arthroplasty with a novel, extended-release epidural morphine formulation. *Anesthesiology* 102(5), 1014-1022 (2005).

32 Viscusi ER, Kopacz D, Hartrick C, Martin G, Manvelian G. Single-dose extended-release epidural morphine for pain following hip arthroplasty. *Am. J. Ther.* 13(5), 423-431 (2006).

33 Hartrick CT, Martin G, Kantor G, Koncelik J, Manvelian G. Evaluation of a single-dose, extended-release epidural morphine formulation for pain after knee arthroplasty. *J. Bone Joint Surg. Am.* 88(2), 273-281 (2006).

34 Hartrick CT, Hartrick KA. Extended-release epidural morphine (DepoDur): review and safety analysis.

Expert Rev. Neurother. 8(11), 1641-1648 (2008).

• Good summarizing review of this new preparation for epidural use.

35 Oh C. Efficacy of tapentadol immediate release in patients with pain after bunionectomy. Presented at: *American Pain Society meeting.* (Eds). Tampa, FL, USA (2008)

36 Hartrick C. Analgesic Efficacy of tapentadol immediate release in patients with pain from end stage joint disease. Presented at: *American Pain Society Meeting.* Tampa, FL, USA (2008).

37 Oh C. Tapentadol immediate release is associated with improved gastrointestinal tolerability compared with oxycodone immediate release over 90 days in patients with lower back or osteoarthritis pain. Presented at: *American Pain Society Meeting.* Tampa, FL, USA (2008).

38 Hollingshead J, Duhmke RM, Cornblath DR. Tramadol for neuropathic pain. *Cochrane Database Syst. Rev.* 3, CD003726 (2006).

39 Perrot S, Krause D, Crozes P, Naim C. Efficacy and tolerability of paracetamol/tramadol (325 mg/37.5 mg) combination treatment compared with tramadol (50 mg) monotherapy in patients with subacute low back pain: a multicenter, randomized, double-blind, parallel-group, 10-day treatment study. *Clin. Ther.* 28(10), 1592-1606 (2006).

40 Barkin RL. Extended-release tramadol (ULTRAM ER): a pharmacotherapeutic, pharmacokinetic, and pharmacodynamic focus on effectiveness and safety in patients with chronic/persistent pain. *Am. J. Ther.* 15(2), 157-166 (2008).

41 Carville SF, Arendt-Nielsen S, Bliddal H *et al.* EULAR evidence-based recommendations for the management of fibromyalgia syndrome. *Ann. Rheum. Dis.* 67(4), 536-541 (2008).

• Current recommendations for the management of the complex issues related to fibromyalgia are presented here with supporting evidence.

42 Goldenberg DL. Pharmacological treatment of fibromyalgia and other chronic musculoskeletal pain. *Best Pract. Res. Clin. Rheumatol.* 21(3), 499-511 (2007).

43 Sandoval JA, Furlan AD, Mailis-Gagnon A. Oral methadone for chronic noncancer pain: a systematic literature review of reasons for administration, prescription patterns, effectiveness, and side effects. *Clin. J. Pain* 21(6), 503-512 (2005).

44 Nicholson AB. Methadone for cancer pain. *Cochrane Database Syst. Rev.* 4, CD003971 (2007).

45 Fredheim OM, Moksnes K, Borchgrevink PC, Kaasa S, Dale O. Clinical pharmacology of methadone for pain. *Acta Anaesthesiol. Scand.* 52(7), 879-889 (2008).

46 Pearson EC, Woosley RL. QT prolongation and torsades de pointes among methadone users: reports to the FDA spontaneous reporting system. *Pharmacoepidemiol. Drug Saf.* 14(11), 747-753 (2005).

47 Thomas J, Karver S, Cooney GA *et al.* Methylnaltrexone for opioid-induced constipation in advanced illness. *N. Engl. J. Med.* 358(22), 2332-2343 (2008).

48 Leslie JB. Alvimopan for the management of postoperative ileus. *Ann. Pharmacother.* 39(9), 1502-1510 (2005).

49 McNicol E, Boyce DB, Schumann R, Carr D. Efficacy and safety of mu-opioid antagonists in the treatment of opioid-induced bowel dysfunction: systematic review and meta-analysis of randomized controlled trials. *Pain Med.* 9(6), 634-659 (2008).

•• The use of peripheral opioid antagonists in the the treatment of constipation caused by opioid use.

50 Meissner W, Leyendecker P, Mueller-Lissner S *et al.* A randomised controlled trial with prolonged-release oral oxycodone and naloxone to prevent and reverse opioid-induced constipation. *Eur. J. Pain* 13(1), 56-64 (2009).

51 Vondrackova D, Leyendecker P, Meissner W *et al.* Analgesic efficacy and safety of oxycodone in combination with naloxone as prolonged release tablets in patients with moderate to severe chronic pain. *J. Pain* 9(12), 1144-1154 (2008).

52 Kucukemre F, Kunt N, Kaygusuz K *et al.* Remifentanil compared with morphine for postoperative patient-controlled analgesia after major abdominal surgery: a randomized controlled trial. *Eur. J. Anaesthesiol.* 22(5), 378-385 (2005).

53 Baltali S, Turkoz A, Bozdogan N *et al.* The efficacy of intravenous patient-controlled remifentanil versus morphine anesthesia after coronary artery surgery. *J. Cardiothorac. Vasc. Anesth.* 23(2), 170-174 (2008).

54 Blair JM, Dobson GT, Hill DA, McCracken GR, Fee JP. Patient controlled analgesia for labour: a comparison of remifentanil with pethidine. *Anaesthesia* 60(1), 22-27 (2005).

55 Volmanen P, Sarvela J, Akural EI *et al.* Intravenous remifentanil vs. epidural levobupivacaine with fentanyl for pain relief in early labour: a randomised, controlled, double-blinded study. *Acta Anaesthesiol. Scand.* 52(2), 249-255 (2008).

56 Dunn MJ, Mitchell R, Souza CD, Drummond G. Evaluation of propofol and remifentanil for intravenous sedation for reducing shoulder dislocations in the emergency department. *Emerg. Med. J.* 23(1), 57-58 (2006).

57 Phillips WJ, Halpin J, Jones J, McKenzie K. Remifentanil for procedural sedation in the emergency department. *Ann. Emerg. Med.* 53(1), 163 (2009).

58 Blancas Gomez-Casero R, Martin Delgado C, Nevado Losada E *et al.* Sedoanalgesia with remifentanil in definitive pacemaker implant. *Med. Intensiva* 30(8), 370-373 (2006).

59 Bombardier C, Laine L, Reicin A *et al.* Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. VIGOR Study Group. *N. Engl. J. Med.* 343(21), 1520-1528 (2000).

60 Silverstein FE, Faich G, Goldstein JL *et al.* Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: a randomized controlled trial: celecoxib long-term arthritis safety study. *JAMA* 284(10), 1247-1255 (2000).

61 Bresalier RS, Sandler RS, Quan H *et al.* Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. *N. Engl. J. Med.* 352(11), 1092-1102 (2005).

62 FitzGerald GA. Cardiovascular pharmacology of nonselective nonsteroidal anti-inflammatory drugs and coxibs: clinical considerations. *Am. J. Cardiol.* 89(6A), 26D-32D (2002).

63 McGettigan P, Henry D. Cardiovascular risk and inhibition of cyclooxygenase: a systematic review of the observational studies of selective and nonselective inhibitors of cyclooxygenase 2. *JAMA* 296(13), 1633-1644 (2006).

64 Graham DJ, Campen D, Hui R *et al*. Risk of acute myocardial infarction and sudden cardiac death in patients treated with cyclo-oxygenase 2 selective and non-selective non-steroidal anti-inflammatory drugs: nested case-control study. *Lancet* 365(9458), 475-481 (2005).

65 Hippisley-Cox J, Coupland C. Risk of myocardial infarction in patients taking cyclo-oxygenase-2 inhibitors or conventional non-steroidal anti-inflammatory drugs: population based nested case-control analysis. *BMJ* 330(7504), 1366 (2005).

66 Hudson M, Richard H, Pilote L. Differences in outcomes of patients with congestive heart failure prescribed celecoxib, rofecoxib, or non-steroidal anti-inflammatory drugs: population based study. *BMJ* 330(7504), 1370 (2005).

67 Moore RA, Derry S, McQuay HJ. Cyclo-oxygenase-2 selective inhibitors and nonsteroidal anti-inflammatory drugs: balancing gastrointestinal and cardiovascular risk. *BMC Musculoskelet. Disord.* 8, 73 (2007).

•• Careful systematic review/meta-analysis on the contentious issue of cardiovascular risk of non-steroidal anti-inflammatory drugss.

68 Ott E, Nussmeier NA, Duke PC *et al*. Efficacy and safety of the cyclooxygenase 2 inhibitors parecoxib and valdecoxib in patients undergoing coronary artery bypass surgery. *J. Thorac. Cardiovasc. Surg.* 125(6), 1481-1492 (2003).

69 Nussmeier NA, Whelton AA, Brown MT *et al*. Complications of the COX-2 inhibitors parecoxib and valdecoxib after cardiac surgery. *N. Engl. J. Med.* 352(11), 1081-1091 (2005).

70 Schug SA, Joshi GP, Camu F, Pan S, Cheung R. Cardiovascular safety of the cyclooxygenase-2 selective inhibitors parecoxib and valdecoxib in the postoperative setting: an analysis of integrated data. *Anesth. Analg.* 108(1), 299-307 (2009).

• Confirmation of the cardiovascular safety of short-term use of coxibs in the perioperative setting.

71 Gan TJ, Joshi GP, Zhao SZ *et al*. Presurgical intravenous parecoxib sodium and follow-up oral valdecoxib for pain management after laparoscopic cholecystectomy surgery reduces opioid requirements and opioid-related adverse effects. *Acta Anaesthesiol. Scand.* 48(9), 1194-1207 (2004).

72 Hegi TR, Bombeli T, Seifert B *et al*. Effect of rofecoxib on platelet aggregation and blood loss in gynaecological and breast surgery compared with diclofenac. *Br. J. Anaesth.* 92(4), 523-531 (2004).

73 Marret E, Kurdi O, Zufferey P, Bonnet F. Effects of nonsteroidal antiinflammatory drugs on patient-controlled analgesia morphine side effects: meta-analysis of randomized controlled trials. *Anesthesiology* 102(6), 1249-1260 (2005).

•• Excellent meta-analysis confirming the role of NSAIDs as a relevant component of multimodal analgesia.

74 Gajraj NM. COX-2 inhibitors celecoxib and parecoxib: valuable options for postoperative pain management. *Curr. Top. Med. Chem.* 7(3), 235-249 (2007).

75 DeMaria AN, Weir MR. Coxibs - beyond the GI tract: renal and cardiovascular issues. *J. Pain Symptom Manage.* 25(2 Suppl.), S41-S49 (2003).

76 Sowers JR, White WB, Pitt B *et al.* The effects of cyclooxygenase-2 inhibitors and nonsteroidal anti-inflammatory therapy on 24-hour blood pressure in patients with hypertension, osteoarthritis, and Type 2 diabetes mellitus. *Arch. Intern. Med.* 165(2), 161-168 (2005).

77 Chang IJ, Harris RC. Are all COX-2 inhibitors created equal? *Hypertension* 45(2), 178-180 (2005).

78 Ziemer M, Wiesend CL, Vetter R *et al.* Cutaneous adverse reactions to valdecoxib distinct from Stevens-Johnson syndrome and toxic epidermal necrolysis. *Arch. Dermatol.* 143(6), 711-716 (2007).

79 Murat I, Baujard C, Foussat C *et al.* Tolerance and analgesic efficacy of a new i.v. paracetamol solution in children after inguinal hernia repair. *Paediatr. Anaesth.* 15(8), 663-670 (2005).

80 Moller PL, Juhl GI, Payen-Champenois C, Skoglund LA. Intravenous acetaminophen (paracetamol): comparable analgesic efficacy, but better local safety than its prodrug, propacetamol, for postoperative pain after third molar surgery. *Anesth. Analg.* 101(1), 90-96 (2005).

81 Gorocs TS, Lambert M, Rinne T, Krekler M, Modell S. Efficacy and tolerability of ready-to-use intravenous paracetamol solution as monotherapy or as an adjunct analgesic therapy for postoperative pain in patients undergoing elective ambulatory surgery: open, prospective study. *Int. J. Clin. Pract.* 63(1), 112-120 (2009).

82 Sinatra RS, Jahr JS, Reynolds LW *et al.* Efficacy and safety of single and repeated administration of 1 gram intravenous acetaminophen injection (paracetamol) for pain management after major orthopedic surgery. *Anesthesiology* 102(4), 822-831 (2005).

83 Toms L, McQuay HJ, Derry S, Moore RA. Single dose oral paracetamol (acetaminophen) for postoperative pain in adults. *Cochrane Database Syst. Rev.* 4, CD004602 (2008).

84 McNicol E, Strassels SA, Goudas L, Lau J, Carr DB. NSAIDS or paracetamol, alone or combined with opioids, for cancer pain. *Cochrane Database Syst. Rev.* 1, CD005180 (2005).

85 Hyllested M, Jones S, Pedersen JL, Kehlet H. Comparative effect of paracetamol, NSAIDs or their combination in postoperative pain management: a qualitative review. *Br. J. Anaesth.* 88(2), 199-214 (2002).

86 Remy C, Marret E, Bonnet F. Effects of acetaminophen on morphine side-effects and consumption after major surgery: meta-analysis of randomized controlled trials. *Br. J. Anaesth.* 94(4), 505-513 (2005).

87 Aronoff DM, Oates JA, Boutaud O. New insights into the mechanism of action of acetaminophen: its clinical pharmacologic characteristics reflect its inhibition of the two prostaglandin H2 synthases. *Clin. Pharmacol. Ther.* 79(1), 9-19 (2006).

88 Chandrasekharan NV, Dai H, Roos KL *et al.* COX-3, a cyclooxygenase-1 variant inhibited by acetaminophen and other analgesic/antipyretic drugs: cloning, structure, and expression. *Proc. Natl Acad. Sci. USA* 99(21), 13926-13931 (2002).

89 Kis B, Snipes JA, Busija DW. Acetaminophen and the cyclooxygenase-3 puzzle: sorting out facts, fictions, and uncertainties. *J. Pharmacol. Exp. Ther.* 315(1), 1-7 (2005).

90 Hogestatt ED, Jonsson BA, Ermund A *et al.* Conversion of acetaminophen to the bioactive *N* -acylphenolamine AM404 via fatty acid amide hydrolase-dependent arachidonic acid conjugation in the

nervous system. *J. Biol. Chem.* 280(36), 31405-31412 (2005).

91 Ottani A, Leone S, Sandrini M, Ferrari A, Bertolini A. The analgesic activity of paracetamol is prevented by the blockade of cannabinoid CB1 receptors. *Eur. J. Pharmacol.* 531(1-3), 280-281 (2006).

92 Pickering G, Esteve V, Loriot MA, Eschalier A, Dubray C. Acetaminophen reinforces descending inhibitory pain pathways. *Clin. Pharmacol. Ther.* 84(1), 47-51 (2008).

93 Pickering G, Loriot MA, Libert F *et al.* Analgesic effect of acetaminophen in humans: first evidence of a central serotonergic mechanism. *Clin. Pharmacol. Ther.* 79(4), 371-378 (2006).

• Interesting study reporting that 5-HT3 antagonist anti-emetics block the analgesic effect of paracetamol, thereby suggesting a serotonergic mechanism of action of paracetamol.

94 Visser E, Schug SA. The role of ketamine in pain management. *Biomed Pharmacother.* 60(7), 341-348 (2006).

• Review of the current literature on the increasing use of low-dose ketamine to manage acute and chronic pain.

95 Webster LR, Walker MJ. Safety and efficacy of prolonged outpatient ketamine infusions for neuropathic pain. *Am. J. Ther.* 13(4), 300-305 (2006).

96 Chung WJ, Pharo GH. Successful use of ketamine infusion in the treatment of intractable cancer pain in an outpatient. *J. Pain Symptom Manage.* 33(1), 2-5 (2007).

97 Bell R, Eccleston C, Kalso E. Ketamine as an adjuvant to opioids for cancer pain. *Cochrane Database Syst. Rev.* 1, CD003351 (2003).

98 Elia N, Tramer MR. Ketamine and postoperative pain - a quantitative systematic review of randomised trials. *Pain* 113(1-2), 61-70 (2005).

99 Bell RF, Dahl JB, Moore RA, Kalso E. Perioperative ketamine for acute postoperative pain. *Cochrane Database Syst. Rev.* 1, CD004603 (2006).

100 Subramaniam K, Subramaniam B, Steinbrook RA. Ketamine as adjuvant analgesic to opioids: a quantitative and qualitative systematic review. *Anesth. Analg.* 99(2), 482-495 (2004).

101 Migita RT, Klein EJ, Garrison MM. Sedation and analgesia for pediatric fracture reduction in the emergency department: a systematic review. *Arch. Pediatr. Adolesc. Med.* 160(1), 46-51 (2006).

102 Weinbroum AA. A single small dose of postoperative ketamine provides rapid and sustained improvement in morphine analgesia in the presence of morphine-resistant pain. *Anesth. Analg.* 96(3), 789-795 (2003).

103 Joly V, Richebe P, Guignard B *et al.* Remifentanil-induced postoperative hyperalgesia and its prevention with small-dose ketamine. *Anesthesiology* 103(1), 147-155 (2005).

104 Boezaart AP. Perineural infusion of local anesthetics. *Anesthesiology* 104(4), 872-880 (2006).

105 Cheng GS, Choy LP, Ilfeld BM. Regional anesthesia at home. *Curr. Opin. Anaesthesiol.* 21(4), 488-493 (2008).

106 Capdevila X, Ponrouch M, Choquet O. Continuous peripheral nerve blocks in clinical practice. *Curr.*

Opin. Anaesthesiol. 21(5), 619-623 (2008).

107 Davies PS, Galer BS. Review of lidocaine patch 5% studies in the treatment of postherpetic neuralgia. *Drugs* 64(9), 937-947 (2004).

108 Herrmann DN, Barbano RL, Hart-Gouleau S, Pennella-Vaughan J, Dworkin RH. An open-label study of the lidocaine patch 5% in painful idiopathic sensory polyneuropathy. *Pain Med.* 6(5), 379-384 (2005).

109 Baron R, Mayoral V, Leijon G *et al.* Efficacy and safety of 5% lidocaine (lignocaine) medicated plaster in comparison with pregabalin in patients with postherpetic neuralgia and diabetic polyneuropathy: interim analysis from an open-label, two-stage adaptive, randomized, controlled trial. *Clin. Drug Invest.* 29(4), 231-241 (2009).

•• Complex but excellent clinical trial in neuropathic pain; useful to clinical practice as it compares with active compounds and assesses the effects of combinations in patients failing monotherapy.

110 Finnerup NB, Otto M, McQuay HJ, Jensen TS, Sindrup SH. Algorithm for neuropathic pain treatment: an evidence based proposal. *Pain* 118(3), 289-305 (2005).

111 Dworkin RH, O'Connor AB, Backonja M *et al.* Pharmacologic management of neuropathic pain: evidence-based recommendations. *Pain* 132(3), 237-251 (2007).

•• The definitive current paper on evidence-based management of neuropathic pain.

112 Galer BS, Gammaitoni AR, Oleka N, Jensen MP, Argoff CE. Use of the lidocaine patch 5% in reducing intensity of various pain qualities reported by patients with low-back pain. *Curr. Med. Res. Opin.* 20(Suppl 2), S5-S12 (2004).

113 Gammaitoni AR, Galer BS, Onawola R, Jensen MP, Argoff CE. Lidocaine patch 5% and its positive impact on pain qualities in osteoarthritis: results of a pilot 2-week, open-label study using the neuropathic pain scale. *Curr. Med. Res. Opin.* 20(Suppl. 2), S13-S19 (2004).

114 Saber AA, Elgamal MH, Rao AJ, Itawi EA, Martinez RL. Early experience with lidocaine patch for postoperative pain control after laparoscopic ventral hernia repair. *Int. J. Surg.* 7(1), 36-38 (2008).

115 Ng HP, Nordstrom U, Axelsson K *et al.* Efficacy of intra-articular bupivacaine, ropivacaine, or a combination of ropivacaine, morphine, and ketorolac on postoperative pain relief after ambulatory arthroscopic knee surgery: a randomized double-blind study. *Reg. Anesth. Pain Med.* 31(1), 26-33 (2006).

116 Axelsson K, Gupta A, Johanzon E *et al.* Intraarticular administration of ketorolac, morphine, and ropivacaine combined with intraarticular patient-controlled regional analgesia for pain relief after shoulder surgery: a randomized, double-blind study. *Anesth. Analg.* 106(1), 328-333, table of contents (2008).

117 Harvey GP, Chelly JE, AlSamsam T, Coupe K. Patient-controlled ropivacaine analgesia after arthroscopic subacromial decompression. *Arthroscopy* 20(5), 451-455 (2004).

118 Parvataneni HK, Shah VP, Howard H *et al.* Controlling pain after total hip and knee arthroplasty using a multimodal protocol with local periarticular injections: a prospective randomized study. *J. Arthroplasty* 22(6 Suppl. 2), 33-38 (2007).

119 Forastiere E, Sofra M, Giannarelli D, Fabrizi L, Simone G. Effectiveness of continuous wound infusion of 0.5% ropivacaine by On-Q pain relief system for postoperative pain management after open nephrectomy. *Br. J. Anaesth.* 101(6), 841-847 (2008).

120 Saarto T, Wiffen PJ. Antidepressants for neuropathic pain. *Cochrane Database Syst. Rev.* 4, CD005454 (2007).

121 Dick IE, Brochu RM, Purohit Y *et al.* Sodium channel blockade may contribute to the analgesic efficacy of antidepressants. *J. Pain* 8(4), 315-324 (2007).

122 Verdu B, Decosterd I, Buclin T, Stiefel F, Berney A. Antidepressants for the treatment of chronic pain. *Drugs* 68(18), 2611-2632 (2008).

123 Sultan A, Gaskell H, Derry S, Moore RA. Duloxetine for painful diabetic neuropathy and fibromyalgia pain: systematic review of randomised trials. *BMC Neurol.* 8, 29 (2008).

124 Mease PJ, Clauw DJ, Gendreau RM *et al.* The efficacy and safety of milnacipran for treatment of fibromyalgia: a randomized, double-blind, placebo-controlled trial. *J. Rheumatol.* 36(2), 398-409 (2008).

125 Clauw DJ, Mease P, Palmer RH, Gendreau RM, Wang Y. Milnacipran for the treatment of fibromyalgia in adults: a 15-week, multicenter, randomized, double-blind, placebo-controlled, multiple-dose clinical trial. *Clin. Ther.* 30(11), 1988-2004 (2008).

126 Attal N, Cruccu G, Haanpaa M *et al.* EFNS guidelines on pharmacological treatment of neuropathic pain. *Eur. J. Neurol.* 13(11), 1153-1169 (2006).

127 Wiffen PJ, McQuay HJ, Edwards JE, Moore RA. Gabapentin for acute and chronic pain. *Cochrane Database Syst. Rev.* 3, CD005452 (2005).

128 Guay DR. Pregabalin in neuropathic pain: a more "pharmaceutically elegant" gabapentin? *Am. J. Geriatr. Pharmacother.* 3(4), 274-287 (2005).

129 Hendrich J, Van Minh AT, Heblich F *et al.* Pharmacological disruption of calcium channel trafficking by the a2d ligand gabapentin. *Proc. Natl Acad. Sci. USA* 105(9), 3628-3633 (2008).

130 Lyseng-Williamson KA, Siddiqui MA. Pregabalin: a review of its use in fibromyalgia. *Drugs* 68(15), 2205-2223 (2008).

131 Hayashida K, Parker R, Eisenach JC. Oral gabapentin activates spinal cholinergic circuits to reduce hypersensitivity after peripheral nerve injury and interacts synergistically with oral donepezil. *Anesthesiology* 106(6), 1213-1219 (2007).

132 Ho KY, Gan TJ, Habib AS. Gabapentin and postoperative pain - a systematic review of randomized controlled trials. *Pain* 126(1-3), 91-101 (2006).

133 Tiippana EM, Hamunen K, Kontinen VK, Kalso E. Do surgical patients benefit from perioperative gabapentin/pregabalin? A systematic review of efficacy and safety. *Anesth. Analg.* 104(6), 1545-1556 (2007).

• Identifies the role of gabapentinoids as a component of multimodal postoperative pain management.

134 Wiffen PJ, Rees J. Lamotrigine for acute and chronic pain. *Cochrane Database Syst. Rev.* 2, CD006044 (2007).

135 Azad SC, Rammes G. Cannabinoids in anaesthesia and pain therapy. *Curr. Opin. Anaesthesiol.* 18(4), 424-427 (2005).

136 Wissel J, Haydn T, Muller J *et al.* Low dose treatment with the synthetic cannabinoid Nabilone

significantly reduces spasticity-related pain: a double-blind placebo-controlled cross-over trial. *J. Neurol.* 253(10), 1337-1341 (2006).

137 Pinsger M, Schimetta W, Volc D *et al.* Benefits of an add-on treatment with the synthetic cannabinomimetic nabilone on patients with chronic pain - a randomized controlled trial. *Wien Klin Wochenschr.* 118(11-12), 327-335 (2006).

138 Skrabek RQ, Galimova L, Ethans K, Perry D. Nabilone for the treatment of pain in fibromyalgia. *J. Pain* 9(2), 164-173 (2008).

139 Frank B, Serpell MG, Hughes J, Matthews JN, Kapur D. Comparison of analgesic effects and patient tolerability of nabilone and dihydrocodeine for chronic neuropathic pain: randomised, crossover, double blind study. *BMJ* 336(7637), 199-201 (2008).

140 Barnes MP. Sativex: clinical efficacy and tolerability in the treatment of symptoms of multiple sclerosis and neuropathic pain. *Expert Opin. Pharmacother.* 7(5), 607-615 (2006).

141 Lin TF, Yeh YC, Lin FS *et al.* Effect of combining dexmedetomidine and morphine for intravenous patient-controlled analgesia. *Br. J. Anaesth.* 102(1), 117-122 (2009).

142 Unlugenc H, Gunduz M, Guler T, Yagmur O, Isik G. The effect of pre-anaesthetic administration of intravenous dexmedetomidine on postoperative pain in patients receiving patient-controlled morphine. *Eur. J. Anaesthesiol.* 22(5), 386-391 (2005).

143 Esmaoglu A, Mizrak A, Akin A, Turk Y, Boyaci A. Addition of dexmedetomidine to lidocaine for intravenous regional anaesthesia. *Eur. J. Anaesthesiol.* 22(6), 447-451 (2005).

144 Al-Metwalli RR, Mowafi HA, Ismail SA *et al.* Effect of intra-articular dexmedetomidine on postoperative analgesia after arthroscopic knee surgery. *Br. J. Anaesth.* 101(3), 395-399 (2008).

145 Dray A. Neuropathic pain: emerging treatments. *Br. J. Anaesth.* 101(1), 48-58 (2008).

146 Gilron I, Coderre TJ. Emerging drugs in neuropathic pain. *Expert Opin. Emerg. Drugs* 12(1), 113-126 (2007).

147 Broad LM, Mogg AJ, Beattie RE *et al.* TRP channels as emerging targets for pain therapeutics. *Expert Opin. Ther. Targets* 13(1), 69-81 (2009).

148 Backonja M, Wallace MS, Blonsky ER *et al.* NGX-4010, a high-concentration capsaicin patch, for the treatment of postherpetic neuralgia: a randomised, double-blind study. *Lancet Neurol.* 7(12), 1106-1112 (2008).

149 Aasvang EK, Hansen JB, Malmstrom J *et al.* The effect of wound instillation of a novel purified capsaicin formulation on postherniotomy pain: a double-blind, randomized, placebo-controlled study. *Anesth. Analg.* 107(1), 282-291 (2008).

150 Gunthorpe MJ, Chizh BA. Clinical development of TRPV1 antagonists: targeting a pivotal point in the pain pathway. *Drug Discov. Today* 14(1-2), 56-67 (2009).

151 Amir R, Argoff CE, Bennett GJ *et al.* The role of sodium channels in chronic inflammatory and neuropathic pain. *J. Pain* 75(Suppl. 3), S1-S29 (2006).

152 Silos-Santiago I. The role of tetrodotoxin-resistant sodium channels in pain states: are they the next target

for analgesic drugs? *Curr. Opin. Investig. Drugs* 9(1), 83-89 (2008).

153 Wermeling DP. Ziconotide, an intrathecally administered N-type calcium channel antagonist for the treatment of chronic pain. *Pharmacotherapy* 25(8), 1084-1094 (2005).

154 McGivern JG. Targeting N-type and T-type calcium channels for the treatment of pain. *Drug Discov. Today* 11(5-6), 245-253 (2006).

155 Bleakman D, Alt A, Nisenbaum ES. Glutamate receptors and pain. *Semin. Cell Dev. Biol.* 17(5), 592-604 (2006).

156 Guindon J, Hohmann AG. Cannabinoid CB2 receptors: a therapeutic target for the treatment of inflammatory and neuropathic pain. *Br. J. Pharmacol.* 153(2), 319-334 (2008).

157 Di Marzo V. Targeting the endocannabinoid system: to enhance or reduce? *Nat. Rev.* 7(5), 438-455 (2008).

158 Scholz J, Woolf CJ. The neuropathic pain triad: neurons, immune cells and glia. *Nat. Neurosci.* 10(11), 1361-1368 (2007).

•• Excellent and very current review on the pathogenesis of neuropathic pain.

159 Milligan ED, Watkins LR. Pathological and protective roles of glia in chronic pain. *Nat. Rev. Neurosci.* 10(1), 23-36 (2009).

160 Watson JJ, Allen SJ, Dawbarn D. Targeting nerve growth factor in pain: what is the therapeutic potential? *BioDrugs* 22(6), 349-359 (2008).

161 Merighi A, Salio C, Ghirri A *et al.* BDNF as a pain modulator. *Prog. Neurobiol.* 85(3), 297-317 (2008).

Websites

201 European Medicines Agency press office. www.emea.europa.eu/humandocs/PDFs/EPAR/ionsys/61385208en.pdf

202 Department of Health and Aging therapeutic goods administration. www.tga.gov.au/alerts/prexige.htm

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