Expert Opinion

Extended-release opioids for the management of chronic non-malignant pain

Paul Sloan† & Najib Babul
†*University of Kentucky Medical Center, Department of Anesthesiology, 800 Rose Street, Suite N212, Lexington, KY 40536, USA*

Recent clinical trials have documented the use of extended-release (ER) opioids in the management of chronic non-malignant pain. This manuscript reviews the clinical pharmacology of investigational and current marketed ER opioids. Recent randomised clinical trials of ER opioids that document the efficacy and safety of opioid therapy for chronic pain are reviewed. Finally, the abuse liability of ER opioids is discussed. Current technologies aimed at defeating the abuse of ER opioids will also be presented.

Keywords: abuse deterrence, chronic pain, extended release, neuropathic pain, opioids, sustained release

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1. Introduction

Chronic pain is one of the most feared consequences of cancer and often adversely affects the quality of life of patients. Fortunately, a number of studies have demonstrated that use of the WHO guidelines can successfully ameliorate cancer pain in a majority of patients [1]. Clinical experience in England and early clinical trials have demonstrated the efficacy of immediate-release (IR) oral opioids in the treatment of cancer pain in the 1970s and 1980s [2,3]. The introduction of extended-release (ER) opioid analgesics has been widely viewed as a major advance in the management of chronic cancer pain. A number of clinical trials in cancer patients over the last 20 years have demonstrated the efficacy and safety of chronic oral ER opioids [4-7]. Widespread clinical experience and success with the use of opioid analgesics for the treatment of cancer pain led some to advocate their use in chronic non-malignant pain (CNMP) starting in the early 1990s. However, only recently have opioid analgesics been evaluated in well-controlled clinical trials in chronic pain of non-malignant origin.

CNMP is a major health problem that afflicts a significant number of patients, resulting in personal suffering, reduced productivity and substantial healthcare costs. According to the Institute of Medicine, musculoskeletal conditions such as lower back pain, osteoarthritis and myofascial pain are the leading causes of disability in individuals of working age. Recently, the Centers for Disease Control and Prevention issued revised estimates of the number of adults with arthritis and chronic joint symptoms to 70 million, a substantial increase over the previous estimate [8]. Total disability expenditures among US working adults cost the economy > $200 billion a year, and social security disability insurance benefits are far outstripping the increase in the working population who are insured for disability.

Although treatment for chronic pain is frequently initiated with non-opioid analgesics, many patients fail to get adequate pain relief with such agents. Consequently, opioid analgesics are often used either alone or as an add-on therapy in such patients. Data from published clinical trials support the safety and efficacy of opioid analgesics in patients with chronic pain [9,10]. In the past, a concern of clinicians treating chronic pain with opioids was the risk of addiction. The current consensus view is

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that, except in individuals who have a previous history of substance abuse, addiction is not a common observation in carefully screened patients who take opioids to control chronic pain [11]. This shift in attitude, although not universally embraced, has fundamentally changed the treatment landscape for patients with chronic pain.

The purpose of this paper is to review oral ER opioids that may help in the management of CNMP, focusing on recent clinical trials that suggest the benefits and limitations of current practice.

2. Pharmacology of extended-release opioids

Opioids have been used as analgesics for several millennia, and long before opioid receptors were discovered in animals and humans in the early 1970s. Opioids act on three separate CNS receptors: μ, δ and κ, coupling with G proteins and producing analgesia via decreased neuronal neurotransmitter release and decreased nociceptive impulse propagation [12]. Morphine is the prototypical opioid acting at the μ-receptor producing analgesia, as well as side effects such as constipation, respiratory depression, nausea, vomiting, sedation and cognitive dysfunction.

Available oral ER opioids in the US include morphine (every 12 and 24 h) and oxycodone (every 12 h). A hydromorphone ER every 24 h capsule formulation was recently withdrawn from the market by the manufacturer due to concerns of significant dose dumping when co-ingested with large amounts of alcohol. A hydromorphone ER tablet formulation is presently under investigation. Other ER opioids that are the subject of clinical investigation or available in other countries include codeine, oxymorphone, tramadol and dihydrocodeine. The basic pharmacology of each of these opioids will be briefly reviewed in this section. Several opioids, important in the management of chronic pain, will not be included in this paper as they are not available as ER opioids. These other opioids include:

- fentanyl, a short-acting intravenous opioid that is widely used in a long-acting transdermal patch applied every three days;
- methadone, a long-acting oral opioid with an elimination half-life of ~ 1 day;
- levorphanol, a long-acting oral opioid with a half-life of 12 h.

Other opioids that are available either as oral or intravenous preparations but that are not currently under investigation as ER opioids include meperidine, sufentanil, remifentanil and alfentanil. There are several opioids that behave as partial agonists-antagonists with a ceiling effect and have very limited use in the management of chronic pain: butorphanol, nalbuphine and pentazocine. These medications will not be reviewed in this manuscript.

Morphine is the most extensively studied opioid and is the prototype of all pure μ-agonist opioids used in the management of chronic pain [13]. IR oral morphine has a bioavailability of 30 – 60%, with significant biotransformation on its first-pass through the liver. Morphine is extensively metabolised in the liver, primarily to morphine-6-glucuronide (M6G) and morphine-3-glucuronide (M3G). M6G is an opioid agonist, producing analgesia, whereas M3G has been implicated as a neuroexcitatory metabolite. Both M3G and M6G accumulate in patients with renal impairment. Oral IR morphine has a peak effect of 1 h, with a half-life of 3 – 4 h and similar duration of action. Morphine, along with most opioids, should be used more cautiously in patients with extensive liver or renal disease. Any CNS depressant or intracranial process that results in sedation may potentiate the sedative side effect of morphine and other opioids.

Oxycodone is a widely used semisynthetic opioid with an excellent oral IR bioavailability of 60 – 87% and less absorption variability than morphine [14]. It is a μ-opioid agonist with some κ-receptor activity as well, and oral IR oxycodone has a peak effect of 1 h with a duration of action of 3 – 4 h. It is extensively metabolised in the liver by CYP enzymes, with a consequence that common medications may increase or decrease (e.g., fluoxetine) its metabolism. A minor active metabolite of oxycodone is the opioid oxymorphone. It is unlikely that oxymorphone contributes significantly to the analgesic activity of oxycodone [15].

Hydromorphone is structurally very similar to morphine and acts at the μ, and to a lesser degree at the δ, opioid receptor. The oral IR preparation is widely used as an analgesic with a bioavailability of ~ 30% after extensive first-pass liver metabolism. Oral IR hydromorphone has a peak effect of 45 min, with a duration of action of 3 – 4 h. The 3-glucuronide metabolite of hydromorphone may be responsible for some neurotoxicity but there do not seem to be any active analgesic metabolites [16].

Codeine IR is widely used in fixed-dose combinations with acetaminophen for the treatment of acute and chronic pain. Codeine itself is a poor μ-receptor agonist. Its binding to the μ-receptor is ~ 1/4000th that of morphine and intracerebroventricularly administered codeine is virtually devoid of analgesic effects. When given orally, codeine is principally metabolised to codeine-6-glucuronide, norcodeine and morphine [17]. At steady-state, the percentage ratio of the AUC for morphine relative to codeine is ~ 30% [17]. The demethylation of codeine to morphine is mediated by CYP2D6, which shows considerable polymorphism in the Caucasian population. Of Caucasians, ~ 4 – 7% have a polymorphic gene for CYP2D6, making those poor metabolisers for codeine to morphine. Studies in experimental pain suggest that both poor metabolisers of codeine (to morphine) and extensive metabolisers of codeine who have their CYP2D6 inhibited (e.g., with quindine) demonstrate a suboptimal antinociceptive effect (hypoalgesia) after oral codeine administration [18,19]. Thus, codeine substantially exerts all of its analgesic effect through biotransformation to morphine and M6G.

Oxymorphone is a semisynthetic opioid with μ-opioid receptor selectivity. Currently, oxymorphone is only available

Table 1. Characteristics of opioid analgesics that are suitable for ER formulation and potential benefits to patients with chronic pain.

Properties of IR opioids that support ER opioid development	Potential benefits of ER opioid formulations in chronic pain
Short duration of effect	Improved convenience
Large peak to trough fluctuation in plasma concentrations	Improved compliance
	Improved pain control
Peak-related toxicity	Reduced side effects
Narrow therapeutic index	Reduced pill burden
Night-time pain	Reduced night time pain
High pill burden	Improved sleep

ER: Extended release; IR: Immediate release.

as a parenteral and suppository formulation. Oxymorphone has been under investigation as an oral IR and ER formulation [20,21]. It is metabolised in the liver by glucuronidation with at least one metabolite showing some analgesic activity [20] but does not interact with CYP enzymes [21]. A possible disadvantage is that among the oral opioids, it has the lowest bioavailability, ~ 10%.

Tramadol is an interesting oral opioid with two mechanisms of analgesic activity: μ-opioid agonism and re-uptake inhibition of serotonin and noradrenaline [22]. Tramadol is well absorbed orally with a peak analgesia at 2 h and a duration of analgesia of 4 – 6 h. Tramadol is metabolised in the liver to an active metabolite that has greater affinity for the μ-opioid receptor than the parent compound [23]. Of clinical interest, tramadol may cause seizure activity in a minority of patients and should be avoided in patients with a history of stroke, head injury, or those receiving serotonin re-uptake inhibitors [24].

Dihydrocodeine IR is available in Europe as an opioid analgesic that is related to codeine. It is well absorbed orally and is metabolised in the liver, yielding an active metabolite dihydromorphine, which contributes little to the analgesic activity of dihydrocodeine [25].

Table 1 provides the pharmacological characteristics that support the development of ER opioids and potential benefits that can be derived from such ER opioid formulations. ER opioids seek to provide patients with improved compliance, reduced side effects, enhanced quality of life and more constant pain relief compared with IR opioid preparations. Clinical trials comparing ER opioids with comparable IR opioids, however, often show little difference with regard to pain relief or side effect profile [2,5,26]. Nonetheless, the convenience of once or twice daily dosing is appreciated by patients and the ER formulation is often much preferred to the IR dosing in the setting of chronic pain [27].

3. Extended-release opioids for chronic pain management

Morphine was the first oral opioid to be prepared in an ER formulation and shown to be effective and safe in the management of chronic cancer pain [4]. Oral ER morphine use in the management of CNMP has been studied over the past 15 years; however, a review paper from 2004 [11] found only six studies of oral morphine with at least 10 patients in each group, and following a randomised, double-blind protocol. Two more randomised controlled trials have been added to this number, along with several open-label, randomised clinical trials. Moulin and colleagues published the first significant randomised, active placebo, double-blind clinical trial of ER morphine [28]. A total of 46 patients with chronic musculoskeletal pain underwent treatment for 5 weeks each, followed by crossover to the other treatment. Patients showed modest reductions in pain intensity on 12-h morphine (doses titrated up to 120 mg) compared with placebo; however, functional status did not change. Caldwell and colleagues demonstrated pain relief in a randomised, placebo-controlled, double-blind trial with both a 12- and a 24-h preparation of morphine in patients with grade II – IV osteoarthritis [29]. This large trial included ~ 75 patients in each treatment group using doses of morphine 30 mg/day p.o. The 24-h morphine preparation showed greater improvement in quality of sleep, compared with the 12-h preparation. A potential criticism of this study is that the daily morphine dose was low. A recent large (680 patients) open, randomised clinical trial among patients with chronic lower back pain showed pain relief with oral ER 12-h morphine titrated to effect [30]. Followed over 13 months, pain relief was accompanied by patient improvement in physical function and no cases of addiction were noted [30]. Side effects were frequent, but minor, with expected symptoms, such as constipation, nausea, vomiting and somnolence.

At least eight randomised, double-blind clinical trials for CNMP have been completed with ER oxycodone during the past decade. Watson and Babul evaluated 38 patients with postherpetic neuralgia using a placebo-controlled, double-blind crossover trial design [31]. Oxycodone ER was titrated to pain relief with a maximum dose of 30 mg every 12 h. It had been previously thought that neuropathic pain was resistant to opioid analgesia; however, compared with placebo, patients on oxycodone ER achieved statistically significant pain relief [31]. Importantly, oxycodone ER was effective for all

dimensions of pain seen in peripheral neuropathy, including ongoing pain, allodynia and paroxysmal spontaneous pain. Global effectiveness, disability and blinded patient preference all favoured oxycodone ER over the placebo. Two subsequent, controlled studies have also demonstrated the analgesic efficacy of oxycodone ER for the management of painful diabetic neuropathy [32,33]. Gimbel and colleagues, using a randomised controlled trial for 159 patients with diabetic neuropathy, found ER oxycodone to be effective for pain relief over a 6-week trial with typical opioid-related adverse effects [32]. A recent 107 patient randomised controlled trial in osteoarthritis demonstrated that oxycodone ER provided significantly better pain relief, improved physical function (walking, work, sleep and so on) over a 3-month period [34].

Hydromorphone ER was first studied for the treatment of CNMP using a 24-h preparation in an open-label study over a 2-week period [35]. Patients (404) already receiving chronic opioids were easily converted and pain relief was titrated to a maintenance dose of 24-h ER hydromorphone. A recent randomised controlled trial used a crossover design (1 week for each arm) for patients with CNMP, and found comparable analgesia and side effect profile comparing the 24-h ER hydromorphone with the IR preparation [36]. The authors hope that a new improved formulation of hydromorphone ER will be returned to the market.

Codeine ER has been evaluated in a handful of clinical studies for the management of CNMP. One randomised controlled trial of 66 patients with osteoarthritis demonstrated improvements in pain, physical function and patient global evaluation compared with placebo [37] over a 1-month trial. Oxymorphone ER has been evaluated in two recent randomised controlled trials in osteoarthritis and chronic lower back pain. In one 4-week study of 491 patients with grade II – IV osteoarthritis and moderate-to-severe pain, oxymorphone ER was compared with oxycodone ER and placebo [38]. Oxymorphone ER was superior to placebo for arthritis pain intensity, physical function, patient global evaluation and measures of sleep, whereas oxycodone ER, in contrast to several previous positive studies, was not significantly better than placebo on the primary end point. In another randomised controlled trial of oxymorphone ER versus oxycodone ER and placebo in 213 patients with chronic lower back pain, both oxymorphone ER and oxycodone ER provided superior pain relief compared with placebo. The safety profile of oxymorphone ER was comparable with oxycodone ER [39].

Tramadol ER has been investigated recently for the management of CNMP. As tramadol IR has been used for many years in the management of both acute and chronic pain, tramadol ER may represent an important new therapeutic option in the treatment of chronic pain. Four clinical trials have recently been published with different formulations of tramadol ER, with at least two double-blind randomised controlled trials. Babul and colleagues evaluated 246 patients using tramadol ER (24-h dosing) for osteoarthritis pain over 3 months compared with placebo [40]. The mean tramadol dose was 276 mg, and tramadol ER provided superior pain relief, physical function scores, patient global evaluation and improvements in sleep, compared with placebo. In a similar European study over 2 weeks, a different formulation of tramadol ER (24-h dosing) significantly reduced pain compared with placebo in patients with osteoarthritis [41].

Typical opioid side effects are seen with all opioid ER formulations to date. Most patients have opioid side effects that are easily managed with dose reduction, medical management, such as with the use of laxatives, or opioid rotation [42]. Occasionally, opioid-induced sedation may be managed with dose titration or with the use of medications such as donepezil [43]. Several recent papers have addressed the issue of patients driving while taking chronic opioid medications. Most investigators conclude that there is no impairment of psychomotor abilities or of cognitive functioning in opioid-maintained patients [44], which supports the contention that patients on opioids may be allowed to drive after a period of stable dosing.

4. Abuse liability of extended-release opioids

Over the past decade, there has been a growing recognition about the undertreatment of CNMP, which has had significant adverse impact on the quality of life of patients. The availability of ER formulations of opioids combined with evidence-based support for their use has led to increased opioid use in the CNMP population. This has, in turn, resulted in growing concerns about the risk of iatrogenic addiction from long-term opioid therapy. The misuse of ER opioids is partly due to the relatively large dose of drug per tablet, compared with IR opioids.

The terms physical dependence, psychological dependence (addiction) and tolerance are often used inconsistently, resulting in considerable misunderstanding among clinicians, patients and regulators. In order to meaningfully discuss abuse liability, the authors believe that it is important to define the relevant terms. Physical dependence is characterised by an abstinence syndrome following the abrupt cessation of an opioid or following administration of opioid antagonists. Physical dependence to opioids is to be expected with long-term opioid therapy at therapeutic doses. In such patients, symptoms of opioid withdrawal can be avoided or minimised by gradually tapering the dose of an opioid [45]. Psychological dependence (addiction), on the other hand, is a behavioural syndrome that is characterised by an intense desire for the opioid, evidence of compulsive use, and acquisition of opioids by manipulation of the medical system or from a non-medical source [46]. According to the American Academy of Pain Medicine, the American Pain Society and the American Society of Addiction Medicine [101], addiction is a neurobiological disease that is characterised by behaviours with at least one of the following: impaired control over drug use, compulsive use, use despite harm and craving for the drug. Tolerance is a phenomenon resulting from continued exposure to the drug, resulting in a decreased pharmacological effect over time.

The use of opioids for non-medical purposes has existed throughout recorded human history. Pharmaceutical dosage forms containing opioids have been used for non-medical purposes in a variety of settings:

- by patients with pain who have developed an addiction disorder following initiation of opioid therapy;
- by patients with pain who had a pre-existing addiction disorder;
- by patients with an addiction disorder seeking opioids for their non-analgesic properties;
- by recreational drug users seeking episodic mood-altering effects of opioids.

Experience with the use of opioid analgesics in cancer pain and, more recently, in patients with CNMP indicates that in patients with no prior history of drug abuse, the risk of addiction to opioids is low [10]. Our increased understanding of the clinical pharmacology of opioids and data from well-controlled clinical trials have resulted in their more widespread use in patients with non-cancer pain. This, in turn, has led to concerns about the increased non-medical use of opioids through both licit and illicit channels. For instance, unsuspecting clinicians may prescribe opioids for pain to individuals with an addiction disorder or individuals with pain who divert a portion of their prescribed dose to other persons. There have also been documented cases of inappropriate prescribing or dispensing of opioids by physicians and pharmacists, with its eventual diversion into the non-medical marketplace. In addition, the non-medical supply of pharmaceutical-grade opioids is often achieved through prescription forgeries and theft from pharmacies.

Non-medical users of opioids analgesics are either recreational drug users who may use such agents episodically, or individuals with an addiction disorder who may require frequent maintenance doses. Opioid analgesics may be ingested whole, crushed and ingested, crushed or vaporised and inhaled, or injected intravenously after attempted extraction of the active pharmaceutical ingredient.

The introduction of oxycodone ER and its widespread prescription for the treatment of CNMP was also associated with its diversion into the non-medical supply for use both by addicts and recreational drug users. The popularity of ER oxycodone among addicts and recreational drug users was, at least in part, due to the relatively large dose of drug per tablet (a 12- or 24-h supply). Commercially available IR opioid tablets and capsules are usually administered every 4 – 6 h and they release their dose into the systemic circulation over 1 – 2 h. New ER formulations are designed to gradually release their much larger opioid content over a 12- or 24-h period. Most recreational drug users and addicts have a unit of use that is one tablet or capsule. The 12- or 24-h supply of opioid that is contained in one tablet or capsule, instead of 4 – 6 tablets or capsules, means that there is a greater risk that such formulations may be highly sought by recreational drug users for non-medical use. Intentional or inadvertent tampering of ER formulations will rapidly deliver a massive opioid dose and produce a variety of serious and life-threatening side effects, including respiratory depression and failure, sedation, cardiovascular collapse, coma and death. However, the popularity of oxycodone ER among addicts and recreational users cannot be explained by the large amount of drug per tablet alone, as both every 12- and every 24-h morphine ER formulations were also commercially available at that time. Others have suggested that the popularity of oxycodone ER among drug abusers may have been a consequence of its differential pharmacology, including its effects at both the μ- and κ-opioid receptors.

5. Pharmaceutical strategies to deter abuse of extended-release opioids

Although the diversion and non-medical use of pharmaceutical opioids involves both IR and ER opioids, there is presently little in the way of new pharmaceutical development work with IR opioids. Consequently, much of the attention in the area of abuse deterrent pharmaceutical development has focused on ER opioids, particularly in light of the total amount of drug per tablet or capsule, and the recent experience with oxycodone ER. Pharmaceutical companies also understand that the incorporation of abuse deterrence technology into new ER formulations of opioids may facilitate the approval, safety and commercial success of their ER products.

A number of strategies have been introduced to minimise the abuse of opioid analgesics. Primary among these schemes is a legal infra-structure that controls the manufacture, distribution and sale of such drugs. Excessive controls on the manufacture, distribution and particularly the sale of opioids has the unintentional effect of causing physicians, fearful of being accused of permitting opioid overuse, to prescribe suboptimal doses of opioids to patients or to prescribe unscheduled and less effective drugs. This phenomenon is described in the literature as opiophobia or narcophobia [47].

It is evident that controls on the manufacture, distribution and sale of opioids alone are not adequate to deter the abuse of opioid analgesics. Several pharmaceutical strategies have been proposed to deter the abuse of ER formulations of opioid analgesics which contain a 12- or 24-h supply of opioid per dosage. These strategies include:

- formulations that contain a sequestered, orally bioavailable opioid antagonist that is released only following product tampering (e.g., crushing, extraction);
- formulations that contain a sequestered aversive agent that is released only upon product tampering (e.g., crushing, extraction);
- formulations that deter abuse by resisting crushing and drug extraction with the use of common solvents;
- development of covalently bound inactive moieties that modulate the absorption and/or biotransformation of the opioid moiety.

Initial pharmaceutical attempts to deter or minimise the abuse of orally administered opioids occurred prior to the advent of

ER opioids. These attempts generally focused on the inclusion in the oral dosage form of an opioid antagonist, which was not orally active, but that substantially antagonised the analgesic effects of the opioid when attempts were made to dissolve the opioid and administer it parenterally. A further evolution of this strategy involved the inclusion in the oral dosage form of a sequestered, orally bioavailable opioid antagonist, which is released only following product tampering (e.g., crushing, extraction). In this circumstance, the opioid antagonist is not expected to be orally active under normal conditions of its use, but would nullify the euphoriant effects of either oral or intravenous administration following product tampering. For instance, pentazocine, a synthetic opioid, was crushed, extracted and injected intravenously by drug addicts. When this practice became widespread, the manufacturer of pentazocine reformulated the dosage form to incorporate a small amount of the opioid antagonist, naloxone. When taken orally, naloxone is rapidly and almost completely biotransformed on its first pass through the liver to an inactive metabolite. Consequently, small doses of naloxone could be safely administered orally without antagonising the analgesic effects of pentazocine. However, intravenous administration of reformulated pentazocine containing naloxone would either nullify the euphoriant effects of pentazocine or precipitate a characteristic abstinence syndrome in opioid tolerant individuals. Similar approaches have been used with tilidine and naloxone, and buprenorphine and naloxone. A major disadvantage of this approach was its limitation to deterring opioid abuse only by the parenteral route of administration.

The use of a sequestered opioid antagonist in ER formulations, especially in multiparticulate capsule formulations, represents an advance over the basic technology as, in theory, it can deter the abuse by both the oral and parenteral routes of administration. A variant of this approach involves the use of a sequestered aversive agent, such as capsaicin or resiniferatoxin, both of which are extremely pungent when placed in contact with the oral or nasal mucosa. A potential drawback with the incorporation of a sequestered opioid antagonist into an ER opioid agonist preparation is that if a tampered product is used by an addict, even small doses may precipitate an abstinence syndrome in opioid tolerant patients, resulting in drug withdrawal. Symptoms of opioid withdrawal can include body aches, diarrhoea, gooseflesh, loss of appetite, nervousness or restlessness, runny nose, sneezing, tremors or shivering, stomach cramps, nausea, trouble with sleeping, increased sweating, increased yawning, weakness, increased heart rate or fever. An opioid abstinence syndrome can be severe, requiring hospitalisation and reinstitution of the opioid agonist. Similarly, abuse deterrent pharmaceutical compositions containing sequestered aversive substances have the potential to cause harm to subjects if injected intravenously. Such formulations are likely to release at least small amounts of the sequestered aversive agent and the safety of such aversive substances are not known.

Alternative ER abuse deterrent systems generally operate by resisting crushing and chemical or physical opioid extraction. Such formulations are difficult to tamper with and are generally designed to form a viscous substance following contact with a solvent such that the opioid agent cannot be easily filtered or drawn into a syringe for intravenous drug abuse. They are also resistant to extraction with common solvents, including alcohol. A potential advantage of such a passive abuse deterrent system is that it may protect both medical and non-medical users of opioids from intentional or unintentional opioid toxicity, without unnecessary harm to either group from the abuse deterrent technology. Of all the abuse deterrent formulations that are described in this paper, an ER oxycodone (Remoxy™; DURECT Corporation, Pain Therapeutics) using the passive technology described above is probably the most advanced. Other approaches to abuse deterrence include the use of opioids that are covalently bound to other substances to produce inactive moieties that become active only on contact with the gastrointestinal milieu or through biotransformation *in vivo*.

Recently, a serious new clinical problem has arisen with the therapeutic use of ER opioids, particularly ER-encapsulated spheroids, when co-ingested with alcohol. In this setting, the opioid analgesic was being used for legitimate medical purposes (e.g., to treat pain) and was being ingested as an untampered or intact formulation. Although subjects with chronic pain are discouraged from using opioids with alcohol, the co-ingestion of opioids with alcohol, especially in the setting of intractable pain is widespread. The problem was discovered with a once-daily ER formulation of the opioid hydromorphone hydrochloride (Palladone® capsules; Purdue Pharma). Palladone capsules were introduced in the US and Canada in 2004 [48]. In 2005, Palladone capsules were withdrawn from the market in both countries due to concerns of dose dumping when co-ingested with alcohol [49]. In a 24-subject study, patients consuming 40% ethanol 240 ml had a 6-fold mean increase in peak plasma hydromorphone concentration compared with co-ingestion of Palladone capsules with water [102]. One subject experienced a 16-fold increase when the drug was ingested with 40% alcohol compared with water. In requesting the withdrawal of Palladone capsules, the FDA noted that the manufacturer of Palladone provided the FDA with data that showed that 'drinking alcohol while taking Palladone capsules may cause rapid release of hydromorphone, leading to high drug levels in the body, with potentially fatal effects' [103].

Since then, the FDA has noted that a number of other encapsulated spheroid formulations of ER opioids may be similarly vulnerable to dose dumping when co-ingested with alcohol. *In vitro* studies performed by the FDA have demonstrated that when Avinza® 30 mg (once-daily ER morphine; Elan) was mixed with 900 ml of buffer solutions containing ethanol, the dose of morphine that was released was alcohol concentration dependent. Although the relevance of *in vitro* lab tests regarding Avinza to the clinical setting remains to be determined, this acceleration of morphine release may correlate with *in vivo* rapid release of the total morphine dose,

which could result in the absorption of a potentially fatal dose of morphine [104]. A number of proposed abuse deterrent ER opioid formulations involving sequestered opioid antagonists or aversive agents involve capsule-based spheroid formulations that may also be vulnerable to dose dumping when co-ingested with alcohol. In contrast, the passive abuse deterrent systems described above have the effect of providing protection against alcohol-induced dose dumping in the therapeutic setting.

6. Conclusion

In summary, data from well-controlled clinical trials with a variety of ER opioids demonstrate their efficacy in patients with a variety of chronic painful states, including osteoarthritis, chronic lower back pain, postherpetic neuralgia and painful diabetic neuropathy. The most recent randomised clinical trials of opioids analgesics have ranged in duration from 4 to 12 weeks, followed by open-label treatment. Painful neuropathic conditions have been successfully treated with chronic ER opioids that were previously thought to be resistant to opioid therapy. Current ER opioids include morphine and oxycodone, with the development of ER preparations underway for codeine, oxymorphone, tramadol and hydromorphone.

Recent experience with oxycodone ER suggests that ER formulations have the potential to be abused. When the timed-release mechanism of such formulations is defeated, the entire 12- or 24-h dose of the opioid may be released, presenting an increased risk to patients who inadvertently crush the formulation, to opioid tolerant addicts and to recreational drug users. Recreational drug users are probably the most vulnerable population, as such subjects are likely to be opioid naive and, therefore, more prone to serious and life-threatening opioid toxicity.

7. Expert opinion

The treatment of chronic pain with ER opioids will be aided by the development of new, alternative opioids in an ER formulation. Rotation of opioid therapy is a well-accepted practice to achieve optimal pain relief without undue side effects. The use of opioid rotation as a strategic intervention is hampered with the lack of alternative ER opioid formulations. It is critical that the treating physician should regularly monitor the patient for signs of adequate pain relief, side effects and any suggestion of opioid misuse or diversion.

A variety of abuse deterrent technologies for use with ER opioid formulations are being developed. With few exceptions, these technologies are in their infancy and each approach has its theoretical advantages and disadvantages. Although abuse deterrence is probably an achievable goal, there are several important issues to keep in mind:

- the introduction of abuse-deterrent formulation may simply shift the problem of opioid abuse to other low-cost non-deterrent formulations;
- the ultimate use of these abuse-deterrent strategies may only become apparent through postmarketing surveillance of several formulations with competing technologies;
- the ingenuity of individuals who abuse drugs and their ability to defeat the abuse-deterrent formulations should never be underestimated;
- the introduction of abuse-deterrent formulations has significant potential economic implications on patients and third-party payers (e.g., what is an appropriate price differential between an abuse deterrent and a non-deterrent for every 12-h formulation of oxycodone?);
- abuse deterrence technologies should never be confused with abuse resistance technologies.

Conflict of interest

P Sloan has no current financial relationship or interest with any organisation relevant to this review paper. During the past two decades, he has been on the Speaker's Bureau of Purdue, Knoll, Janssen and Endo Pharmaceuticals.

N Babul works at TheraQuest, a pharmaceutical company that is involved in the development of opioid and non-opioid analgesics for acute and chronic pain. He has consulted with a variety of pharmaceutical companies that are involved with the development of analgesics.

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Affiliation

Paul Sloan[†1] MD & Najib Babul[2] PharmD
[†]Author for correspondence
[1]Professor of Anesthesia, University of Kentucky Medical Center, Department of Anesthesiology, 800 Rose Street, Suite N212, Lexington, KY 40536, USA
Tel: +1 859 323 5956;
Fax: +1 859 323 1080;
E-mail: paulsloan1956@yahoo.com
[2]Chief Executive Officer, TheraQuest Biosciences, Blue Bell, PA, USA