Pharmacogenetics of chronic pain management

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ABSTRACT

Objective: The experience of chronic pain is one of the commonest reasons individuals seek medical attention, making the management of chronic pain a major issue in clinical practice. Drug metabolism and responses are affected by many factors, with genetic variations offering only a partial explanation of an individual’s response. There is a paucity of evidence for the benefits of pharmacogenetic testing in the context of pain management.

Design and methods: We reviewed the literature between 2000 and 2013, and references cited therein, using various keywords related to pain management, pharmacology and pharmacogenetics.

Results: Opioids continue to be the mainstay of chronic pain management. Several non-opioid based therapies, such as treatment with cannabinoids, gene therapy and epigenetic-based approaches are now available for these patients. Adjuvant therapies with antidepressants, benzodiazepines or anticonvulsants can also be useful in managing pain. Currently, laboratory monitoring of pain management patients, if performed, is largely through urine drug measurements.

Conclusions: Drug half-life calculations can be used as functional markers of the cumulative effect of pharmacogenetics and drug–drug interactions. Assessment of half-life and therapeutic effects may be more useful than genetic testing in preventing adverse drug reactions to pain medications, while ensuring effective analgesia. Definitive, mass spectrometry-based methods, capable of measuring parent drug and metabolite levels, are the most useful assays for this purpose. Urine drug measurements do not necessarily correlate with serum drug concentrations or therapeutic effects. Therefore, they are limited in their use in monitoring efficacy and toxicity.

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Introduction

According to the International Association for the Study of Pain (IASP), pain is defined as an “unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage”. Several different subtypes of pain can be described, based on their neuropsychological basis and duration, including neuropathic, nociceptive, psychogenic, referred, phantom, acute and chronic [1]. Chronic pain is very common, with one in three Americans and one in five Canadians reported to suffer from this problem [2,3]. It is one of the most frequent reasons for individuals to seek medical care. If untreated, chronic pain can lead to physical and social dysfunction and diminished quality of life.

Successful pain management provides adequate analgesia without excessive adverse effects. Current pain management strategies largely employ the use of the World Health Organization (WHO) pain ladder, beginning with non-opioid medications, such as NSAIDs, progressing to weak opioids, and culminating with strong opioids, particularly in cancer pain [4]. The WHO also recommends adjuvant therapy with antidepressant medications to aid in reducing anxiety often associated with chronic pain [4].

Management of pain can be complicated by lack of adherence, the potential for abuse or dependence on the medications used and adverse drug side effects. Many factors can influence drug disposition, including genetic variation, which can further complicate management of these patients.

Genetic studies have identified several loci in which polymorphic changes can influence the pharmacodynamics and kinetics of analgesic drugs. Current patient monitoring in pain management (if performed at all) is largely based on urine drug measurements. However, therapeutic drug monitoring (TDM) via plasma drug levels and half-life may prove more useful in monitoring patients prescribed pain medications to ensure efficacy while minimizing adverse drug reactions. TDM can also be very useful for the identification of drug-related side effects and patient-reported lack of effect (e.g., tolerance).

Finally, non-opioid analgesics are often tried as options for management of pain, particularly in individuals where opioids are not a suitable choice. In addition, novel therapies, including targeting of epigenetic changes and gene therapy-based approaches are further broadening future options for the treatment of chronic pain.

Methods

We conducted an online systematic search for papers and related abstracts published between 2000 and 2013 using the National Library of Medicine database, PubMed. Using the following headings: “pain management medications”, “pain management drugs”, “chronic pain management”, “pharmacogenetics and pain management”, and “drug monitoring and pain management”, we identified 6670 papers. The abstracts of all papers were reviewed and those that appeared to be relevant to the subject were selected for further study. References cited therein, including original publications, were also selected for further review.

Pain

Pain is the most common presenting physical symptom in primary care, accounting for an enormous burden of patient suffering, quality of life, work and social disability, and health care and societal costs [5]. Pain is defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage [1]. However, the experience of pain is highly subjective and idiosyncratic, and individuals develop pain thresholds through experiences of injury or pathology in early life [1].

Neuropathic pain results from actual damage to nerve fibers themselves in the central or peripheral nervous system [6]. This damage can lead to nerve dysfunction, causing numbness, weakness and/or loss of reflexes. Common descriptions accompanying neuropathic pain include “burning”, “shooting” or “shock-like” sensations [7]. The most common causes of chronic neuropathic pain include diabetic neuropathy, post-herpetic neuralgia, fibromyalgia, lower back pain (radiculopathy due to disc herniation) and osteoarthritis [8].

Nociceptive pain is caused by stimulation of specialized sensory neurons, called nociceptors, by noxious stimuli including extremes of
temperature, or mechanical or chemical excitation. It is often categorized as somatic (derived from skin and deep tissue) or visceral (originating from internal organs). Due to high concentrations of nociceptors in somatic tissues, chronic somatic pain is typically localized, and often results from degenerative or inflammatory processes. Nociceptive pain is frequently described as stabbing, pricking, burning, throbbing or cramping [9].

Psychogenic pain refers to painful sensations caused or amplified by mental or emotional factors with no evident physical tissue damage [10]. Referred pain is perceived at a site adjacent to or distant from the site of painful stimulus; the mechanism for this process is not yet well understood [11]. Phantom pain, a sub-type of referred pain, is the feeling of painful sensations from a part of the body which has been lost, and from which the brain no longer receives signals. Individuals who have undergone limb amputation often experience phantom pain [12].

Acute and chronic are terms commonly used to describe the duration of painful sensations, but are difficult to categorically define. In general, acute pain resolves within weeks of the initial causative insult, whereas chronic pain is continuous, long-term pain which can last months or years [13].

Chronic pain

The IASP defines chronic pain as that pain which persists past the normal time of healing following an injury. However, since determining the end of the healing phase is problematic, most clinical definitions use a fixed time of persistent pain after initial onset. This demarcation between acute and chronic pain is somewhat arbitrary, and typically ranges from three months (e.g., for post-herpetic neuralgia) to six months (e.g., for chronic low back pain) [14,15]. The treatment of chronic pain can be difficult because it is a complex condition influenced by genetic makeup as well as physiological and psychological factors.

Chronic pain is a problem in many societies, with prevalence ranging from 2% to 40% in the adult population, resulting in social and economic impacts [16–18]. Chronic pain can interfere with an individual’s activities of daily living, leading to work or school absenteeism, inability to participate in leisure activities, sleep disturbances and problems eating. In the United States, one in three Americans experiences chronic pain and chronic pain is the most common reason for people to visit their family doctor [3]; one in five Canadians is reported to suffer from chronic pain [2]. It is therefore important that chronic pain be diagnosed accurately and treated effectively. Recently, an increased focus on pain management has led to a six-fold increase in the sales of prescription opioids in the U.S. between 1997 and 2006 [19]. Use of analgesics has increased from 7.2% of the U.S. population in 1988–1994 to 10.2% during the period 2007–2010 [20].

Pharmacogenetics and pain management

Pharmacogenetics refers to the way in which genetic differences between individuals influence patient drug responses and drug disposition [21]. Empirically, it is well understood that large inter-individual variations exist with respect to the response to analgesics [22]. With conventional drug dosing, some patients will experience toxicity whereas other patients will not receive adequate analgesia from the same dose. Variations in drug efficacy can vary as much as 2- to 10-fold or even 100-fold among members of the same family [23–25]. These differences can be due to pharmacodynamics factors, based on variations in drug target receptors and downstream signal transduction, and pharmacokinetic factors, which affect drug metabolism and/or elimination, altering the relationship between drug dose and steady state serum drug concentrations. Development of tolerance, which may occur through both dynamic and kinetic mechanisms, can also play a significant role in this response variation.

Genetic variability is one factor playing a role in the way in which drugs affect physiology. Generally, genes affecting outcome of treatment can be divided into two broad categories: those genes affecting pharmacokinetics, and those affecting pharmacodynamics [22]. In the case of pain management drugs, genes associated with altered pharmacokinetics include those which encode members of the cytochrome P450 family of enzymes, enzymes responsible for glucuronidation and drug transporter proteins [21,22]. Genes encoding cyclooxygenase enzymes, the opioid receptors and the enzyme catecholamine methyltransferase (COMT) can affect drug pharmacodynamics [21,22]. Světlík and colleagues provide an up-to-date review of results from pharmacogenetic studies of candidate genes in both the kinetic and dynamic domains [26].

Cytochrome P450 enzymes

The cytochrome P450 (CYP) enzymes comprise a category of proteins whose biosynthesis is controlled by a large super-family of genes. Members of the CYP family play important roles in drug metabolism and therefore influence the concentration of a drug present in circulation. The primary catalytic function of CYP enzymes is identified as the transfer of one oxygen atom from molecular oxygen into various substrates. Additionally, some CYP enzymes act as isomerases, reducers, dehydrases, or nitric oxide (NO) synthases, and some can catalyse oxidative cleavage of esters [27].

CYPs are responsible for approximately 80% of all phase I metabolism reactions (Fig. 1) [27,28]. Genetic changes in CYP genes can result in alterations in enzyme activities. One CYP isoform which has been extensively studied with respect to genetic variation is CYP2D6. This enzyme accounts for a very small percentage (<2%) (Fig. 1b) of all CYPs expressed in the human body, but is responsible for the metabolism of almost 20% of all drugs (Fig. 1a), including many drugs used in management of pain [29]. Most of these enzymes are polymorphic [30]; more than 80 CYP2D6 variants have been identified which, functionally, are associated with four general phenotypes: extensive metabolizer (EM), intermediate metabolizer (IM), poor metabolizer (PM) and ultra-rapid metabolizer (UM) [31]. The prevalence of these phenotypes varies by ethnicity [22] and there are several examples in which phenotypic differences in individuals have led to adverse drug reactions.

In 2004, a case reported by Gasche and colleagues described a 62-year-old male, with a history of chronic lymphocytic leukemia, who presented with fatigue, dyspnea, fever and cough with a bronchoalveolar lavage culture revealing yeast [33]. He was treated with codeine as a cough suppressant. However on day 4 of treatment, he deteriorated rapidly and became unresponsive. He was given naloxone, an opioid receptor antagonist, which resulted in rapid improvement in his condition. Several factors were at play in this case, leading to the patient’s rapid deterioration. Genetic studies revealed that he had CYP2D6 duplications, causing him to be an ultra-rapid metabolizer of the pro-drug (codeine) to the active metabolite (morphine). Furthermore, CYP3A4 is also involved in codeine metabolism, specifically in the conversion of codeine to (relatively inactive) norcodeine. In this case, co-treatment with clarithromycin and voriconazole, both CYP3A4 inhibitors, resulted in decreased conversion of codeine to norcodeine, shunting more codeine into the CYP2D6 morphine pathway. The patient also developed acute renal failure which resulted in the accumulation of glucuronide metabolites with opioid activity (morphine-6-glucuronide) [33].

Opioids, including codeine, are among the pain medications metabolized by CYP2D6. In 2006, Koren and colleagues reported a case of a breast-fed infant who died at 13 days of age [34]. The infant’s mother had been prescribed codeine for episiotomy pain. Stored breast milk was found to contain higher than expected levels of morphine (87 ng/ml; expected 1.9–20.5 ng/ml). CYP2D6 genotyping revealed that the infant’s mother was heterozygous for a CYP2D6 duplication, making her an UM of codeine to morphine. The infant died from CNS depression and this, along with the genetic results, were consistent with opioid toxicity resulting from increased conversion of codeine to morphine. This case prompted the FDA in the USA as well as Health
Canada to advise physicians against the prescription of codeine to nursing mothers [35,36].

Studies have also shown that CYP polymorphisms have an influence on the metabolism of non-steroidal anti-inflammatory drugs (NSAIDs) and have the potential to cause adverse drug reactions, most notably gastrointestinal (GI) bleeding, a frequent reaction resulting in significant patient morbidity and mortality. The risk of GI bleeding is particularly high with higher doses of NSAIDs [37]. Many NSAIDs are metabolized by CYP2C9, which has been shown to have two allelic variants, referred to as CYP2C9*2 and CYP2C9*3 [37]. The CYP2C9 enzymes encoded by the *2 and *3 alleles are reported to have 50% and 15% of the activity of the wild-type enzyme, respectively, resulting in poor metabolism, and thus prolonged action, of NSAIDs in individuals with either of these two alleles [38,39].

Due to their platelet-inhibiting action, NSAIDs are also responsible for an increased risk of bleeding, particularly in patients taking the anticoagulant warfarin [38], since CYP2C9 is also important for warfarin metabolism. Patients with the CYP2C9*2 or *3 genotypes taking both an NSAI and warfarin have been shown to have a significantly higher risk for an elevated prothrombin time, compared to patients with the wild-type 2C9 genotype [38].

Celecoxib is a selective COX-2 inhibitor which is metabolized by CYP2C9. In a study of patients prescribed celecoxib for rheumatoid or osteoarthritis, patients with the *2 or *3 genotypes showed an increased elimination half-life compared to patients with the wild-type genotype [40]. In a similar study, the investigators looked at patients prescribed one of several different NSAIIs, including celecoxib, ibuprofen and naproxen. They grouped the patients into those who experienced GI bleeding and those who did not, and performed CYP2C9 genotype analysis on all patients. Within the group of patients with GI bleeding, a higher number of individuals had the *2 or *3 genotype compared to the group not experiencing gastrointestinal bleeding [41]. The increased risk of bleeding was believed to result from reduced CYP2C9 enzyme activity in patients with the *2 or *3 alleles, leading to increased NSAID concentrations [41].

P-glycoprotein

The ABCB1/MDR1 gene encodes P-glycoprotein, an efflux transporter that influences drug transport in several tissues, particularly the intestine, kidney and brain [42,43]. P-glycoprotein is highly expressed in endothelial cells of the brain vasculature, and is believed to effect the efflux of drugs across the blood brain barrier [43]. ABCB1/MDR1 is a highly polymorphic gene, with 38 single nucleotide polymorphisms (SNPs) identified in the coding region [44]. The activity of P-glycoprotein is thought to be affected by genetic variability, with certain SNPs leading to decreased P-glycoprotein expression and activity.

One study, which examined individuals prescribed oxycodone, found that people homozygous or heterozygous for variant ABCB1/MDR1 alleles reported larger decreases in pain, but also a higher frequency of adverse drug reactions to oxycodone, presumably due to decreased efflux and therefore higher plasma concentrations of the drug [42]. Genetic variability of ABCB1/MDR1 has also been found to be associated with inter-individual differences in pain relief achieved by morphine [43]. In a study of Korean patients receiving intravenous fentanyl, certain ABCB1/MDR1 genotypes were associated with prolonged fentanyl-induced suppression of respiration rate [45].

Cyclooxygenases 1 and 2

Cyclooxygenases 1 and 2 are encoded by two separate genes, PTGS1 (COX1) and PTGS2 (COX2). Genetic variation in either of these enzymes would be expected to cause altered pharmacodynamic responses to NSAIDs. In a study which investigated post-surgical expression of PTGS1 and PTGS2, in relation to SNPs in each gene, certain SNPs were shown to be associated with altered expression of the PTGS2 transcript [46]. The authors also reported differences in patient response to two NSAIDs, rofecoxib, a selective COX-2 inhibitor and ibuprofen, a non-selective COX inhibitor. In particular, the G → C polymorphism at −765, in the promoter region of PTGS2, was found to be associated with lower PTGS2 expression in individuals heterozygous (G/C) or homozygous (C/C) for the minor allele, compared to those homozygous for the major allele (G/G) [46]. Subjects with G/G genotype also reported lower pain intensity with rofecoxib treatment for 48 h following surgery, compared to G/C or C/C subjects. This difference was not demonstrated for patients treated with ibuprofen. However, subjects with G/Cand C/C genotypes reported decreased pain intensity with ibuprofen treatment at 48 h following surgery, compared to G/G patients. This difference was not seen in subjects treated with rofecoxib [46]. These data suggest that patients with increased PTGS2 expression (G/G genotype) benefitted more from treatment with rofecoxib, whereas patients with decreased PTGS2 expression (G/C or C/C genotypes) benefitted more from treatment with ibuprofen [46]. These findings are likely explained by the selectivity of rofecoxib for COX-2, encoded by PTGS2.

Opioid receptor μ

Opioid receptor μ is the primary site of action for many endogenous opioids, as well as those used for analgesia. A number of SNPs have been described in OPRM1, the gene encoding this receptor. The most well characterized SNP in OPRM1 is A118G. A study by Janicki et al. [47] found the minor allele (G) present at lower frequency in subjects with chronic pain treated with opioids, compared to a control group of opioid

Fig. 1. Cytochrome p450: Abundance and proportions. a) Proportions of drugs metabolized by CYP 450 enzymes. Adapted from: Rendic S and Di Carlo FJ [27]. b) CYP Abundance in human liver. Adapted from Yeo et al. [32].
Epidural opioids are commonly used to provide analgesia to women during labor. Women heterozygous or homozygous for the OPRM1 A118G allele have been demonstrated to have higher pressure pain thresholds than women homozygous for the more common A allele [48]. The A → G nucleotide substitution leads to an amino acid change from asparagine to aspartic acid, and is thought to result in higher binding affinity of β-endorphin to the opioid-μ receptor. In another study of women in labor, the median effective dose (ED50) of intrathecal fentanyl required to achieve effective analgesia was significantly higher in women homozygous for the A allele (26.8 μg) compared to women heterozygous or homozygous for the G allele (17.7 μg) [49].

**Catechol-O-methyltransferase (COMT)**

The COMT enzyme is responsible for the inactivation of catecholamines such as dopamine, norepinephrine and epinephrine. Several polymorphisms have been identified in the COMT gene; however, the most widely studied variant is a G to A nucleotide substitution resulting in an amino acid change from valine to methionine at codon 158 (Val158Met). This amino acid change is reported to decrease the thermal stability of the COMT protein, resulting in reduced enzymatic activity. In studies of cancer patients experiencing chronic pain, patients homozygous for the more common Val 158 were found to require higher doses of morphine to achieve analgesia, compared to patients heterozygous or homozygous for Met 158 [50,51]. These findings suggest that variable COMT activity may influence the effects of opioids. Animal studies have demonstrated reduced neuronal enkephalin content in the brain with chronic activation of dopaminergic transmission. The reduced enkephalin content has been shown to be followed by an upregulation of the opioid-μ receptor [52,53]. The lower doses of morphine required by individuals with the Met158 variant may be explained by reduced COMT activity which is associated with increased dopaminergic stimulation, resulting in upregulation of opioid-μ receptor expression in the brain, making morphine more effective. Another study demonstrated differences in morphine side effects, such as drowsiness, confusion and hallucinations, associated with certain COMT variants, which influence how well patients tolerated morphine [54].

**Clinical use of pharmacogenetics in pain management**

Ideally, pharmacogenetic studies aim to aid in the selection and dosing of an optimal drug therapy for a specific patient. Choosing the optimal therapy should lead to maximized therapeutic benefit, improved patient adherence and a reduction in adverse drug reactions [55]. The cases of opioid overdose discussed above illustrate instances where knowledge of patient genotypes may be helpful to improve patient outcomes. However, most pharmacogenetic studies to date have examined variability in single candidate genes, such as CYP2D6, and associated outcomes [22]. There are limitations to this approach, as very few drugs are metabolized by a single enzyme. Genome-wide association studies (GWAS) may possibly improve upon this limitation. Furthermore, in addition to genetics, many other factors affect drug responses, such as patient age, disease co-morbidities and, in particular, co-medication [22,56] (Fig. 2). Genetics can only partially explain the variability in patient responses to analgesic drugs. Patients are very commonly prescribed several medications for multiple co-morbidities. Some medications induce CYP enzyme activity [57], as illustrated in the case above [33], while others inhibit activity [57], which can lead to altered metabolism unrelated to the patient’s CYP phenotype. In general, pharmacogenetic studies thus far in pain management have failed to yield evidence of improved clinical outcomes associated with knowledge of patient genotypes when prescribing pain medications. As GWAS studies continue, and panels of gene testing become more widely accessible, pharmacogenetics of pain management may yet become more clinically useful [58].

**Genetics and pain susceptibility**

An individual’s genetic susceptibility to chronic pain is thought to be complex, involving multiple genes, similar to the genetics of other chronic diseases, such as diabetes [21]. As discussed above, several candidate genes have been identified, with specific mutations shown to alter pain perception profiles between individuals. Examples include: OPRM1, the gene encoding the μ-opioid receptor; COMT, encoding catechol-O-methyltransferase, involved in the metabolism of catecholamines; GCH1, encoding an enzyme involved in phenylalanine metabolism and the production of dopamine; the melanocortin-1 receptor with mutations showing sex-specific differences in pain perception; and...
members of the cytochrome P450 enzyme family, important for the biotransformation of many drugs. Genome-wide association studies and other types of genetic investigations will likely identify many more genes involved in pain perception.

**Chronic pain management**

Successful pain management can be viewed as providing adequate analgesia without excessive adverse effects [59]. In 1982, Rane and colleagues [60] proposed a pharmacological approach to treat cancer pain with morphine. They proposed a step-wise approach that was later adopted by the World Health Organization (WHO) in 1986 [61,62]. Although this WHO step ladder approach was originally aimed at the treatment of chronic cancer pain (Fig. 3) [61,62], it is also widely used in the treatment of chronic non-cancer pain [63]. The WHO analgesic ladder recommends initial treatment of pain with non-opioids, such as NSAIDs and acetaminophen. If pain persists, treatment with a weak opioid, such as codeine or tramadol is recommended, followed by a strong opioid, such as morphine, until the patient is free of pain. At each stage of the treatment ladder, adjuvant medications, such as antidepressants or anticonvulsants, may also be given to aid in alleviating patient anxiety; some of these adjuvant drugs may also act directly to counter pain [4,61]. Evident from this scheme is the fact that opioids remain the mainstay of chronic pain management and will be discussed further below.

**Drugs used in pain management**

**NSAIDs and acetaminophen in pain management (Table 1)**

NSAIDs such as aspirin and ibuprofen, as well as acetaminophen, act by inhibiting the enzymes cyclooxygenase-1 and -2, which catalyze the synthesis of prostaglandins. The inhibition of prostaglandin synthesis results in the analgesic, anti-pyretic and anti-inflammatory properties of these drugs, with the exception of acetaminophen, which does not show anti-inflammatory affects. Due to the widespread use of NSAIDs, they are the drugs most commonly associated with adverse effects, the most common of which are those involving the GI tract. Reduced prostaglandin levels in the gastrointestinal mucosa decrease mucus and bicarbonate secretions, thereby reducing their protective effects against the acidic gastric environment. In addition, NSAIDs can be directly toxic to the gastric mucosa, leading to ulceration, and potentially fatal bleeding in the most extreme cases. Furthermore, reduced prostaglandin synthesis in the kidney has been shown to cause renal impairment. Chronic or acutely toxic acetaminophen exposure can lead to liver toxicity through hepatocellular necrosis [64,65]. Additionally, aspirin (acetylsalicylic acid) is associated with Reye’s syndrome, primarily affecting children [66,67], and high doses of salicylates can cause metabolic acidosis and respiratory depression. More recently, cardiovascular risks associated with the use of NSAIDs have gained attention. NSAIDs, particularly COX-2 selective agents, such as celecoxib, have been reported to increase the risk for thrombotic events, myocardial infarction and stroke in patients with coronary artery disease and atherosclerosis [68,69]. These findings have prompted the American Heart Association to recommend use of acetaminophen or non-acetylated salicylates for the treatment of chronic pain in patients with coronary artery disease [70]. Although classified with nonsteroidal anti-inflammatory agents, acetaminophen has minimal peripheral anti-inflammatory activity.

IV acetaminophen has become a part of the multimodal analgesia approach for pain. Intravenous acetaminophen was made available over 10 years ago in Europe, but in the United States only very recently. Three randomized placebo controlled trials provided the bases of its approval. Clinical studies show that for management of pain, intravenous acetaminophen injection was at least as effective as morphine injection in renal colic and oral ibuprofen after cesarean delivery. In children a single-dose acetaminophen injection was similar to meperidine intramuscular (IM) for pain after tonsillectomy [71]. Effects begin 5 to 10 min after IV administration, and peak effects occur in about 1 h with an effective duration of 4 to 6 h. Table 1 provides pharmacokinetic details of specific NSAIDs and acetaminophen, as used in pain management.

**Opioids and pain management (Table 2)**

Opioids remain the most potent analgesics available and are the mainstay of chronic pain management in both cancer patients and patients with non-malignant pain [2,72]. To manage chronic cancer pain, oral morphine is commonly administered at regular intervals. Chronic dosing can lead to pharmacological tolerance, but not to therapeutic failure. In simple pharmacological terms, opioid-induced tolerance can be described as a “shift to the right” in the dose–response curve; that is, a higher dose is required over time to maintain the same level of analgesia. Different mechanisms have been proposed for the development of tolerance. Säwe and colleagues [73] investigated the metabolic correlate to the development of tolerance to therapeutic effects by measuring morphine, morphine-3- and morphine-6-glucuronide in plasma and urine samples. They showed that the conjugation of morphine with glucuronic acid is proportional to the dose during long-term treatment with escalating doses, suggesting that this metabolic pathway is subject to neither auto-induction nor saturation. Both in vitro and in vivo studies have shown that, on the cellular level, chronic opioid treatment leads to a rapid reduction of agonist response, accompanied by internalization of opioid receptors [74]. These early adaptive processes as well as long-term adaptations, such as receptor downregulation, or counter-regulatory processes such as adenylyl cyclase superactivation, have been suggested to be crucial to the development of opioid tolerance [75–77].

In recent years, there has been an increased focus on pain management which has resulted in a societal escalation in opioid use, with opioids being currently among the most commonly prescribed medications in developed nations [78]. Despite this, the suitability of opioids for chronic non-cancer pain treatment is under debate. The efficacy of opioids in this clinical situation has only been reported in short-term trials, and evidence for their overall benefit in long-term therapy is lacking [79].

The analgesic properties of opioids begin with their binding to opioid receptors in the central nervous system (CNS). There are three opioid receptor subtypes, mu (μ), kappa (κ) and delta (δ), which differ in their function and specificity for the drugs they bind. Opioids themselves can be classified, based on their interactions with these receptors, as agonists, mixed agonists–antagonists and antagonists. The binding of opioids to their G-protein coupled receptors produces signals causing hyperpolarization of neuronal cell membranes and the suppression of neurotransmitter release, resulting in analgesia [78,80,81].
**Issues with opioids**

The increased use of opioids for pain management has led to an expansion in opioid misuse, resulting in an increased number of emergency room visits related to drug-seeking behavior as well as in the number of opioid-related overdose deaths [82,83]. Although opioids are among the most commonly used analgesics, their clinical use is limited by the development of tolerance and physical dependence. Another growing concern relates to the diversion of opioids from patients to other individuals not under medical supervision.

Opioids have several well-known side effects, including nausea, sedation and bowel dysfunction [84]. The most serious potential adverse effect is respiratory depression and failure, which is the most common cause of death related to opioid use [80]. Prolonged use leads to tolerance, resulting in higher dose requirements, which can lead to physical dependence, demonstrated by withdrawal symptoms in patients experiencing chills, muscle aches, vomiting, diarrhea, hyperthermia, anxiety and hostility [80]. Additionally, opioid use can result in feelings of euphoria which can promote compulsive use leading to psychological dependence.

A detailed medical assessment is recommended prior to prescription of opioids. This should include a detailed medical history, review of medical records, urine toxicology screen and psychological evaluation, including questionnaires aimed at determining an individual’s risk for abuse [84,85]. This is of particular importance in those populations at higher risk for opioid misuse. Chronic pain frequently occurs in individuals with psychological conditions, including anxiety and depression; it is estimated that 30%-60% of individuals with depression also experience chronic pain [86]. Psychological conditions are often comorbid in individuals with substance-abuse disorders, resulting in a high risk for opioid abuse in many chronic pain patients including those with substance abuse issues and mental health disorders [85].

Newer opioid formulations have been designed in efforts to prevent abuse. These include Embeda™, an extended-release morphine co-formulated with the opioid antagonist naltrexone, produced by Pfizer; and an extended-release form of oxycodone, called OxyNeo™, by Purdue Pharma [84]. OxyNeo™ contains polyethylene oxide, which forms a viscous gel when in contact with water, rendering it unsuitable for injection or snorting, and also more difficult to chew or crush [87]. Buprenorphine, a semi-synthetic opioid was approved by the FDA in 2002. Sublingual preparations, used in addiction medicine, are co-formulated with the antagonist naloxone to prevent abuse.

**Specific opioids used in pain management**

Opioids can be classified as either weak or strong, depending on their “analgesic ceiling”. This term is defined as the dose above which a drug has no further effect on pain [88]. Weak opioids include tramadol, codeine and hydrocodone; strong opioids include morphine, methadone, buprenorphine, fentanyl, oxycodone, hydromorphone, oxymorphone, meperidine and levorphanol. Detailed pharmacokinetic information for each of these drugs can be found in Table 2.

**Weak opioids**

**Codeine**

Codeine is considered a weak opioid, and is used for its analgesic, anti-tussive and anti-diarrheal properties. It is a pro-drug which requires biotransformation via hepatic CYP2D6 to the active metabolite morphine [89]. Approximately 5%-10% of codeine is converted to morphine in the liver, while the remainder is either conjugated, forming...
Table 2
Properties of opioid medications commonly used in the management of chronic pain.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Common route of administration</th>
<th>Protein binding</th>
<th>Bioavailability*</th>
<th>Route of elimination</th>
<th>Vd** L/kg</th>
<th>t½** (h)</th>
<th>CYP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buprenorphine [170,171]</td>
<td>TD, B, IV</td>
<td>96%</td>
<td>31% (sublingual)</td>
<td>Renal biliary</td>
<td>2–3 (IV)</td>
<td>19 (B)</td>
<td>3A4</td>
</tr>
<tr>
<td>Codeine [89]</td>
<td>Oral</td>
<td>&lt;1%</td>
<td>~90% (oral)</td>
<td>Renal</td>
<td>2.5–3.5</td>
<td>1.2–3.9</td>
<td>3A4, 2D6</td>
</tr>
<tr>
<td>Fentanyl [89,172]</td>
<td>TD, oral</td>
<td>79%</td>
<td>92% (transdermal)</td>
<td>Renal</td>
<td>3–8</td>
<td>3–12</td>
<td>3A4</td>
</tr>
<tr>
<td>Hydro Hydrocodone codeone [89,90]</td>
<td>Oral</td>
<td>20%–50%</td>
<td>????????</td>
<td>Renal</td>
<td>3.3–4.7</td>
<td>3.4–8.8</td>
<td>2D6, 3A4</td>
</tr>
<tr>
<td>Hydromorphone [89,173]</td>
<td>Oral, IV</td>
<td>19%</td>
<td>30%–35%, (Oral)</td>
<td>Renal</td>
<td>2–4</td>
<td>3–9</td>
<td>glucuronidation</td>
</tr>
<tr>
<td>Levorphanol [89,120]</td>
<td>IV, oral</td>
<td>40%</td>
<td>70% (oral); 100%</td>
<td>Renal</td>
<td>10–13</td>
<td>11–16</td>
<td>glucuronidation</td>
</tr>
<tr>
<td>Drug</td>
<td>Route(s)</td>
<td>Bioavailability</td>
<td>Metabolism</td>
<td>Half-Life</td>
<td>Comments</td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------</td>
<td>----------</td>
<td>-----------------</td>
<td>------------</td>
<td>-----------</td>
<td>----------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morphine</td>
<td>IV, IM, oral</td>
<td>35%</td>
<td>20%–40% (oral), 36%–71% (rectally), 100% (IV/IM)</td>
<td>Renal (90%), Biliary (10%)</td>
<td>2–5, 1.3–6.7</td>
<td>Glucuronidation (major), 2D6 (minor)</td>
<td></td>
</tr>
<tr>
<td>Meperidine</td>
<td>Oral, IV</td>
<td>45–64%</td>
<td>50%–60% (oral), 80%–90% (oral, in cases of hepatic impairment)</td>
<td>Hepatic</td>
<td>3.7–4.2, 2–5</td>
<td>2B6, 3A4 &amp; 2C19 (minor)</td>
<td></td>
</tr>
<tr>
<td>Oxycodone</td>
<td>Oral</td>
<td>45%</td>
<td>60%–87%</td>
<td>Renal</td>
<td>1.8–3.7, 3–6</td>
<td>2D6</td>
<td></td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>Oral</td>
<td>10–12%</td>
<td>10% (oral), 40% (Intranasal), 100% (IV, IM)</td>
<td>Renal, fecal</td>
<td>2.4, 4–12</td>
<td>Glucuronidation</td>
<td></td>
</tr>
<tr>
<td>Remifentanil</td>
<td>i.v</td>
<td>70% (bound to plasma proteins)</td>
<td>Not applicable</td>
<td>-</td>
<td>-</td>
<td>1–20 min</td>
<td>Nonspecific esterases</td>
</tr>
<tr>
<td>Tramadol</td>
<td>Oral</td>
<td>15–20%</td>
<td>70%–75% (oral), 77% (rectal), 100% (IM)</td>
<td>Renal</td>
<td>2.6–2.9, 4.3–6.7</td>
<td>2D6 &gt; 2B6, 3A4</td>
<td></td>
</tr>
</tbody>
</table>

* All chemical formulas and bioavailability are from their respective pages in Wikipedia.
*depends on formulation; 2–3 h for immediate release; 5 h for continuous release; TD transdermal; B buccal; IV intra venous.
**[169].
codeine-6-glucuronide (active), or methylated via CYP3A4, producing norcodeine (inactive) [89].

**Hydrocodeone**

This is a semi-synthetic drug, similar to codeine in structure and to morphine in its effects [89]. Hydrocodeone is metabolized by CYP2P6 to active hydromorphone, which binds to the μ-opioid receptor, and by CYP3A4 to the inactive metabolite norhydrocodeone [90].

**Tramadol**

Tramadol is a synthetic codeine analog that binds to the μ-opioid receptor and inhibits the reuptake of serotonin and norepinephrine [89]. Tramadol has a lower risk of addiction than other opioids; however, it is associated with two significant adverse drug reactions: seizure and serotonin syndrome [91]. Tramadol seizures usually occur in patients already taking anticonvulsant medications. Serotonin syndrome is characterized by neuromuscular and autonomic hyperactivity as well as altered mental status, due to excess serotonin activity in the CNS. Higher risk of this syndrome is associated with tramadol overdose or co-administration of antidepressant medications, such as tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRIs), which, in addition to tramadol, inhibit serotonin reuptake to high serotonin levels in the synaptic space[92,93].

Tramadol is metabolized by CYP2P6 in the liver to its main metabolite, O-desmethyl-tramadol which shows a higher affinity for opioid receptors than the parent drug [94]. Metabolism to the minor metabolite, N-desmethyl-tramadol occurs via CYP2B6 and CYP3A4 [95].

**Strong opioids**

**Morphine**

Morphine increases the threshold for pain perception by binding strongly to the μ-opioid receptor; it also has activity towards κ- and δ-opioid receptors. Morphine administered orally undergoes a large first-pass effect, resulting in oral bioavailability of 38% on average [96]. The major morphine metabolites result from glucuronidation by the hepatic isoenzyme UGT2B7 to inactive morphine-3-glucuronide (approximately 60%) and active morphine-6-glucuronide (up to 10%) [97]. CYP2D6 plays a minor role in morphine metabolism. Side effects of morphine include sedation, nausea, a feeling of warmth, urinary retention, euphoria, reduced ability to concentrate and constipation. The most serious side effect of morphine is potentially fatal respiratory depression with morphine toxicity [89,98].

**Hydromorphone**

Hydromorphone, a hydrogenated ketone of morphine, is a synthetic opioid with effects similar to morphine [89]. When given orally, hydromorphone is rapidly absorbed by the GI tract and undergoes extensive first-pass metabolism in the liver. Like morphine, it is glucuronidated in the liver to hydromorphone-3-glucuronide and hydromorphone-6-glucuronide; hydromorphone-3-glucuronide has no analgesic properties, but has been shown to exhibit neuroexcitatory effects [99]. Hydromorphone suppresses the cough reflex, similar to other opioids. Side effects of hydromorphone are dose-related and can include mood changes, euphoria, nausea, vomiting, and hypotension, as well as respiratory depression in large doses [89].

**Fentanyl**

Fentanyl is a highly lipophilic, synthetic opioid which is 100 times more potent than morphine. Its potency is due to its efficiency in crossing the blood brain barrier, rapidly gaining access to the central nervous system [89,100,101]. Given intravenously, fentanyl has a very rapid onset but short duration of action, and is thus administered as a continuous infusion. In managing pain, fentanyl is most often provided through transdermal patches or buccal tablets [89]. This allows the drug to distribute throughout fatty tissues, leading to slower release and prolonged effects. Fentanyl undergoes extensive pulmonary first-pass metabolism as well as hepatic metabolism to the inactive metabolite norfentanyl via CYP3A4 [89].

**Remifentanil**

Remifentanil is a μ-opioid receptor agonist with an analgesic potency similar to that of fentanyl. It was studied for analgesic efficacy correlating with expression of the serotonin transporter (5-HTT), as serotonin can influence the antinociceptive effects of opioids at the spinal cord. Remifentanil has a significantly better analgesic effect in individuals with a genotype coding for low 5-HTT expression (SA/SA and SA/LG) compared to those with high expression (LA/LA) [102]. It is predominantly metabolized by non-specific esterases [103], and because of its rapid systemic elimination and ultra-short half-life, it has a pharmacokinetic advantage in clinical situations requiring predictable termination of effect such as analgesia during labor [104]. In a systematic review, Leong and colleagues compared remifentanil with meperidine for labor analgesia. They found remifentanil to be superior in reducing mean visual analog scale pain scores for labor pain after 1 h [105]. Remifentanil crosses the placenta, but is rapidly metabolized and redistributed. Although maternal sedation and respiratory changes do occur, they are without adverse neonatal or maternal effects [106].

**Methadone**

Methadone is a synthetic opioid with morphine-like effects. It is commonly used in the treatment of opioid addiction, but also in the treatment of chronic pain [89,107,108]. Given orally, methadone has a much higher bioavailability compared with oral morphine (70%–90%, compared to 38%, respectively). Due to its relatively slow metabolism and high lipid solubility, methadone also has a long half-life (between 8 and 60 h), leading to longer term analgesia than with morphine [107,108]. Methadone is extensively metabolized by CYP3A4, and to a lesser extent by CYP1A2, -2D6, -2D8, -2C9/2C8, -2C19, and -2B6, to its inactive metabolite, 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP) [107–110]. Caution must be exercised when co-prescribing methadone with QT-prolonging cardiac drugs due to methadone’s ability to interact with voltage-gated potassium channels in the myocardium, also leading to QT prolongation [111] and ventricular arrhythmias such as Torsades de Pointes. Significant drug–drug interactions have been reported for methadone, when combined, for example, with fluoxetine, quetiapine, or promethazine [110].

**Buprenorphine**

As an alternative to methadone, buprenorphine can be used for the treatment of opioid addiction [89]. It has also been approved for the treatment of moderate to severe pain [112]. Similarly to morphine, buprenorphine must be used with caution in the setting of co-administration of other QT-prolonging medications or in individuals with hyperkalemia [112]. Buprenorphine has a ceiling effect with respect to respiratory depression, thereby reducing the likelihood of this potentially fatal consequence, making it an attractive choice for analgesia [113]. Given orally, buprenorphine undergoes extensive first-pass metabolism and is therefore usually administered by transdermal or buccal routes to improve bioavailability [112]. Prolonged analgesia can be achieved with buprenorphine due to its lipophilic properties and its slow dissociation from opioid receptors. Buprenorphine is metabolized by CYP3A4 in the liver primarily to nor-buprenorphine.
Oxycodone

Oxycodone is a synthetic opioid, similar in structure to codeine and prescribed for moderate to severe pain [89]. This drug is commonly compounded with other drugs, such as acetaminophen or ibuprofen [89]. Side effects of oxycodone treatment include euphoria, sedation, constipation, cough suppression and respiratory depression. The euphoria caused by oxycodone is quite pronounced and can therefore lead to abuse of and dependence on the drug. Oxycodone is metabolized, via CYP2D6, to the potent metabolite oxymorphone (see below) as well as noroxycodone, a weakly active metabolite [114].

Oxymorphone

Oxymorphone offers excellent analgesia, comparable to that of morphine, but with less sedative effects [115]. This results from the lipophilic nature of oxymorphone, allowing ease of access to the central nervous system. Oxymorphone undergoes extensive hepatic

Table 3

Antidepressants commonly used in pain management.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Common route of administration</th>
<th>Protein binding</th>
<th>Bioavailability *</th>
<th>Route of elimination</th>
<th>$V_d^*$ (L/kg)</th>
<th>$t_1/2^*$ (h)</th>
<th>CYP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline [176]</td>
<td>Oral</td>
<td>&gt; 90%</td>
<td>30%–60% due to first pass metabolism</td>
<td>Renal</td>
<td>6–10</td>
<td>8–51</td>
<td>2D6</td>
</tr>
<tr>
<td>Bupropion [177]</td>
<td>Oral</td>
<td>85%</td>
<td>??????</td>
<td>Renal, Fecal</td>
<td>40</td>
<td>4–24</td>
<td>2B6</td>
</tr>
<tr>
<td>Citalopram [178]</td>
<td>Oral</td>
<td>50%</td>
<td>80%</td>
<td>Renal</td>
<td>12–16</td>
<td>25–40</td>
<td>2C19, 3A4, 2D6</td>
</tr>
<tr>
<td>Desipramine [179]</td>
<td>Oral</td>
<td>70%-90%</td>
<td>73%-92%</td>
<td>Renal</td>
<td>22–59</td>
<td>12–54</td>
<td>2D6</td>
</tr>
<tr>
<td>Duloxetine [180]</td>
<td>Oral</td>
<td>&gt;90%</td>
<td>32% to 80%</td>
<td>Renal, Fecal</td>
<td>17–26</td>
<td>8–17</td>
<td>1A2,2D6</td>
</tr>
<tr>
<td>Fluoxetine [181]</td>
<td>Oral</td>
<td>94%</td>
<td>72%</td>
<td>Renal, Fecal</td>
<td>20–42</td>
<td>1–3 days</td>
<td>2D6</td>
</tr>
<tr>
<td>Venlafaxine [182]</td>
<td>Oral</td>
<td>27%</td>
<td>42% ± 15%</td>
<td>renal</td>
<td>4–12</td>
<td>3–7</td>
<td>2D6, 3A4</td>
</tr>
</tbody>
</table>

\* All chemical formulas and bioavailability data are from their respective pages in Wikipedia.

\* [169].
first-pass metabolism, and its major route of metabolism is via glucuronidation [89,115].

Meperidine (pethidine)

Meperidine (Demerol™), also known as pethidine, is a synthetic μ-opioid receptor agonist that is structurally similar to atropine. Pharmacologically, it represents both morphine and atropine. This unique property of an analgesic with spasmolytic and sedative action accounts for its wide range of clinical applications [116]. Although meperidine efficacy has been questioned [117], a survey of intrapartum analgesia practice in United Kingdom and Norway reported that this opioid is still commonly used during labor [118,119].

Levorphanol

Levorphanol is a synthetic opioid, similar in structure to morphine, but more potent in its analgesic effects [89,120] and also has anticholinergic effects [120]. This drug is usually given orally or intravenously and is eliminated through glucuronidation in the liver [120].

Other medications in the treatment of chronic pain

Antidepressants

Tricyclic antidepressants (TCAs) and selective serotonin re-uptake inhibitors (SSRIs), are commonly used as adjuvant therapy in the treatment of chronic pain. The mechanisms by which these medications alleviate pain are not fully understood, but are believed to be mediated through their inhibition of neurotransmitter reuptake in the synaptic cleft. These mechanisms are related to pain signaling in descending spinal pain pathways [121]. In addition to their analgesic role, antidepressants are commonly used in pain management because depression is often a co-morbidity of chronic pain. Patients experiencing chronic pain have been shown to have 2–5 times the risk of developing depression than the general population [122].

Common TCAs used in pain management include amitriptyline and imipramine (Table 3), administered at much lower doses for pain management than for psychiatric indications [22]. These two drugs are metabolized to the active metabolites nortriptyline and desipramine, respectively, by hepatic CYP2D6 [22]. Side effects of TCAs that can limit their use include weight gain, anticholinergic effects, hypoten- sion and cardiovascular effects [22,121]. TCAs have been better characterized for their role in pain management than SSRIs [121]. SSRIs used in pain management include fluoxetine and citalopram (Table 3). SSRIs are often better tolerated than TCAs, due to their milder side effects; however, data regarding their efficacy in the treatment of chronic pain have been inconsistent [121].

More recently, antidepressants able to target several neurotransmitters, such as venlafaxine (serotonin, norepinephrine, and dopamine), duloxetine (serotonin and norepinephrine) and bupropion (serotonin and dopamine) have been more widely used in pain management (Table 3). Venlafaxine has been shown to be particularly efficacious when prescribed in combination with gabapentin, a GABA analogue often used to treat neuropathic pain [123].

Anticonvulsants

Anticonvulsants (Table 4) have been used in pain management since the 1960’s when these drugs were originally introduced for the treatment of epileptic seizures [124]. These medications work by a variety of mechanisms to suppress the rapid firing of neurons. Phenytoin, one of the first anticonvulsants introduced, reduces neuronal excitability by blocking sodium channels. It has been used in the treatment of chronic neuropathic pain, but today its use for this indication is limited due to side effects, namely, sedation and motor disturbances [125].

<table>
<thead>
<tr>
<th>Drug†</th>
<th>Common route of administration</th>
<th>Protein binding</th>
<th>Bioavailability</th>
<th>Route of elimination</th>
<th>( V_d )</th>
<th>( t_{1/2} )</th>
<th>CYP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine [183,184]</td>
<td>Oral</td>
<td>75%</td>
<td>??????</td>
<td>Renal</td>
<td>0.8–1.8</td>
<td>18–65</td>
<td>3A4</td>
</tr>
<tr>
<td>Gabapentin [185]</td>
<td>Oral</td>
<td>&lt; 3%</td>
<td>27%–60% (inversely proportional to dose)</td>
<td>Renal</td>
<td>0.8–1.3</td>
<td>5–9</td>
<td>Not metabolized</td>
</tr>
<tr>
<td>Lamotrigine [186]</td>
<td>Oral</td>
<td>55%</td>
<td>98%</td>
<td>Renal</td>
<td>0.9–1.3</td>
<td>12–62</td>
<td>glucuronidation</td>
</tr>
<tr>
<td>Phenytoin [187,188]</td>
<td>Oral, IV</td>
<td>87%–93%</td>
<td>70%–100%</td>
<td>Biliary</td>
<td>0.5–0.8</td>
<td>8–60</td>
<td>2C19</td>
</tr>
</tbody>
</table>

* All chemical formulas and bioavailability data are from their respective pages in Wikipedia.

† [169].
Carbamazepine has largely replaced phenytoin in chronic pain management and has been shown to be effective in the treatment of neuropathic pain, in particular trigeminal neuralgia [124,126] (a disorder characterized by episodes of intense facial pain, originating from the trigeminal nerve) [126]. Side effects of carbamazepine include drowsiness, blurred vision, nausea and vomiting. There is a dose–effect relationship and it can be difficult to achieve a therapeutic effect in patients who are sensitive to these side effects [125]. This is of particular relevance in elderly patients, where conditions such as cardiac disease and hypernatremia can further complicate adverse effects [127]; thus, close monitoring of these patients is required [124,125].

Newer anticonvulsants, such as lamotrigine and gabapentin, are showing promise in chronic pain management; gabapentin, in particular, has been shown to be well tolerated with few side effects [128]. Gabapentin binds to voltage-gated calcium channels, leading to a reduction in the release of the neurotransmitters glutamate and substance P. It has demonstrated effectiveness in the treatment of diabetic neuropathy, post-herpetic neuralgia, trigeminal neuralgia, multiple sclerosis, migraine as well as in chronic pain caused by malignancy [128]. Lamotrigine has been shown to be useful in the treatment of trigeminal neuralgia and diabetic neuropathy [124]. However, careful titration of lamotrigine dose is required because of the risk of Stevens–Johnson syndrome, a life-threatening dermatological condition leading to cell necrosis, causing the epidermis to separate from the dermis [129].

**Triptans**

Triptans are serotonin agonists with high affinity for the 5HT1B and 5HT1D receptors [130,131]. The serotonergic system is known to play a role in the pathophysiology of migraines, leading to the development and prescription of triptans for this condition. Binding of these drugs to 5HT receptors in the brainstem and thalamus leads to the blockade of vasoactive peptide release from perivascular trigeminal neurons, and thus reduced cerebral vasodilation [131]. Currently, there are seven triptan molecules available, each with its unique pharmacokinetic and pharmacodynamic profile. The four most commonly prescribed and well characterized triptans are sumatriptan, naratriptan, zolmitriptan and rizatriptan (Table 5) [132]. Triptans are not recommended for migraine treatment in individuals with poorly controlled hypertension.

![Table 5: Triptans used in migraine therapy [130,132].](image)

<table>
<thead>
<tr>
<th>Drug#</th>
<th>Common route of administration</th>
<th>Protein binding</th>
<th>Bioavailability#</th>
<th>Route of elimination</th>
<th>( V_d^{**} ) L/kg</th>
<th>( t_{1/2}^{**} ) h</th>
<th>CYP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Almotriptan [131]</td>
<td>Oral</td>
<td>35%</td>
<td>70%</td>
<td>Renal, Fecal</td>
<td>2.5–4</td>
<td>3–4</td>
<td>3A4, MAO*, 2D6</td>
</tr>
<tr>
<td>Eletriptan [131]</td>
<td>Oral</td>
<td>85%</td>
<td>50%</td>
<td>Renal</td>
<td>2.1–3.3</td>
<td>3–7</td>
<td>3A4</td>
</tr>
<tr>
<td>Frovatriptan [131]</td>
<td>Oral</td>
<td>15%</td>
<td>20%–30%</td>
<td>Renal</td>
<td>3–4.2</td>
<td>20–30</td>
<td>1A2, 2D6</td>
</tr>
<tr>
<td>Naratriptan [131]</td>
<td>Oral</td>
<td>20%–30%</td>
<td>74%</td>
<td>Renal</td>
<td>2–3</td>
<td>5–6</td>
<td>Unknown CYP</td>
</tr>
<tr>
<td>Rizatriptan [131]</td>
<td>Oral</td>
<td>14%</td>
<td>45%</td>
<td>Renal</td>
<td>1.3–2.2</td>
<td>1.6–3.2</td>
<td>MAO, 1A2</td>
</tr>
<tr>
<td>Sumatriptan [131]</td>
<td>Oral</td>
<td>14%–21%</td>
<td>15% (oral) 96% (s.c.)</td>
<td>Renal</td>
<td>1.3–4.6</td>
<td>1–4</td>
<td>MDA</td>
</tr>
<tr>
<td>Zolmitriptan [131]</td>
<td>Oral, nasal</td>
<td>25%</td>
<td>40% (oral)</td>
<td>Renal, Fecal</td>
<td>7.0</td>
<td>1.6–3.8</td>
<td>1A2, MAO, 3A4</td>
</tr>
</tbody>
</table>

* All chemical formulas and bioavailability data are from their respective pages in Wikipedia.
* MAO: monoamine oxidase.
** [169].
hepatic or renal impairment or coronary artery disease, as serotonergic blockade may exacerbate these conditions [131].

Benzodiazepines

Benzodiazepines play a role in the treatment of insomnia, muscle tension, and, in particular, anxiety related to chronic pain [133]. Chronic pain patients experience increased anxiety compared to the general population, and this can often worsen the subjective experience of pain. Evidence suggests that benzodiazepines are only effective in treating acute anxiety related to chronic pain, but are not effective in the setting of chronic anxiety [133] (for which antidepressants have been found to be more effective). The caveats to benzodiazepine treatment for chronic pain are the potential for abuse as well as side effects, including paradoxical reactions (increased hostility, psychosis and behavioral disturbances) [133].

Cannabinoids

Cannabis is an annual plant that grows wild in regions of mild or tropical weather, and has been used to treat pain for centuries. It is by far the most widely cultivated, trafficked and abused illicit drug; half of all drug seizures worldwide are of cannabis. The geographical spread of those seizures is also global, covering practically every country of the world. Delta-9-tetrahydrocannabinol (THC) is the active component in cannabis, responsible for its analgesic and psychoactive effects. Ingestion of THC results in feelings of euphoria, relaxation and a general sense of well-being. However, heavy cannabis use can result in hallucinations, anxiety and depression [134,135].

Endogenous cannabinoids, referred to as endocannabinoids, have been identified, as well as two endocannabinoid receptors, the G-protein coupled receptors CB1 and CB2. High levels of CB1 are expressed in the brain and spinal cord, particularly in areas known to be involved in nociception. CB2 is not as well characterized, but has been shown to have lower expression levels in the brain than CB1. Endocannabinoids are bioactive lipids which regulate neural activity by binding to CB1 and CB2, causing inhibition of neurotransmitter release. Endogenous and exogenous cannabinoid activity results in anti-nociceptive effects as well as short-term memory impairment, stimulation of appetite and antiemetic effects [134–136].

THC acts synergistically with other analgesic agents, such as morphine and some NSAIDs, though the mechanism for the synergistic action between morphine and THC is unknown [134]. In the case of NSAIDs, cannabinoids and prostaglandin share a similar structure which is believed to result in a convergence of signals. Activity of CB1 receptors is increased by NSAIDs including ibuprofen and indomethacin. Furthermore, CB1 receptor antagonists block the analgesic effects of ibuprofen [134].

Evidence for the use of cannabinoids in pain management is lacking due to the small number of clinical trials in this area. The best evidence for cannabinoid use in chronic pain comes from HIV and multiple sclerosis studies in which cannabinoids were used to treat the chronic neuropathic pain associated with these conditions [136]. Smoking cannabis 3–5 times per week was shown to be effective in alleviating neuropathic pain associated with HIV as well as AIDS-related anorexia [137,138]. Several studies demonstrated benefit of oral treatment with synthetic THC for central pain and spasticity associated with multiple sclerosis [139–142].

There are several issues associated with the use of cannabinoids in pain management. Firstly, the method of drug delivery poses a problem. Smoking of cannabis is the easiest delivery route and allows for adequate control of dose [135,136]. However, the adverse effects of smoking are well known, with THC contents varying depending on where and how the cannabis plants are grown. Canada, which allows prescription of cannabis for chronic pain therapy, requires that patients obtain their medicinal cannabis from a centralized source so that the THC content may be monitored over time [136]. Similar strategies are now under consideration in different parts of the world including the United States. Synthetic cannabinoids, such as dronabinol and nabilone, are available in the U.S. and Canada for use as antiemetics during cancer chemotherapy, and as adjunct therapies for neuropathic and chronic pain. They are not yet widely used, and are under further study to delineate their efficacy and pharmacological parameters in various clinical contexts [143]. Side effects include increased heart rate, blood pressure changes, anxiety, psychomotor retardation, impaired memory and psychosis. Cannabinoids are contraindicated in pregnancy, uncontrolled hypertension, active ischemic heart disease, arrhythmias and schizophrenia. Clark and co-workers suggest guidelines for the use of these cannabinoid compounds [144].

Cannabis and cannabinoids have a potential for dependence, which can lead to preoccupation and compulsion. Prescription of cannabinoids for chronic pain management requires clinician to appropriately select patient and adequately monitor to avoid the development of dependence [134,136]. Recently, Donoghue and colleagues report the interaction effect of cannabis use on gender and age of onset of schizophrenia and schizoaffective disorder. They show that use of cannabis is associated with an earlier age of onset of schizophrenia. There is a significant interaction between gender and cannabis use whereby the gender difference in age of onset is diminished in cannabis users [145].

Ziconotide

Ziconotide is a synthetic conopeptide that selectively inhibits N-type voltage-gated calcium channels, reducing the release of pain-modulating neurotransmitters. Conopeptides are derived from the venom of predatory cone snails, and ziconotide is specifically derived from the venom of a Pacific fish-hunting snail, Conus magus [146].

Ziconotide has been approved for intrathecal administration by continuous infusion for the treatment of severe chronic pain in situations where patients are not responding to conventional therapies [147]. Evidence indicates that this drug is useful in the treatment of both neuropathic and non-neuropathic pain. Intrathecal administration is required because, given intravenously, ziconotide demonstrates poor penetration of the blood brain barrier and results in sympatholytic effects leading to orthostatic hypotension [147]; oral preparations are not available. Ziconotide is highly hydrophilic and is thought to move slowly through the CSF to its target receptor, leading to a lag time to analgesia upon administration. The efficacy of ziconotide shows a wide inter-individual variation [147,148].

The most common side effects of ziconotide include dizziness, confusion, ataxia, memory impairment and hallucinations. However, there is also large inter-individual variation in the experience of side effects [147]. Toxicity appears to be related to the rate of infusion and is reversible after discontinuation, but, because of low tissue diffusion, the effects can persist for several weeks [147,148]. Data regarding ziconotide metabolism is sparse. The drug is not believed to be metabolized in the CSF but rather cleared by transport into the systemic circulation where it is degraded by serum proteases [147].

Novel therapies in pain management

Targeting epigenetic modifications

Epigenetics refers to functionally relevant genomic changes not involving alterations in nucleotide sequence, in response to developmental or environmental cues. Epigenetic mechanisms are manifested through dynamic, reversible chemical modifications in the genome and are involved in differential gene expression throughout life [149]. The most well characterized epigenetic modifications are DNA methylation and histone acetylation.

DNA methylation is regulated by DNA methyltransferases, while histone modifications are largely regulated by histone deacetylases (HDAC) [149]. Abnormal DNA methylation [150] and histone
acetylation [151,152] have been demonstrated to occur in pain states. It has also been proposed that primary injuries may result in lasting epigenetic marks leading to an increased risk of chronic pain [149], which may even persist trans-generationally. Drugs aimed at targeting the enzymes responsible for epigenetic modifications are under development and in some cases have been approved by the FDA. While these drugs have been developed largely for the purpose of cancer treatment, they are also believed to have potential in pain management. In animal injury models, rat hind-paw injection of Freund’s complete adjuvant (CFA) followed by intrathecal injection of zebularine, a DNA methyltransferase inhibitor, was shown to reduce pain sensitivity [153]. In a similar rat model, pre-injection treatment with HDAC inhibitors was reported to delay CFA-induced thermal hyperalgesia whereas post-injection treatment was shown to reduce the intensity of CFA-induced thermal hyperalgesia [154]. In human patients with type 2 diabetes, treatment with valproic acid, which is known to act as a strong HDAC inhibitor, conferred improved pain sensitivity scores after treatment compared to before treatment [155].

**Gene therapy**

Gene therapy involves the use of viral vectors where the viral genome is replaced with nucleic acid sequences encoding a promoter to drive gene expression as well as a transgene of interest [156]. For pain management therapies, the transgene encodes for an analgesic agent. Gene therapy based approaches have several advantages in pain management. In contrast to pharmacotherapies, gene therapy allows for persistent expression of a protein-based analgesic agent at the site of action. These methods avoid the first-pass effect and can improve bioavailability [156]. Gene therapy can also reduce side effects associated with systemic drug use. There are limitations to these approaches, including inadequate transgene expression and the evocation of immune responses against the viral vectors [156]. Nevertheless, new paradigms using non-viral insertion of therapeutic transgenes are under way to bypass some of these limitations.

In a recent study, terminal cancer patients were given different gene doses of human PENK, encoding preproenkephalin, the protein precursor that is processed to 6-met-enkephalin and 1-leu-enkaphalin, endogenous opioid peptide ligands for the delta opioid receptor [157]. Patients in the two highest virus dose groups reported decreases in numeric rating scale (NRS) pain scores of up to 50% from before treatment. Patients in the higher dose groups reported substantial reductions in pain compared to patients in the lowest dose group. This study demonstrates proof-of-concept for gene therapy in pain management.

**Therapeutic drug monitoring in pain management**

In pain management, the rationale for drug monitoring has largely focused on monitoring patient adherence, detecting diversion, and detecting the presence of illicit, non-prescription drugs. Traditionally, drug monitoring in pain management patients has been in the form of urine drug testing.

Urine drug testing has been demonstrated to reduce illicit drug use and has been widely used in monitoring patients in treatment for drug addiction [158,159]. However, most urine methodologies have been adapted from occupational deterrent-based testing for illicit drug use and have not been optimized for use in the pain management setting [160]. Given the chronicity of treatment drug administration, and the wide range of drug half-lives (Tables 1–5) a “positive” urine result is to be expected if a patient is adherent in taking his/her medication. A “negative” urine results suggests non-compliance with the treatment protocol or urine sample tampering. To be used effectively in monitoring pain management patients, urine drug testing requires understanding of the principles of drug pharmacokinetics and pharmacodynamics, and an understanding of the type of information urine drug testing can provide along with an appreciation of the limitations of such testing [161].

Urine drug concentrations are often calculated relative to urine creatinine concentrations in order to correct for in vivo dilution, which can vary through time, depending on an individual’s fluid intake. However, these calculations assume stable renal function and creatinine production, an assumption which can lead to errors if unjustified. Pain medications are usually prescribed to be taken in a chronic manner so that steady state plasma concentrations and therapeutic pharmacodynamic effects can be achieved. Steady state drug concentrations in serum imply that the urine excretion window (UEW) of the drug/metabolite is also at “steady state” in patients with stable renal function. Fig. 4 shows the concentration of methadone metabolite 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP) in a patient receiving methadone chronically. This figure clearly shows that urine creatinine correction does not add value to the EDDP adherence monitoring. Here, patient non-adherence can be detected when the urine EDDP concentration falls outside the UEW [162]. Extremely low creatinine concentrations are indicative of potential adulteration and can be useful in detecting specimens that have been tampered with [161]. Unfortunately, urine drug testing is not effective in estimating serum drug concentrations or assessing drug efficacy.

In light of the limitations associated with urine drug testing, monitoring of pain management patients through serum or plasma drug measurements has been advocated. Therapeutic drug monitoring

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**Fig. 4. EDDP urine excretion window at steady state.** Legend: *UEW urinary excretion window. The green lines represent the 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP) excretion window.*
[TDM] involves the measurement of serum or plasma drug levels at timed intervals to determine whether steady state drug concentrations are within the therapeutic or expected range given the drug dosage [163]. TDM can be used by clinicians to explain drug toxicity or lack of efficacy, and can aid in adjusting drug doses or in choosing specific medications [163]. A major advantage of plasma drug measurement is that it integrates many factors affecting drug metabolism, as outlined in Fig. 2. Half-life measurement can be a functional marker of the cumulative effect of pathophysiological and drug–drug interactions and provide an overall picture of the specific drug disposition and pharmacodynamics in the individual patient. However, TDM requires the collection of serial blood samples from patients, which can be difficult and inconvenient [160,163]. Timing of sample collection also becomes an important consideration, depending on whether peak or trough measurements (or both) are to be monitored. The time window within which a particular drug or its metabolite can be detected in serum is an important consideration for sample collection. To assist in appropriate clinical interpretation, knowledge of tolerance and pharmacokinetics of particular drug(s) under investigation is essential.

Summary and conclusions

The experience of chronic pain is one of the commonest reasons individuals seek medical attention, making the management of chronic pain a major issue in clinical practice. Left untreated, chronic pain can lead to diminished quality of life and socioeconomic difficulties. Opioids continue to be the mainstay of chronic pain management. However, opioid use can lead to abuse, diversion and physical dependence, meaning that opioids may not be suitable for all patients. An individual's risk for abuse should be considered, by way of a detailed history, before opioids are prescribed. Several non-opioid based therapies are now potentially available for these patients, such as triptans, ziconotide, as well as novel therapeutics, such as treatment with cannabinoids and, in the not-so-distant future, gene therapy or epigenetic-based approaches. Adjutant therapies with antidepressives, benzodiazepines or anticonvulsants can also be useful in managing pain, particularly in the treatment of anxiety and depression, which are commonly associated with chronic pain.

Genetic variability can have profound effects on drug metabolism and contribute to the inter-individual diversity in responses to pain medications. However, there is a paucity of evidence for the benefits of pharmacogenetic testing in the context of pain management. Drug metabolism and responses are affected by many factors, including pharmacogenetics, with genetics offering only a partial explanation of an individual's response.

At this point in time, therapeutic drug monitoring, through plasma drug measurements, may be more useful than pharmacogenetics in preventing adverse drug reactions to pain medications, while ensuring effective analgesia. Definitive, mass spectrometry based methods, capable of measuring parent drug and metabolite levels, are the most useful assays for this purpose. Drug half-life can be a functional marker of the cumulative effect of drug–drug interactions as well as pathophysiological interactions that may affect the treatment drug's disposition. Currently, monitoring of pain management patients, if performed at all, is largely through urine drug measurements, which do not correlate with serum drug concentrations therefore limiting their use in monitoring efficacy and toxicity. Direct determination of serum or plasma drug levels may provide a more clinically useful, if logistically more difficult, avenue for optimization of drug therapy, particularly in the context of chronic pain management.

References


