

Abuse-Deterrent and Tamper-Resistant Opioid Formulations

What is their Role in Addressing Prescription Opioid Abuse?

Jennifer P. Schneider,¹ Michele Matthews^{2,3} and Robert N. Jamison³

1 Arizona Community Physicians, Tucson, Arizona, USA

2 Massachusetts College of Pharmacy and Health Sciences, Boston, Massachusetts, USA

3 Pain Management Center, Departments of Anesthesia and Psychiatry, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA

Abstract

About one in every three individuals will experience chronic pain in their lifetime, and opioids are known to be an effective means to treat this condition. Much attention, however, has been given to the fact that prescription opioid analgesics are some of the most frequently abused drugs, and misuse is prominent in patients with chronic pain. Several new opioid formulations that are designed to prevent or deter the abuse of opioids are currently in development, and two have been approved for marketing (morphine sulphate co-formulated with naltrexone hydrochloride [Embeda[®]] and a new formulation of the extended-release oxycodone [OxyContin[®]]).

In this article, we review the various types of abuse-deterrent and tamper-resistant formulations in clinical development. We believe that continued advances in opioid formulations can help mitigate risk for those with legitimate need for pain control, but only if used rationally in the context of good clinical practice.

1. Background

1.1 The Burden of Pain

Epidemiological studies have independently documented that chronic pain is an immense international problem.^[1-3] Symptoms of pain are experienced by more than 90 million Americans (about one-third of the US population), and pain affects more Americans than diabetes mellitus, heart disease and cancer combined.^[4] Chronic pain accounts for 21% of emergency department visits and 25% of annual missed workdays in the US. Including both direct and indirect costs, chronic pain is estimated to be responsible for up to \$US100 billion in annual costs, imposing the greatest economic burden of any condition.^[5-8]

While acute pain can be treated effectively with pharmacological therapies, the treatment of chronic pain remains a challenge and can be further complicated by the presence of patient risk factors for medication misuse, abuse or addiction.

1.2 Opioid Therapy: Balancing Need versus Risk of Abuse

Since 1998, the prescribing of opioids such as methadone, fentanyl, oxycodone and hydrocodone has increased significantly.^[9] The rate of unintentional drug overdose deaths has risen simultaneously, with opioids contributing to almost 12 000 such deaths between 1999 and 2006.^[10] This increase in opioid use may be due in part to

support from professional organizations that encourage their use as part of a comprehensive treatment plan, along with the increasing number of patients seeking treatment for chronic pain.^[11,12]

There is mounting evidence to support the efficacy of opioids for chronic pain:^[13-18] however, the abuse liability of these products has fuelled a controversy that is difficult for many clinicians to navigate. There remains a split between clinicians who believe opioids are over-prescribed, leading to widespread abuse and addiction, and those that believe they are under-prescribed, leading to the massive under-treatment of legitimate pain. This argument masks one major underlying point: the importance of proper patient selection. The decision to initiate opioid therapy should be based on a comprehensive patient assessment accompanied by risk assessment to identify behaviours that may signal future issues with opioid use. This approach, combined with continual monitoring and exit strategies, is essential for the successful long-term management of patients receiving opioid therapy.^[19,20]

Efforts have been made to develop abuse-deterrent and tamper-resistant opioid formulations to reduce opioid abuse among patients and those who acquire them by diversion. With the emergence of these opioid formulations, clinicians are now faced with additional questions regarding their ability to actually deter abuse, how to integrate these new formulations into clinical practice and the means to identify which patients are appropriate candidates for this therapy. Nonetheless, these agents are now available, and the pipeline of similar products is growing. In this review, we describe the abuse-deterrent and tamper-resistant mechanisms for these products and discuss the evidence supporting their use for the treatment of chronic pain and reduction of opioid abuse.

2. Formulations of Oral Prescription Opioids Designed to Prevent or Deter Abuse

2.1 Overview and History of Abuse-Deterrent and Tamper-Resistant Formulations

Abuse-deterrent formulations are those that do not necessarily resist tampering but contain

substances that are designed to make the formulation less attractive to abusers. Examples of these formulations are Suboxone[®] (buprenorphine co-formulated with the opioid receptor antagonist naloxone), Embeda[®] (an extended-release morphine co-formulated with the opioid receptor antagonist naltrexone), ELI-216 (an extended-release oxycodone co-formulated with naltrexone) and Acurox[®] (an immediate-release oxycodone co-formulated with an aversive agent [niacin]). Tamper-resistant formulations are not co-formulated with an antagonist or aversive agent but are designed to be very difficult to crush or dissolve and thus would prevent chewing, snorting or injecting the medication. Examples include Remoxy[™], COL-003 and the re-formulation of OxyContin[®], all of which are extended-release formulations of oxycodone, and TQ-1017, which is an extended-release formulation of tramadol.

One of the first abuse-deterrent formulations to be introduced to the market was Suboxone[®], an oral opioid formulation that combines buprenorphine and naloxone at a 4:1 ratio. It was developed in response to the increased abuse of Subutex[®], the original buprenorphine formulation used for opioid substance abuse treatment. Suboxone[®] was approved by the US FDA in October 2002. Controlled studies in subjects addicted to opioids suggested that Suboxone[®] produced either no euphoria or unpleasant withdrawal symptoms when taken intravenously.^[21-26] Therefore, as a result of the lower abuse liability in opioid-addicted individuals, most countries have now mandated that substance abuse treatment centres prescribe Suboxone[®] instead of Subutex[®]. However, the diversion of Suboxone[®] can increase the risk of abuse for nonmedical purposes, particularly because it can produce euphoria if injected in people not physically dependent upon opioids.^[27]

2.2 New Formulations for Pain

In sections 2.2.1–2.2.4, we review current and investigational abuse-deterrent and tamper-resistant formulations for the treatment of pain (table I).

Table 1. List of new formulations that aim at deterring or preventing opioid misuse and abuse

Current name	Active drug	Type of formulation	Manufacturer
Remoxy™	Oxycodone (extended release)	Gelatin capsule containing highly viscous liquid	Pain Therapeutics King Pharmaceuticals
COL-003	Oxycodone (extended release)	Multi-particulate matrix with particles in waxy excipient base	Collegium Pharmaceutical Inc.
ELI-216	Oxycodone (extended release)	Capsule containing separate oxycodone and naltrexone pellets	Elite Pharmaceuticals
Unknown (reformulation of OxyContin®)	Oxycodone (extended release)	Hard polymer that transforms into a viscous gel with hydration	Purdue Pharma
Embeda® (ALO-01)	Morphine (extended release)	Pellets of morphine surrounding an inner core of naltrexone	King Pharmaceuticals
TQ-1017	Tramadol (extended release)	Transforms into viscous substance in the presence of solvents	TheraQuest Biosciences
Acurox®	Oxycodone (immediate release)	Co-formulated with subtherapeutic doses of niacin	Acura Pharmaceuticals King Pharmaceuticals

2.2.1 Extended-Release Oxycodone

Remoxy™ (Pain Therapeutics, San Mateo, CA, USA and King Pharmaceuticals, Bristol, TN, USA) is an extended-release formulation of oxycodone contained in a highly viscous liquid formulation matrix. The capsule is intended to resist abuse by crushing, by freezing and crushing, or by dissolution in water, alcohol or other common liquids. The gel is a viscous mass of sucrose acetate isobutyrate, a common food additive with a taffy-like consistency, that is designed to be difficult to snort or inject.^[28] The intent of this formulation is to prevent oxycodone 'dumping' from the capsule when it is ingested with alcohol, common solvents or aqueous buffers across a wide range of pH, rendering oxycodone extraction from this formulation substantially more difficult. Remoxy™ has not been studied in head-to-head trials with other extended-release opioids; therefore, it is unknown if the formulation sustains or reduces the efficacy of oxycodone and if the tamper-resistant mechanism contributes to tolerability issues such as gastrointestinal distress. The manufacturer intends to submit to the FDA a new drug application (NDA) for Remoxy™ in 2010 after gathering additional stability data.

Another tamper-resistant product is a reformulation of OxyContin® (Purdue Pharma, Stamford, CT, USA). This product was approved for marketing in April 2010 and is based on a polymer that makes tablets difficult to break or crush. If hydrated, the formulation transforms

into a viscous gel that resists extraction of oxycodone for injection. This formulation holds some promise. Very little published data on this formulation are available; however, the manufacturer will be required to conduct postmarketing studies on the extent of misuse and abuse of the new formulation and will have a Risk Evaluation and Mitigation Strategy (REMS) that requires a medication guide to be dispensed with the prescription along with required prescriber education on the use of opioids for pain.^[29]

Additional formulations of extended-release oxycodone in the pipeline include COL-003 (Collegium Pharmaceutical Inc., Cumberland, RI, USA) and ELI-216 (Elite Pharmaceuticals, Northvale, NY, USA). COL-003 is a tamper-resistant capsule utilizing DETERx™ (Collegium Pharmaceutical Inc.) technology, which consists of a multi-particulate matrix containing particles of oxycodone formulated in a waxy excipient base. The capsule can be opened and administered as particles, and crushing or chewing reduces particle size; however, the formulation is designed to retain its sustained-release property. Thus, abuse by chewing would not result in a rapid spike in plasma concentrations of oxycodone.^[30] ELI-216 is an oral formulation of capsules containing separate oxycodone and naltrexone pellets. The naltrexone pellets are nonporous and do not release naltrexone when the intact capsule is ingested orally; the pellets are designed to release naltrexone only when

crushed. Both products are currently in phase II development.

2.2.2 Extended-Release Morphine

Embeda[®] (King Pharmaceuticals) is morphine sulphate with sequestered naltrexone. The product was approved for marketing in 2009 and is formulated as pellets contained in a capsule. Each pellet contains a sequestered naltrexone core surrounded by morphine. When ingested orally, morphine is absorbed but the naltrexone core remains intact, and no or little naltrexone is released. However, when crushed or dissolved, naltrexone is released and mixed with morphine, thus blunting the euphoric effects of morphine. Most patients who received Embeda[®] in studies had undetectable concentrations of naltrexone, and the few patients who had detectable concentrations of naltrexone had no increase in pain.^[31] Under tampering conditions, this drug releases concentrations of naltrexone that are similar to those achieved with immediate-release naltrexone.^[32]

2.2.3 Extended-Release Tramadol

Tramadol, a weak opioid receptor agonist and inhibitor of the reuptake of serotonin and noradrenaline (norepinephrine), has been used for the treatment of moderate to moderately severe nociceptive and neuropathic pain. Although it has less affinity for opioid receptors compared to full agonists such as morphine, its abuse liability is greater than what was expected with its introduction to the market in 1995.^[33-36] An extended-release investigational tramadol formulation (TQ-1017) using SECUREL technology (TheraQuest Biosciences, Blue Bell, PA, USA) was approved in 2005 with orphan drug status for the treatment of neuropathic pain. This formulation reportedly resists tampering and becomes viscous when subjected to common solvents. Preliminary data on four prototype formulations showed less extraction and filtration efficiency compared with extended-release tramadol and extended-release oxycodone.^[37]

2.2.4 Immediate-Release Oxycodone

Acurox[®] (King Pharmaceuticals) is an immediate-release formulation of oxycodone that uses several deterrent mechanisms to make

abuse via the oral, nasal and parenteral route less desirable to the abuser. Oxycodone is co-formulated with subtherapeutic doses of niacin, which causes temporary unpleasant effects such as warmth, flushing, itching, sweating and/or chills if an excess number of tablets are swallowed. The formulation is designed to be void of the effects of niacin at the recommended dose,^[38] thereby providing a deterrent against oral abuse. The tablets also contain three commonly used inactive excipients that are intended to deter abuse by intravenous injection of dissolved tablets and by nasal snorting of crushed tablets. This 'aversive' strategy is one of the few approaches that addresses intentional abuse via swallowing excessive amounts of whole tablets.^[39] After an FDA ruling in April 2010 determining that there was insufficient evidence to support the abuse deterrent effects of Acurox[®], the manufacturer announced that it would resubmit an NDA for a formulation that does not contain niacin in early 2011.

3. Present and Future Considerations

The introduction of abuse-deterrent and tamper-resistant opioid formulations begins to address the growing concerns associated with both medical and nonmedical uses of prescription opioids. However, there are still many issues that are yet to be addressed about their integration into clinical practice and their true abuse liability in real-world scenarios. The cost of these new preparations will likely present a challenge, particularly for insurance carriers and pharmacy benefit managers attempting to justify their use based on cost-benefit analyses. For example, prescription opioids that are obtained by prescription forgery or obtained via legitimate prescriptions but diverted can, by estimation, cost public and private insurance and tax payers up to \$US72 billion per year; these costs include not only insurance schemes, but also the larger hidden costs of treating patients who develop serious medical problems from abusing opioid medications.^[40] Although theoretical budget-impact models suggest that abuse-deterrent or tamper-resistant formulations could potentially save approximately \$US0.6–1.6 billion per year to third-party payers,^[41] this is only true

if these products indeed deter abuse in the real world. All of these products undergo laboratory and human abuse liability studies (the latter conducted in a small population of recreational drug abusers); however, these studies cannot predict all unforeseen or novel methods by which abusers could subvert the abuse-deterrent or tamper-resistant technology. We are well aware that persons who are addicted to opioids tend to find a way to circumvent any abuse-deterrent formula. We also know that persons can purposely take more of the drug in order to experience the euphoria of an opioid, whether it is purportedly less abusable or not, and plenty of more easily abused opioid formulations will remain available to the public. For these reasons, the true test of these products' benefits can only be determined in large, randomized controlled trials or epidemiological studies designed to track the abuse of these products over time in a range of relevant populations. There is, however, great hope that prescription opioid abuse will be effectively managed with the introduction of these new formulations.

The only substantial real-world experience with these types of formulations is with Suboxone[®] even though this combination of buprenorphine and naltrexone is not approved for the treatment of pain. A study has suggested that the introduction of Suboxone[®] did not reduce buprenorphine injection in Malaysian substance abusers.^[42] Recent findings suggest that Suboxone[®], which is used by 170 000 people in the US on a daily basis, is still crushed and injected by abusers.^[43] Yet, even with a certain level of abuse, Suboxone[®] therapy is still considered the safest treatment for opioid addiction. The Suboxone[®] example suggests that abuse-deterrent or tamper-resistant formulations are not likely to completely prevent or deter abuse, but that the reductions in abuse they provide may be an important incremental step towards safer treatments and safer communities.

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Correspondence: Dr Robert N. Jamison, Pain Management Center, Brigham and Women's Hospital, Harvard Medical School, 850 Boylston Street, Chestnut Hill, Boston, MA 02467, USA.
E-mail: Rjamison@partners.org

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