

# Recent advances in the pharmacological management of acute and chronic pain

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**Abstract:** This review focuses on newer medications for the treatment of pain as well as on new guidelines and indications for the use of established medications. With regard to classical analgesics, the use of non-opioids and opioids is reviewed. Here are relevant new data on the use of the old substance acetaminophen as well as on non-selective non-steroidal anti-inflammatory drugs (NSAIDs) and the newer COX-2 selective agents, which continue to be misunderstood. Amongst the opioids the new compound tapentadol with a new mechanism of action is presented as well as a number of new opioid preparations aiming to increase speed of onset of effect and to reduce abuse and diversion. Many medications, which were not originally developed to treat pain, are now used as components of multimodal analgesia or in specific indications. Here are of relevance anticonvulsants such as pregabalin and gabapentin, which were initially used for neuropathic pain, but are now used successfully in a wide range of indications from postoperative pain to fibromyalgia. The reason for this increased range of indications is the realization of the relevance of central sensitization processes for all pain states. Similarly, the use of antidepressants and the old dissociative anesthetic ketamine is increasing for the same reasons. Calcitonin has also found some new indications in difficult to treat pain conditions, while the discussion on the role of cannabinoids in pain management continues, partially driven by political issues. For localized neuropathic pain, there is increasing interest in topical preparations such as lidocaine and capsaicin patches, in particular in view of their minimal systemic adverse effects. Overall, recent advances in the pharmacological management of pain are not so much the result of new ‘miracle’ drugs, but new preparations and new ways to use old drugs in a variety of settings, often as components of a multimodal approach to pain relief.

**Keywords:** Pain management; analgesics; central nervous system sensitization; tapentadol

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## Introduction

Recognition and management of pain continues to be one of the most commonly encountered clinical situations for practitioners. Pain has a considerable impact on the biological, psychological, sociological and economical welfare of the patient that cannot be underestimated. On a global scale the impact of pain has far reaching effects upon the social structure, function and economic welfare of society as a whole (1).

Pain medicine has evolved over recent years into a large specialty area, being recognized as its own discipline within Australia in 2005. The management of pain remains of great relevance across a wide spectra of medical fields and requires a multidisciplinary approach to recognition, diagnosis, treatment and education. A thorough and holistic approach is encouraged in order to explore the multiple factors affecting patients experiencing pain, whether this be acute, chronic, or in many situations, both.

Multiple options are available for the clinical management of pain, most of which are usually centered on pharmacological therapy. Use of these medications and the literature surrounding them can often be conflicting, confusing and poorly understood. As an area of medicine there are continuous attempts to develop more effective analgesics that are easy to administer, safe and economically viable. As we continue to deepen our understanding of the physiology of pain it can be hoped that this will allow for further research and development into treatments that can improve quality of life for both the individual and society as a whole.

The aim of this review article is to highlight recent advances within the field of pharmacological pain therapy. We will focus as well on newer drugs and newer modes of administration as on recent guidelines and new indications for the use of familiar analgesic agents.

## Non-opioid analgesics

### *Acetaminophen (paracetamol)*

While acetaminophen is one of the oldest and most used analgesics, the debate on its mechanism of action continues. Contrary to previous assumptions, the analgesia is most likely mediated centrally and may involve direct and indirect inhibition of central cyclo-oxygenases, but also the activation of the endocannabinoid system and spinal serotonergic pathways (2).

The more recent availability of an acetaminophen preparation for IV infusion has increased its usefulness, in particular in the perioperative setting (3). Perioperative administration reduces postoperative nausea and vomiting (PONV), in particular if given prophylactically at induction of anesthesia (4).

With regard to adverse effects, concerns about hepatotoxicity with overdose, which is in 50% of cases unintentional, continue (5) and has led the FDA to enforce a reduced dose per tablet. However, in therapeutic doses below 4 g/day, hepatotoxicity is very unlikely to occur (6); surprisingly, even excessive alcohol consumption seems to be no risk factor for acetaminophen-induced hepatotoxicity (2). From a practical point of view, acetaminophen intake has been linked to increase INR with warfarin treatment (7).

Epidemiological studies published in recent years have suggested an association between acetaminophen use and a number of conditions; however, these are retrospective studies and confounding factors may influence these results.

Such associations have been found for renal cancer (8), asthma in childhood (9) and asthma in children after use in pregnancy (10). The effects of acetaminophen on blood pressure remain unclear with a variable association to reduced, unchanged or slightly increased values (11).

### *Non-steroidal anti-inflammatory drugs (NSAIDs)*

The efficacy of all NSAIDs in acute and chronic pain is undisputed with numbers needed-to-treat (NNT) in the range of 1.5 to 2.5 (12). It was recently again confirmed, that fast-acting preparations provide better analgesia than slow-acting ones (13). While there is no difference in analgesic efficacy between non-selective NSAIDs (nsNSAIDs) and COX-2 selective NSAIDs (Coxibs), there remains confusion over their safety despite excellent data available now.

With regard to gastrointestinal complications, in particular bleeds, coxibs carry a lower risk than nsNSAIDs (14); this is even true, when nsNSAIDs are combined with a proton pump inhibitor (PPI) for protection (15). Furthermore, PPIs carry their own risk and may aggravate lower GI tract complications (16). Further advantages of coxibs are their safety in patients with aspirin-sensitive asthma (17). In the perioperative setting, coxibs, which do not impair platelet function (18), do not increase blood loss even after high-risk surgery such as total knee joint replacement (19); this is in contrast to increased risk of bleeding with nNSAIDs (20). With regard to cardiovascular risk, the situation remains confusing, although with short-term use in the acute setting parecoxib/valdecoxib is safe (21). In the chronic setting, celecoxib might be comparable to naproxen with regard to cardiovascular safety (22,23).

There are no recent new substances in this class of analgesics; however, new preparations of older compounds are in development. These include ketorolac as nasal spray, which was recently approved by the FDA (24). Other developments are preparations, which permit use of lower doses of NSAIDs in an attempt to reduce adverse effects. One development here is submicron particle NSAIDs (so called nano formulations); diclofenac (25) as well as indomethacin (26) have been tested in such formulations. A new formulation of injectable diclofenac sodium solubilized with hydroxypropyl-beta-cyclodextrin similarly showed efficacy at much reduced doses (27).

## Opioid analgesics

Opioid use worldwide is increasing; however, this is only

true for a limited number of industrialized countries, while in many countries (around 150) opioid availability is limited by legislation or circumstances (28). While the use to treat acute and cancer pain is well established, the increasing use of opioids in chronic pain of non-malignant origin is more problematic. Here, data on long-term benefits are limited except for highly selected patients, while risks of abuse, diversion and even mortality are high (29). There is only one new molecule, tapentadol, in this group, although multiple new formulations, aimed at increased speed of onset or reduced risk of abuse and diversion, are or have been recently developed.

### *Tapentadol*

Tapentadol is a new centrally acting analgesic that relies on a dual mechanism of action. These are mu opioid receptor agonism and norepinephrine (noradrenaline) reuptake inhibition (30). It is therefore not a classical opioid, but represents a unique class of analgesic drug (MOR-NRI). It is now registered for use in the treatment of moderate to severe chronic pain that proves unresponsive to conventional non-narcotic medications in many countries.

Tapentadol has a much lower affinity (20 times less) to the mu receptor than morphine, but its analgesic effect is only around three times less than morphine. This discrepancy is explained by its inhibitory effect on norepinephrine reuptake, strengthening descending inhibitory pathways of pain control (30). These theoretical considerations have been recently confirmed in patients with neuropathic pain treated with tapentadol, who showed enhanced descending pain inhibition (31). The two mechanisms of action have shown synergy in an animal model (32).

A systematic review of 42 clinical trials compared tapentadol directly with oxycodone and indirectly with other strong opioids; the findings show comparable efficacy in moderate to severe pain and reduced gastrointestinal adverse events compared with fentanyl, hydromorphone, morphine, oxycodone and oxycodone (33). This led to a significant reduction in the incidence of treatment discontinuation. Similarly, a meta-analysis of three randomized controlled trials assessing a composite measure for chronic pain that balances pain relief with tolerability showed significantly better outcomes for tapentadol compared with oxycodone (34).

Another interesting aspect in the current climate of concerns about abuse and diversion of opioids are the

limited data on the reduced abuse potential of tapentadol. A large survey of nearly 150,000 patients found significantly reduced doctor shopping (obtaining prescriptions from multiple prescribers) with tapentadol compared to oxycodone (35). Similarly, data on abuse and diversion are significantly lower than for oxycodone (36) and for other strong opioids and similar to data on tramadol (37). These encouraging results are confirmed in recent post marketing studies (38) and a very low rate of recreational use by college students (39). Last, not least, the risk of death from tapentadol seems to be lower than from conventional opioids, as there is only one reported death from overdose despite increasingly widespread use in USA, Europe and more recently Australia (40).

Tapentadol is seen by some as similar to tramadol, but differs in a number of important points; it is not a racemic mixture of two enantiomers with different pharmacological effects, has no active metabolites (which are relevant for tramadol's mu opioid receptor agonism) and has only minimal serotonin effects (41). This means that interactions with other serotonergic drugs (such as anti-depressants) are unlikely, reliance on metabolism by the cytochrome P450 system for increased efficacy is not required and retention of active metabolites causing potential adverse effects is not a concern.

### *Transmucosal immediate-release formulations of fentanyl (TIRF)*

Fentanyl is a commonly used synthetic phenylpiperidine derivative. It was initially developed for parenteral administration, with the oral route being of limited use due to high first pass metabolism (42). However, its highly lipophilicity and high potency lead to other routes of administration suitable for both acute and chronic pain management. While transdermal fentanyl formulations for the management of cancer and chronic pain have been marketed for a considerable time, a variety of immediate release formulations has become available recently (43).

Oral transmucosal fentanyl citrate (OTFC) was the first of such preparations (42). Since then a number of similar preparations have been developed with the goal of faster onset of effect, targeted to the rapid treatment of breakthrough pain in cancer patients (43). These are relying on a variety of pharmaceutical techniques to achieve these goals.

Oral disintegrating tablets (ODT) of fentanyl are a mixture of carrier particles coated with fentanyl, which

adhere to the oral mucosa through a mucoadhesive agent aiming for rapid absorption and resulted in good control of breakthrough pain (44).

Fentanyl buccal tablets (FBT) are an effervescent disintegrating tablet, which enhances early systemic uptake by changing the mucosal pH to increase unionized fentanyl concentration in the area of absorption (45).

Fentanyl buccal soluble films (FBSF) are small soluble membranes containing fentanyl and adhering to the mucosa enhanced by a mucoadhesive layer with isolating properties to prevent loss by swallowing (46).

Another route of administration for TIRFs is the nasal administration. Here as well plain preparations as a pectin containing formulation are available; the pectin results in formation of a gel increasing adherence of the nasal spray to the mucosa (47).

All these presentations are only indicated for the treatment of breakthrough pain in opioid-tolerant cancer pain patients (42,43). The development of so many different preparations for this limited indication is surprising and the high rate of off-label use in chronic and acute pain patients, even opioid-naïve ones, disconcerting. A large number of deaths have been reported with these preparations if used inappropriately (43). In view of the high risk of abuse and mortality, in 2012 the FDA has initiated a class risk evaluation and mitigation strategy (REMS) for transmucosal immediate-release fentanyl, which restricts prescribing and dispensing of these preparations (<http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM289730.pdf>).

### *Abuse-deterrent formulations of opioids*

The issues of abuse and diversion of opioids discussed previously have resulted in an increasing interest in the development of 'tamper-resistant' or 'abuse-deterrent' formulations. In response to these developments the FDA released in January 2013 a 'Guidance for Industry: Abuse-Deterrent Opioids—Evaluation and Labeling', which addresses this issue from a regulatory perspective (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM334743.pdf>). Such formulations rely on a number of technologies, which include physical or mechanical barriers, aversion or the addition of a noxious components and agonist/antagonist combinations (48).

A typical example is the new slow-release oxycodone formulation now registered in many countries; it relies

on combination of a mechanical (polymer coating makes crushing difficult) and a physical barrier effect (viscous gel reduces ability to draw up drug for injection) (48). The use of aversion by an addition of a noxious substance (niacin) has been attempted in another preparation of oxycodone, which was refused registration by the FDA. Combinations with antagonists such as naloxone (in buprenorphine or oxycodone preparations) and naltrexone (in a morphine preparation) are also available or have been investigated.

A recent review suggests that these preparations require further evaluation, but may well become the expected standard of care (49).

## **Co-analgesics**

### *Alpha-2-delta modulators (gabapentin and pregabalin)*

Gabapentin and pregabalin are anticonvulsant drugs that act by binding to the alpha-2-delta subunit of voltage gated calcium channels within the central nervous system (50). Thereby they are downregulating calcium ion influx into neurons, subsequently reducing the release of a variety of excitatory neurotransmitters (in particular the excitatory amino acid glutamate) (51).

The initial indication for both compounds was neuropathic pain of various origins; there is now overwhelming evidence that gabapentin and pregabalin are effective in the treatment of neuropathic pain from a variety of causes (52). There are good data on postherpetic neuralgia (53), diabetic polyneuropathy (54) and central neuropathic pain after spinal cord injury (55). These two compounds are now one of the first-line medications in all relevant guidelines on the treatment of neuropathic pain (56).

However, the use has widened from this initial indication to a number of other chronic and later acute pain conditions. Fibromyalgia is one of the chronic conditions, assumed to be caused by central sensitization, which has become even a registered indication in a number of countries (57).

However, even more interesting is the increasing use of gabapentin and pregabalin in a number of acute pain indications, either on the assumption that there is acute neuropathic pain (58) or to reduce central sensitization in the acute setting to improve analgesia and reduce opioid requirements. An acute neuropathic pain condition where pregabalin has been used successfully is burns pain (59). In the setting of acute postoperative pain, gabapentin is the only anticonvulsant for which an analgesic effect on its

own was identified (60); however this effect is not clinically relevant, but more of scientific interest, and should not suggest to use gabapentin as a postoperative analgesic on its own. However, a series of meta-analyses have consistently shown that perioperative use of gabapentin and pregabalin (either as a single premedication or as a short perioperative course) has significant benefits with regard to postoperative pain relief and opioid requirements. Gabapentin (61) and pregabalin (62) show consistently improved analgesia, an opioid-sparing effect and reduced incidence and/or severity of opioid-induced adverse effects, in particular on PONV. This latter effect may even be a specific effect of these compounds (63). There is currently some discussion on the appropriate indication, as possibly in minor surgery and operations, which have a low risk of association with neuropathic pain, the effect of these compounds is low (64). However, the beneficial effects have been shown by meta-analysis in certain specific operations such as hysterectomy (65) and laminectomy (66). There has also been a meta-analysis showing a preventive effect of gabapentin and pregabalin with regard to the reduction of chronic postsurgical pain (67); however, this has been criticized due to a risk of publication bias and contradicted by another meta-analysis (68). There is currently no agreement on the ideal doses and treatment duration for the indication of acute postoperative pain.

### *Serotonin-norepinephrine reuptake inhibitors (SNRIs)*

Antidepressants have long been used in the management of chronic pain, with tricyclic antidepressants (TCAs), in particular amitriptyline, commonly being utilized in the treatment of neuropathic pain (69). Their mechanism of analgesic action appears to be related to the inhibitory effects on norepinephrine and serotonin reuptake, thereby strengthening endogenous descending pathways of pain control. These are the inhibitory processes underlying diffuse noxious inhibitory control (DNIC), mediated through the subnucleus reticularis dorsalis (70), which have now been relabeled conditioned pain modulation (CPM) (71). The significant adverse event profile of TCAs (in particular in elderly patients, who are more likely to need them) (72) has resulted in interest in the use of other antidepressants in this indication.

While the group of selective serotonin reuptake inhibitors (SSRIs) has shown disappointing efficacy in the setting of chronic pain (73), the SNRIs have shown to be effective, suggesting that norepinephrine reuptake inhibition is

essential for the effect in this indication (74). In the setting of neuropathic pain, weak inhibitory control measured by CPM predicts increased treatment efficacy (75).

For SNRIs there are now sufficient data for their efficacy in neuropathic pain states, to make them first- or at least second-line treatment options in neuropathic pain guidelines (56). The data are in particular good for treatment of diabetic polyneuropathy, where both, duloxetine and venlafaxine, show better efficacy and a better benefit-risk balance than amitriptyline (76). Duloxetine and, to a lesser extent, milnacipran (77), are also effective in fibromyalgia (78).

Similarly to the data on pregabalin and gabapentin, there is now increasing evidence, that SNRIs might not only be useful in classical neuropathic pain states, but also in conditions, which are more typical of nociceptive pain, but possibly with a significant component of central sensitization (79). There are now meta-analyses showing a beneficial effect of duloxetine in the setting of chronic low back pain (80). Even more surprising, another meta-analysis showed a significant effect of duloxetine on the pain of osteoarthritis, at least non-inferior to commonly used other analgesics such as NSAIDs in this setting (81).

### *Ketamine*

Ketamine was originally introduced into clinical practice as a dissociative anaesthetic in 1963 and continues to play an important role here, in particular in the prehospital setting (82). However, over recent years there has been an increasing interest in its use in the setting of pain management, as well in acute as in chronic pain states (83). The mechanism of action of ketamine is primarily antagonism at the NMDA receptor, a calcium channel, for which glutamate is the natural ligand. This channel has also been linked to the phenomenon of central sensitization, a process associated with the development and maintenance of chronic pain (84). Ketamine appears to reduce the level of sensitisation by modulating the 'wind up' process. Ketamine also has a number of other sites of action including nicotinic, muscarinic, opioid, AMPA and Kainate receptors. It also inhibits serotonin and dopamine reuptake, and down regulates certain ion channels.

In the acute setting, ketamine has shown some efficacy in studies of lower quality (single-arm open-label) in the treatment of acute neuropathic pain, e.g., after spinal cord injury (85) or after major limb trauma (86). After burns injury, it reduces wind-up and secondary

hyperalgesia (87). However, it is also increasingly used as an adjunct to multimodal analgesia in the postoperative and posttraumatic setting. Here it shows benefits with regard to improved analgesia, reduced opioid consumption and less postoperative desaturation when added to opioids via PCA pumps, however not consistently (88). The results were in particular good after thoracotomy (89). Not surprisingly, ketamine is also very useful for the treatment of postoperative pain in opioid-tolerant patients (90). Last, not least, a recent meta-analysis showed a preventive effect of ketamine with regards to the development of chronic postsurgical pain (68), although these results were contradicted by a subsequent meta-analysis (91).

Ketamine is also increasingly used in chronic pain states (92). For example, ketamine has proven efficacy in phantom limb pain in RCTs (93). There is also efficacy in complex regional pain syndrome (CRPS), although further trials are needed, as recommendations on dose, timing and route of administration are lacking (94). Ketamine is also widely used in the cancer pain setting, in particular if pain is poorly responsive even to high opioid doses. While this approach is supported by a meta-analysis of smaller trials (95), a recent larger randomized controlled trial has shown no clinical benefit, when ketamine was added to other cancer pain management strategies (96). While the results of this trial and its inclusion criteria are widely debated, it has influenced prescribing practice in the palliative care setting significantly (97). There is also increasing interest in the topical or peripheral administration of ketamine, although the overall data on efficacy and dosing are still insufficient (98).

Overall, the current recommendation is, that ketamine should only be used to treat chronic neuropathic pain in patients with severe pain unresponsive to other treatments (99). Whenever using ketamine, it needs to be considered that ketamine is a drug with a risk of abuse and therefore scheduled in some countries (100). While death from abuse is rare, long-term abuse may cause toxicity to a number of organ systems.

### **Calcitonin**

Calcitonin is a polypeptide hormone produced naturally by the para-follicular cells of the thyroid gland (101). It was commonly used in osteoporosis and Paget's disease. While already older studies have suggested efficacy in some acute and chronic pain states, recent results have confirmed this role. These include a network meta-analysis supporting a

short-term course of calcitonin in later stages of CRPS (102). Another indication with limited evidence is acute, but not chronic, phantom limb pain after amputation (93,103). There is also good evidence to support the use of calcitonin in acute, but not chronic pain, caused by osteoporotic vertebral compression fractures (104).

### **Cannabinoids**

Cannabinoids comprise a large group of chemical compounds that act upon the cannabinoid receptor. These receptor proteins include the endocannabinoids such as anandamide (produced naturally in the body by humans and animal), the phytocannabinoids (found in cannabis and some other plants), and synthetic cannabinoids (manufactured chemically) (105). Derivatives of the cannabis plant have been used anecdotally to treat a variety of ailments such as anorexia, insomnia, pain and nausea for more than 5,000 years (106).

The primary active component is d-9-tetrahydrocannabinol (THC), which is responsible for many of the commonly known effects. However, there are at least another eighty-five different cannabinoids that exhibit a variety of effects; of particular relevance are cannabidiol (CBD) and cannabinol (CBN) (106). The first of the cannabinoid receptors was identified in 1990 (CB1) with the second being discovered in 1993 (CB2) (107). CB1 receptors are found mainly within the brain and are thought to be responsible for the analgesic, euphoric and anticonvulsive effects; they are however absent from the medulla oblongata, possibly explaining the lack of respiratory and cardiac depressive effects. CB2 receptors are found primarily within the immune system, modulate the cytokine system and are believed to have anti-inflammatory and immunosuppressive effects.

There is widespread interest in the use of cannabinoids for medical purposes (108). This has resulted in the development of a number of pharmaceutical preparations as well as the legalization of 'medical marijuana', for example in a number of states in the USA (>23 states in April 2014) (109,110). There is considerable debate on issues related to this legalization (111).

Pharmaceutical preparations include dronabinol (a synthetic THC), which is commonly used as an antiemetic and as an appetite stimulant in AIDS related weight loss, however with poor evidence for efficacy in the latter indication (112). Another preparation is nabilone, a synthetic THC analogue, which is again used for chemotherapy induced nausea and vomiting, but showed only minimal analgesic benefits in neuropathic

pain, being less effective and with more side effects than dihydrocodeine (113). A cannabinoid whole plant extract oral spray (Sativex<sup>®</sup>) containing THC and CBD in a ratio of 1:1 is registered for MS-related spasticity in 22 countries including England, Canada and Spain (114). It is of note, that there are also currently Phase III trials ongoing with CB2 receptor antagonists (115).

Despite the hype and widespread use of cannabinoids for the treatment of neuropathic pain, the overall data situation remains confusing, but suggests limited efficacy in some neurologic disorders, mainly related to spasticity (116) and some chronic neuropathic pain conditions, in particular those related to MS and AIDS (117,118).

## Topical treatments

### *Lidocaine plaster*

Lidocaine remains one of the most commonly used local anesthetic agents in anesthesia and pain management. It is an amide local anesthetic and its effects are mediated by sodium channel block suppressing the formation of action potentials (119). As peripheral mechanisms of neuropathic pain include ectopic discharges of damaged neurons, lidocaine has a potential to be a treatment for neuropathic pain. This has been shown for systemic use of lidocaine (120), but this approach carries the risk of systemic adverse effects (121) and the need for parenteral administration.

However, the development of a plaster for topical administration of lidocaine has resulted in a new first-line treatment of localized neuropathic pain with minimal systemic adverse effects (122). The preparation is a lidocaine plaster 5%, a 10 cm × 14 cm patch containing around 700 mg lidocaine (50 mg/g of patch). The patch is placed directly over the painful area (intact skin only) for a period of twelve hours followed by twelve hours patch-free time. Pharmacokinetic studies show that only around 3% of the lidocaine dose from the patch is absorbed (123). This explains the low rate of systemic adverse effects due to extremely low plasma concentrations; up to three patches can be used at one time if the painful area is larger.

Lidocaine plaster has been assessed in a number of randomized controlled trials with particular focus on diabetic neuropathy and post herpetic neuralgia (124) and has been shown to be effective in the treatment of neuropathic pain and accompanying allodynia with fewer adverse events than another first-line treatment, pregabalin (125). The efficacy

and lack of apparent systemic adverse effects have rendered the lidocaine medicated plaster the recommended first-line treatment in localized neuropathic pain in a number of guidelines (126). It has also been studied in a number of other neuropathic pain conditions including painful idiopathic sensory polyneuropathy, CRPS, carpal tunnel syndrome, postsurgical and posttraumatic pain (122). Due to the desirable low side effect profile, particularly with regards to systemic effects, lidocaine plasters are an attractive option to use in the elderly population and other high-risk groups. The most common adverse effects are skin irritation in the area of application. They can also be safely combined with systemic medications as part of a multimodal approach to pain management (127).

### *Topical capsaicin*

Capsaicin (8-methyl-N-vanillyl-6-nonenamide), the pungent ingredient of chilli peppers, binds to the transient receptor potential vanilloid 1 (TRPV1) subunits, which are located on peripheral nociceptors and also responsive to heat, acidity and endogenous metabolites of polyunsaturated fatty acids (128). While exposure to capsaicin results initially in a painful burning sensation due to substance P release, multiple administration of low concentration or single administration of high concentration capsaicin will finally lead to reduced sensitization or even complete desensitization.

Capsaicin in low concentrations (<1%) with repeat administration has been used for a long time in an attempt to treat neuropathic pain. However, the overall data on outcome are poor and a recent meta-analysis found that the effect is unlikely to be different from that in placebo creams (129). More recently, a high concentration (8%) capsaicin patch for single administration was commercially developed and is registered in a number of countries. This patch has shown efficacy over control treatment with 0.04% capsaicin (used to maintain blinding) in postherpetic neuralgia and HIV-related neuropathy with NNTs in the range of 7 to 11 with a low incidence of adverse effects (130). Attempts to identify therapeutically useful agonists and antagonists for the TRPV1 receptor continue (131).

## Discussion

The management of pain is of utmost importance. Acute pain after surgery and trauma remains one of the biggest concerns of hospital inpatients (132). Acute and chronic

pain states account for a large proportion of presentations to the family GP and the emergency department. Cancer pain is a major burden for patients and their loved ones and its management is now often more chronic pain management in view of the increasing life expectancy of cancer sufferers (133). Chronic pain has significant effects not only on the quality of life of patients and their families, but also far ranging implications with regard to costs of health care, but even more so societal costs due to absenteeism and early retirement (134). With these factors in mind, the past ten years have witnessed a far greater focus upon the management of acute, cancer and chronic pain; these efforts have culminated an international pain summit leading to the declaration of Montreal that access to pain management is a fundamental human right (135).

The here presented review illustrates that despite massive progress in the understanding of the physiology and pharmacology of pain there is only a limited number of new compounds, that have made it into clinical practice. In an ideal world the management of pain would be accomplished with one medication that produces little to no side effects, and is reliably treating multiple types of pain. With regards to pain management, this is a vastly unrealistic aim given the highly complex nature of pain physiology and the associated social, psychological and economical components.

Therefore pharmacological management of pain will continue to have to rely on a multimodal approach with old medications finding new uses and indications. Pain genetics and brain imaging are areas of growing interest, with the identification of certain pain genes and traits becoming the focus of research. Combined with the increasing understanding of pain perception, and an appreciation of the multifactorial nature of pain, this could lead to future personalization of analgesic therapy.

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