

# Strategies to Reduce the Tampering and Subsequent Abuse of Long-acting Opioids: Potential Risks and Benefits of Formulations With Physical or Pharmacologic Deterrents to Tampering

Steven P. Stanos, DO; Patricia Bruckenthal, PhD, APRN-BC, ANP;  
and Robert L. Barkin, PharmD, MBA

## Abstract

Increased prescribing of opioid analgesics for chronic noncancer pain may reflect acceptance that opioid benefits outweigh risks of adverse events for a broadening array of indications and patient populations; however, a parallel increase in the abuse, misuse, and diversion of prescription opioids has resulted. There is an urgent need to reduce opioid tampering and subsequent abuse without creating barriers to safe, effective analgesia. Similar to the “magic bullet” concept of antibiotic development (kill the bacteria without harming the patient), the idea behind reformulating opioid analgesics is to make them more difficult to tamper with and abuse by drug abusers but innocuous to the compliant patient. As antibiotics exploit differences in bacterial and human physiology, tamper-resistant formulations depend on differences in the way drug abusers and compliant patients consume opioids. Most opioid abusers tamper with tablets to facilitate oral, intranasal, or intravenous administration, whereas compliant patients usually take intact tablets. Pharmaceutical strategies to deter opioid abuse predominantly focus on tablet tampering, incorporating physical barriers (eg, crush resistance) or embedded chemicals that render tampered tablets inert, unusable, or noxious. Deterring tampering and abuse of intact tablets is more challenging. At present, only a few formulations with characteristics designed to oppose tampering for abuse have received approval by the US Food and Drug Administration, and none has been permitted to include claims of abuse deterrence or tamper resistance in their labeling. This review discusses the potential benefits, risks, and limitations associated with available tamper-resistant opioids and those in development.

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Chronic noncancer pain remains undertreated in the United States despite the availability of effective analgesics, with more than 10% of individuals aged 20 years and older reporting pain lasting more than 1 year. Opioids are standard therapy for postoperative and cancer pain and have gained greater acceptance for moderate to severe chronic noncancer pain in selected patients for whom the benefits of treatment have been determined to outweigh the risks.<sup>1-3</sup>

The potential for abuse, misuse, addiction, and diversion of opioids is cited by physicians as an even greater concern than the risk of adverse events (AEs).<sup>4,5</sup> A 2007 US government survey found that 13.2% of individuals reported nonmedical use of pain relievers at some point during their lives.<sup>6</sup>

The US Food and Drug Administration (FDA) now requires manufacturers to develop and submit a risk evaluation and mitigation strategy (REMS) for long-acting and sustained-release opioids. Opioid

REMS mandate that opioid manufacturers educate prescribers regarding proper prescribing and develop medication guidelines for patients regarding the safe use and disposal of opioids.<sup>7</sup> Although state laws such as those in Florida<sup>8</sup> and Washington<sup>9</sup> are intended to restrict prescription of opioids, they may curb the legitimate treatment of chronic pain but do little to limit abuse of prescribed opioids or change illegal behavior (eg, theft, diversion).

## THE RATIONALE FOR TAMPER-RESISTANT FORMULATIONS

A study of prescription opioid abusers in a drug rehabilitation program found that 80% tampered with opioid tablets to accelerate drug release by chewing or administering the drug intranasally or intravenously.<sup>10</sup> Formulations that incorporate physical or pharmacologic impediments to altering the recommended routes of administration may deter tampering. Taking an excess quantity of intact tab-

From the Rehabilitation Institute of Chicago, Center for Pain Management, and Department of Physical Medicine and Rehabilitation, Northwestern University, Feinberg School of Medicine, Chicago, IL (S.P.S.); Department of Graduate Studies in Advanced Practice Nursing, Stony Brook University School of Nursing, Stony Brook, NY (P.B.); and Rush University Medical Center, Department of Anesthesiology, Department of Family Medicine, and Department of Pharmacology, North Shore University Health System Department of Anesthesiology, and Pain Centers of Evanston and Skokie Hospitals, IL (R.L.B.).

## ARTICLE HIGHLIGHTS

- Substance abuse in patients prescribed opioids for chronic noncancer pain is a significant concern to patients and prescribers.
- To limit abuse potential, opioids have been formulated that deter product tampering by 1 of 3 mechanisms: physical barriers to prevent crushing, chewing, or dissolution in liquids; sequestered antagonists to neutralize opioid effects in the event of crushing or chewing; and sequestered aversive components that create adverse effects if the product is crushed or chewed.
- Of the 3 mechanisms, only physical barriers have the potential to deter tampering without creating adverse events in noncompliant patients and those who may accidentally crush or chew an opioid.
- No tamper-resistant formulation deters abuse of intact opioid tablets.
- Oxycodone with physical barriers to tampering and morphine with sequestered naltrexone have been approved for clinical use in the United States but without an approved claim of abuse deterrence in the product labels.
- No opioid formulation intended to deter tampering will be allowed a label claim of abuse deterrence without postmarketing data to support the claim.

lets is another method of opioid abuse, but pharmacologic modifications to deter this without causing AEs in compliant patients are difficult. Because of the phenomenon of tolerance,<sup>3</sup> there is no ceiling dose for most opioids (codeine, meperidine, tramadol, and tapentadol have maximum doses), and some patients might legitimately need to take a higher opioid dose to manage pain than some abusers take recreationally.

To deter tampering that involves the crushing of intact tablets, pharmaceutical companies are developing modified opioid formulations that typically employ the creation of physical barriers to crushing, sequestering an aversive component that is released if the opioid is crushed, or sequestering an opioid antagonist to neutralize opioid effects if the tablet is crushed.<sup>11</sup> Advantages and disadvantages of these strategies are presented in Table 1. The FDA has mandated that postmarketing epidemiologic studies must verify a reduced frequency of abuse before a new formulation is permitted a label claim of abuse deterrence.<sup>12</sup> Without these data extended release (ER) morphine sulfate with embedded naltrexone,<sup>13</sup> a crush-resistant reformulation of controlled release (CR) oxycodone,<sup>14</sup> and a short-acting oxycodone with a sequestered aversive agent<sup>15</sup> may only have labeling describing their technical formulation.

This review discusses efforts to develop tamper-resistant formulations (primarily those in phase III development) and outlines the benefits and risks

associated with each for the patient at risk of opioid abuse and for patients with complicated medical conditions who comply with proper use of the formulation.

## SEARCH METHODS

Articles cited in this review were identified via a search of PubMed for literature published between January 2005 and October 2011. The opioid medication search terms were *Acurox*, *codeine*, *COL-003*, *Egalet hydrocodone*, *Egalet morphine*, *Egalet oxycodone*, *Embeda*, *Exalgo*, *fentanyl*, *hydrocodone*, *hydromorphone*, *methadone*, *morphine*, *opioid*, *opioid analgesic*, *oxycodone*, *oxycodone tamper-resistant tablets*, *oxymorphone*, *Opana*, *OxyNal*, *Remoxy*, *tapentadol*, and *tramadol*. Each opioid medication search term was combined with the following general search terms: *abuse deterrent*, *agonist/antagonist*, *crush-resistant*, *opioid abuse*, *diversion*, *overdose*, and *tamper-resistant*. Reference lists from relevant articles identified during this search were reviewed for additional relevant articles. Abstracts from major pain management conferences were also reviewed for relevant research presentations. Priority was given to clinical research evaluating tamper-resistant opioids.

## RESULTS

## Who Should Be Prescribed Tamper-Resistant Opioids?

Prescribers may fear legal liability issues for either prescribing or failing to prescribe any innovative new drug, depending on the level of potential risk posed by the innovation.<sup>16</sup> Before determining who should be prescribed a tamper-resistant opioid, it is important to review the fundamental steps to determine who should be prescribed any opioids for long-term management. Opioid therapy must not be undertaken lightly because this class of drugs has potential for serious AEs, pharmacokinetic and pharmacodynamic drug interactions, accidental overdose, abuse, addiction, and diversion.

Consideration of opioid therapy for chronic noncancer pain requires a thorough assessment of risks and benefits, including any history of substance abuse and a physical examination to diagnose the etiology of the chronic pain and to assess the level and quality of pain, disability, and impact on quality of life.<sup>3</sup> Validated screening tools, such as the revised Screener and Opioid Assessment for Patients with Pain,<sup>17</sup> Current Opioid Misuse Measure,<sup>18</sup> and the Opioid Risk Tool,<sup>19</sup> should be applied to formally assess the risk of aberrant drug-taking behavior and potential for opioid abuse. Initiation of long-term opioid therapy should also include the use of a written compliance agreement, which may include a review of potential risks, benefits, and harms of opi-

TABLE 1. Current Tamper-Resistant Opioid Formulations: Advantages and Disadvantages

Opioid formulation	Advantage	Disadvantage
Physical barriers	Prevent abusers from crushing or chewing their opioid to facilitate rapid release into the system Prevent accidental crushing or chewing in compliant patients No AEs in compliant patients FDA-approved formulation available	Does not deter abuse of intact tablets Only 1 FDA-approved formulation available
Aversive components	May prevent abuse by chewing or crushing opioids May limit abuse of intact tablets because taking too much will amplify niacin AEs	Potential for AEs in compliant patients who take the product as intended Adverse events with intact tablets may prevent legitimate dose increases to address increasing pain or decreasing efficacy over time Adverse events of niacin may not be sufficient to deter a motivated abuser No FDA-approved formulation
Sequestered antagonist	Prevents abuse by chewing or crushing opioids FDA-approved formulation available	Does not deter abuse of intact tablets Chewing or crushing the tablet may precipitate severe withdrawal symptoms

AE = adverse event; FDA = Food and Drug Administration.

oid use; definitions pertinent to medication use, that is, “dependence,” “tolerance,” and “addiction”; and a definition of the obligations with regard to therapy, regular reassessment, and monitoring.

Confirmatory urine drug testing can reduce substance abuse and possible diversion in opioid-treated patients by as much as 50% and should be practiced as a universal precaution in patients requiring long-term treatment.<sup>20,21</sup> Nonetheless, confirmatory urine drug testing is underused,<sup>4</sup> and many physicians report difficulty interpreting confirmatory test and presumptive screening results.<sup>22</sup> False-negative findings often result from the prescriber ordering a test that is incapable of detecting the drug of interest; to avoid this pitfall, prescribers should advise the laboratory regarding which drugs are of interest.<sup>22,23</sup> Pseudo false-positive results may indicate metabolism of a prescribed drug into an unprescribed drug (eg, codeine metabolized to morphine, hydrocodone metabolized to hydromorphone, oxycodone metabolized to oxymorphone; morphine produces small amounts of hydromorphone).<sup>23,24</sup>

Application of the risk assessment process outlined herein will help identify patients with an elevated risk of opioid abuse and misuse. Opioids with features intended to reduce risk of tampering should be prescribed for patients who appear to have a high risk for abuse on the basis of screening. Even in the absence of approved tamper-resistant opioids, the American Academy of Pain Medicine and the American Pain Society guidelines advise that high-risk patients should not necessarily be denied opioid

therapy when potential benefits outweigh potential risks.<sup>25</sup> However, such patients require close monitoring, controlled substance agreements, and frequent confirmatory urine drug testing.<sup>23,26,27</sup>

Resistance can be expected from patients who feel falsely stigmatized as “abusers”<sup>28</sup> and from patients who more covertly desire a more easily abused formulation. This sense of stigmatization has been one of the rationales for recommending a universal precautions approach to urine toxicology screening.<sup>21</sup> Providing tamper-resistant formulations universally rather than on the basis of individual risk will optimize protection and may also mollify patients who feel as though they are being singled out. However, a universal approach to prescribing tamper-resistant opioids includes the possibility of increased costs that could represent a barrier to effective pain management and raises issues concerning differences in the risk of AEs with tamper-resistant formulations compared with those of traditional formulations.<sup>29</sup>

Limiting prescription of tamper-resistant opioid formulations to patients assessed to have an elevated risk of abuse may prove ineffective if these patients can obtain traditional prescription opioid formulations from another source. Epidemiologic evidence indicates that the prescribing of opioids for chronic noncancer pain in recent years has increased most in the elderly, especially in older women,<sup>30</sup> whereas most abusers of prescription opioids are young men.<sup>31</sup> These data seem to complement the findings of a 2010 Substance Abuse and Mental Health Services Administration survey that found that most

prescription drug abusers (55.0%) obtain their opioids by diversion of prescriptions written for relatives and friends.<sup>32</sup> An additional source of opioids may include drugs diverted from the supply chain before being prescribed.<sup>33</sup> A 2005 survey found that from 2000 to 2003 nearly 13,000 occurrences of theft or loss of controlled substances from pharmacies, manufacturers, distributors, medical practices, and addiction treatment programs had been reported to the Drug Enforcement Agency. These included millions of doses of oxycodone (4,434,731), morphine (1,026,184), methadone (454,503), hydromorphone (325,921), meperidine (132,950), and fentanyl (81,371). The estimate for lost or stolen hydrocodone doses in the year 2003 alone was approximately 4 million doses.<sup>33</sup>

Replacing all current opioids with tamper-resistant formulations may not be the most practical approach considering the numbers of formulations, branded and generic, available in the US market. Legal liability standards may serve as an impediment to medical innovation if prescribing a new drug represents a divergence from standard medical practice. However, if a new drug presents no new risks, then additional legal liability is not likely to be incurred by clinicians prescribing it. Conversely, clinicians may fear legal liability if they prescribe an opioid formulation that is not tamper-resistant when such formulations are available.<sup>28</sup> The question of whether tamper-resistant formulations might pose additional risks compared with traditional formulations for the compliant, nonabusing, majority of patients is of key importance.

### The Risk-Benefit Balance of Tamper-Resistant Opioids

Most patients who are prescribed opioids are not at risk for abusing their medications. Prescribing of opioid therapy becomes more frequent with increasing age.<sup>30</sup> The prevalence of chronic pain increases with age, reaching 50% or more in individuals older than 50 years<sup>34</sup> and up to two-thirds in individuals aged 65 years and older.<sup>35</sup> Nonetheless, despite an age-related increase in chronic pain and opioid use, elderly patients have the lowest risk of abusing opioids. In a 2010 US Department of Health and Human Services survey, 1.0% of individuals aged 65 years or older reported illicit drug use during the previous month, compared with 8.9% in the entire US population aged 12 years and older.<sup>32</sup> However, a survey of drug abusers, police officers, regulatory officials, prescription drug dealers, and pill brokers revealed that many elderly people deceive their physicians to obtain opioid prescriptions, some with the intention of abuse but others primarily with the intention of selling for economic reasons.<sup>36</sup> Thus, the

risk of abuse and particularly diversion remains a serious concern regardless of age.

If tamper-resistant formulations are to universally replace traditional formulations, it is important that they not increase the risk of AEs for patients with pain who may misuse medications inadvertently without the intention of abuse, as might happen if a patient with dementia or dysphagia chewed an opioid formulated with a sequestered antagonist or aversive component. Tamper-resistant formulations should also not increase risks for patients with common problems of senescence, such as reduced renal clearance or hepatic dysfunction. Similarly, they should not increase risks of pharmacokinetic or pharmacodynamic adverse drug interactions in patients taking multiple medications or of AEs in patients with multiple medical problems, such as diabetes, cardiovascular disease, or hepatic dysfunction. Ideally, tamper-resistant formulations might provide additional benefits for patients who are compliant with their proper use, such as preventing accidental crushing or dose dumping.

## CURRENT APPROACHES TO TAMPER-RESISTANT FORMULATIONS

### Physical Barriers to Tampering

The opioids discussed in this section have been formulated to resist crushing, chewing, dissolution, or chemical extraction. The potential benefit to abusers is that crush resistance will thwart their strategies to accelerate opioid release, thus reducing the risk of overdose and the euphoric effects associated with rapid opioid release. The potential benefits of this approach to patients who do not intentionally abuse medications include prevention of misuse. For example, patients with dysphagia or phagophobia will not be able to chew or crush long-acting opioid tablets in a misguided attempt to facilitate swallowing. Patients who wish to reduce their dosage of a long-acting opioid will not be able to inappropriately cut or crush tablets, which could also result in a dangerous increase in the rate of opioid absorption even though only a fraction of the tablet is being crushed or chewed. Patients need to consult their health care provider to develop a mutually agreeable safe and effective plan to take lower doses or taper off a medication. Tablets resistant to chemical extraction may also be less likely to "dose dump" when coingested with hot, alcoholic, acidic, or alkaline beverages. These formulations are not anticipated to cause any adverse consequence in response to attempted abuse except, perhaps, as a consequence of applying excessive bite force in an effort to break the tablet.

**Remoxy (King Pharmaceuticals, Inc. Bristol, TN).** Remoxy is a new ER formulation of oxycodone delivered in a viscous liquid formulation matrix that resists abuse by crushing and dissolution in water or alcohol. Remoxy has not been compared with original-formulation CR oxycodone or other ER opioids in head-to-head trials, making it impossible to determine whether the formulation alters efficacy or increases AEs.<sup>37</sup>

In healthy volunteers, coadministration of Remoxy with a 240-mL solution of 4%, 20%, and 40% ethanol did not significantly alter the maximum concentration or area under the curve compared with 240 mL of water alone.<sup>38</sup> In a 12-week phase III trial,<sup>39</sup> patients treated with Remoxy experienced significant improvements in pain intensity compared with those who were prescribed a placebo, as measured by a Global Assessment ( $P=.007$ ), Quality of Analgesia ( $P=.004$ ), and the Western Ontario and McMaster Universities Arthritis Index pain subscale ( $P=.023$ ). Adverse events included those typically associated with opioids.

In a study that enrolled 32 drug abuse counselors,<sup>40</sup> Remoxy was rated as less attractive for abuse compared with CR oxycodone, hydrocodone, and immediate release oxycodone. Remoxy was rated as having similar attractiveness compared with a product combining pentazocine and naloxone,<sup>40</sup> which has already been established as being unattractive by abusers.<sup>41</sup> The assessment used for this study was the Opioid Attractiveness Scale, which assesses the following variables: positive features of the formulation, such as speed of onset, duration of effect, and extractability; negative features of the formulation, such as presence of impurities, presence of antagonists, and difficulty hiding; and social milieu features of the formulation, including availability, availability of alternatives, cost, and social stigma.<sup>41</sup> Phase III development of Remoxy has been completed, but the initial new drug application for the formulation was not accepted.<sup>42</sup>

**Reformulated OxyContin (Purdue Pharma LP, Stamford, CT).** Approved in April 2010, CR oxycodone has been reformulated in a polymer matrix that makes tampering by crushing or chewing difficult.<sup>43</sup> When immersed in water, the formulation becomes a viscous gel that resists oxycodone extraction for injection.<sup>37</sup>

Published data regarding reformulated CR oxycodone are sparse; however, 8 unpublished phase I clinical trials establishing bioequivalence with original CR oxycodone were completed (Clinical Trials.gov identifiers: NCT01100320, NCT01101321, NCT01101308, NCT01101165, NCT01101178, NCT01100086, NCT01099709, and NCT01101191). To allow for appropriate evaluation of reformulated

CR oxycodone, the FDA has instructed the manufacturer to conduct extensive postmarketing surveillance to gauge the effects of the new formulation on abuse.<sup>43</sup> The FDA has also mandated that the product be dispensed with a REMS, which requires prescriber training on opioid use for chronic pain, and that a medication guide be dispensed with the prescription.

**Reformulated Opana ER (Endo Pharmaceuticals Inc, Chadds Ford, PA).** Endo Pharmaceuticals has developed a formulation of ER oxymorphone with a polyethylene oxide (PEO) matrix (INTAC™; Grünenthal GmbH, Aachen, Germany) designed to resist crushing, oxymorphone ER-PEO. In 3 open-label studies, 5 to 40 mg of oxymorphone ER-PEO was shown to be bioequivalent to the previously marketed ER oxymorphone formulated using the polysaccharide hydrogel (PSH) TIMERx matrix (Endo Pharmaceuticals Inc, Chadds Ford, PA) oxymorphone ER-PSH.<sup>44</sup> In healthy volunteers, concurrent administration of oxymorphone ER-PEO with a 240-mL solution containing 20% and 40% ethanol had no effect on area under the curve for oxymorphone.<sup>45</sup> Administration with the 40% ethanol solution resulted in modest increases in the maximum steady-state plasma drug concentration for oxymorphone. However, it should be noted that the 40% ethanol solution corresponds to heavy alcohol consumption, which is to be avoided when taking any opioid. The pharmacokinetics of oxymorphone ER-PEO were only mildly affected by moderate alcohol consumption, modeled by the 20% ethanol solution.<sup>45</sup> In laboratory tests the product was impervious to crushing with a pill crusher exerting up to 1000 N or striking with a 500-g hammer exerting 5 to 10 kN of force.<sup>46</sup> The maximum achievable bite force is less than 1000 N in men and less than 900 N in women<sup>47</sup>; however, it should be noted that chewing involves shear forces and effects of saliva not considered by a simple measurement of bite force.

There are several reasons why a tamper-resistant version of this opioid would be of interest. First, there are few long-acting opioids from which to choose in the US market. Any long-acting opioid formulation that fails to offer a tamper-resistant formulation will become the default choice for abusers.<sup>28</sup> For example, there was a substantial rise in abuse of oxymorphone ER-PSH after the release of reformulated CR oxycodone.<sup>48</sup> From a clinical standpoint, oxymorphone ER-PSH is often selected for opioid switching or rotation when patients find other long-acting opioids ineffective or intolerable.<sup>49</sup> For patients with chronic pain who are at risk for abusing opioids, it may be preferable to have more tamper-resistant alternatives.<sup>28</sup>

Second, oxymorphone ER-PSH was not widely abused before tamper-resistant CR oxycodone was marketed. Reasons for this may include its relatively recent appearance in the US market (approved in 2006) and lack of familiarity among abusers. Because it is prescribed approximately 10-fold less frequently than CR oxycodone,<sup>50</sup> lack of availability may also contribute to its low rate of abuse.

However, there may be intrinsic characteristics of ER oxymorphone that have made it less attractive to abusers. In a study of experienced opioid abusers, intact tablets of oxymorphone ER-PSH produced less positive subjective effects (eg, euphoria, drug "liking") and were less valued for abuse than intact tablets of CR oxycodone.<sup>51</sup> Oxycodone and oxymorphone are 6-keto opioids.<sup>52</sup> Oxycodone, hydrocodone, and hydromorphone (2 other 6-keto opioids) are similar to one another in subjective effects, so it is puzzling that the 6-keto opioid, oxymorphone, would be dissimilar.<sup>53</sup>

It is possible that differences in subjective effects were more substantial than differences in formulation for oxymorphone ER-PSH vs CR oxycodone. The formulation of CR oxycodone used in this study had a biphasic release pattern, characterized by an initial bolus release of 30% to 40% of the dose within 1 hour, followed by a slow-release phase of 8 to 12 hours.<sup>52</sup> Oxymorphone ER-PSH does not have an initial bolus release phase and has a much slower onset of action, taking up to 3.5 hours to achieve maximum concentration.<sup>52</sup> The attractiveness and value of crushed tablets were not compared, which was a concern when CR oxycodone had a crush-resistant formulation and ER oxymorphone did not. As suggested herein, the availability of 1 opioid in a tamper-resistant formulation may simply divert abusers to opioids for which manufacturers continue to market crushable formulations. Oxymorphone ER-PEO was approved on December 9, 2011, and is expected to replace oxymorphone ER-PSH early in 2012.<sup>54</sup>

**COL-003 (Collegium Pharmaceutical, Inc, Cumberland, RI).** COL-003 is an ER formulation of oxycodone embedded in a multiparticulate matrix containing oxycodone in a waxy excipient base.<sup>37</sup> When opened, crushed, or chewed, the particles maintain their ER properties. In vitro, COL-003 was more resistant than currently available formulations of oxycodone to dissolution in solvents.<sup>55</sup> In healthy volunteers, the pharmacokinetic profile of COL-003 was similar when chewed compared with when it was taken as intended.<sup>55</sup>

**Egalet Morphine (Egalet Ltd, Værløse, Denmark).** Egalet morphine is a once-daily ER morphine formula-

tion in which the opioid is embedded in a water-soluble matrix, keeping the tablet intact until it reaches the gastrointestinal tract.<sup>56</sup> Although susceptible to dissolution by gastrointestinal fluid, the product is resistant to extraction by a variety of solvents, most notably ethanol. In a 2-week, double-blind, randomized, exploratory crossover study, once-daily Egalet morphine was as effective as twice-daily CR morphine in adult patients with cancer.<sup>56</sup> Steady-state trough concentrations of the 2 formulations were similar. No end-of-dose failure was reported. Adverse events were similar for the 2 treatments. It should be noted that Egalet formulations of oxycodone and hydrocodone are in phase I development.<sup>57</sup>

**TQ-1015 (TheraQuest Biosciences, Inc, Blue Bell, PA).** TQ-1015 is a proprietary formulation of CR tramadol that is difficult to crush or extract for intravenous injection.<sup>58</sup> The 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide opioid formulation (Akela Pharma Inc, Austin, TX) uses extrusion technology to embed an opioid (not specified) in a matrix that is water insoluble, only slightly soluble in ethanol, not friable, and resistant to crushing or chewing.<sup>59</sup>

### Sequestered Aversive Agents

Opioids with a sequestered aversive agent are designed to release the aversive agent only if the tablet is crushed, chewed, or chemically tampered with for the purpose of abuse.<sup>11</sup> The concept is analogous to prescribing disulfiram to a recovering alcoholic: abuse will result in an adverse reaction. The benefit for the opioid abuser is reduced attractiveness of the formulation for abuse. However, doubt has been expressed that this approach will prove to be an effective barrier to abuse because the observed behavior of drug abusers suggests that they are prepared to face many challenges, including some physical discomfort, that the average person would consider aversive. Research suggests that the widespread public presumption that illicit drugs are likely to contain potentially harmful adulterants does not deter their abuse.<sup>60</sup> Moreover, the commonly observed AEs of opioid abuse (overdose and death, constipation, depressed mood, psychomotor impairment), opioid withdrawal, and social and legal sequelae of opioid abuse are evidently ineffective deterrents.

OXECTA (King Pharmaceuticals, Inc, Bristol, TN), approved on June 17, 2011,<sup>61</sup> is a short-acting oxycodone formulation designed to discourage common methods of tampering associated with opioid abuse and misuse. OXECTA is formulated using a proprietary AVERSION Technology (Acura Pharmaceuticals, Inc, Palatine, IL) that incorporates

commonly used pharmaceutical ingredients that can be irritating if ingested or inhaled.<sup>15</sup> These include colloidal silicon dioxide,<sup>62</sup> crospovidone,<sup>63</sup> magnesium stearate, microcrystalline cellulose,<sup>64</sup> polyethylene oxide, and sodium lauryl sulfate.<sup>65</sup>

In an unpublished, double-blind, crossover study, 40 nondependent recreational drug users self-administered crushed doses of OXECTA and standard immediate release oxycodone intranasally.<sup>15</sup> Participant “drug liking” responses and the safety of the 2 formulations were compared. “Drug liking” scores were slightly lower with OXECTA than with immediate release oxycodone, such that 30% of participants indicated that they would not take OXECTA again and 5% would not take immediate release oxycodone again. OXECTA was associated with an increased occurrence of nasopharyngeal and facial AEs, and 21 of 40 patients stated they could not completely inhale 2 crushed OXECTA tablets within a set time period.<sup>15</sup>

The clinical significance of these findings is unclear; however, the fact that 70% of nondependent recreational drug users would be willing to use the product again suggests that the AEs produced by chewing may not be sufficient to deter abuse in a dependent, highly motivated drug abuser. Moreover, no data have been published or presented in the product’s package insert regarding the occurrence of AEs when OXECTA is crushed or chewed with the intent to facilitate swallowing. Based on available evidence, the package insert for OXECTA clearly states that there are no data at present demonstrating reduced abuse potential with this formulation.<sup>15</sup>

Similarly, no published data are available regarding potential tolerability differences between OXECTA and immediate release oxycodone when they are taken as intended rather than crushed or chewed. However, such data are available on the effects of intact reformulated oxycodone with niacin as the aversive component. Before being acquired by King Pharmaceuticals, Acura Pharmaceuticals began development of the formulation eventually approved as OXECTA with a product called Acurox, a short-acting oxycodone formulated with subtherapeutic levels of niacin (30 mg).<sup>37</sup> When crushed or chewed, the niacin worked as intended, producing typical niacin effects, such as flushing, warmth, itching, and sweating. However, even when taken intact, the product produced AEs commonly associated with opioids and niacin-associated AEs such as dizziness, flushing, nausea, vomiting, and pruritus.<sup>66-68</sup>

Because of AEs, developing opioids with sequestered noxious components is the only strategy for deterring tampering discussed in this review that might be able to deter abuse by preventing patients from taking intact tablets in excessive

doses. However, this may also make the formulation unsuitable for patients who legitimately require a high opioid dose, if dose escalation necessary to compensate for tolerance is also accompanied by an increase in aversive component-related AEs.<sup>37</sup> This strategy would also prevent the legitimate crushing of opioids for patients with difficulty swallowing tablets.

### Sequestered Opioid Antagonists

Combining an opioid agonist with a low-dose active opioid antagonist is a strategy that is used to reduce opioid AEs, such as constipation, respiratory depression, or addictive potential.<sup>69-71</sup> In tamper-resistant formulations that combine an opioid agonist with an antagonist, the antagonist is not intended to work actively in tandem with the opioid agonist but rather to be sequestered in a higher dose and released to neutralize the opioid agonist only if the tablet is tampered with for the purpose of abuse.

Suboxone (Reckitt Benckiser Pharmaceuticals Inc, Richmond, VA) is a sublingual buprenorphine film formulated with low-dose naloxone. Because Suboxone is a pliable film, crushing it into a powder for intranasal abuse is difficult. If injected, the naloxone component is intended to diminish the opioid effects of buprenorphine and may precipitate withdrawal in opioid-dependent individuals. This buprenorphine-naloxone film is only approved for the treatment of addiction and does not have an approved indication for pain.<sup>72</sup> In contrast, Butrans (Purdue Pharma LP, Stamford, CT), a transdermal buprenorphine patch, is approved for the treatment of chronic pain but incorporates no abuse-deterrent mechanisms. The potential benefit for abusers is to make the formulation less attractive for abuse than an opioid that can be crushed or chewed to intensify its effects. Patients who do not abuse their medications would receive no apparent benefit from a sequestered agonist-antagonist combination. Unlike active agonist-antagonist combinations, the sequestered agonist is not intended to ameliorate opioid AEs.

Risks posed by sequestered agonist-antagonist combinations are the same for abusers and nonabusers who chew the product unintentionally or crush it to facilitate swallowing without realizing the risks. Specifically, there is the potential for reduced opioid agonism, leading not only to inadequate pain relief but also potentially to sudden opioid withdrawal, which can be life-threatening.<sup>73,74</sup>

King Pharmaceuticals received FDA approval on August 13, 2009 for Embeda (morphine sulfate with sequestered naltrexone 100 mg).<sup>75</sup> However, in March 2011, Embeda was voluntarily recalled by the manufacturer because of problems with the formulation,<sup>76</sup> marking the fourth time since the prod-

uct's launch that it has been recalled.<sup>75</sup> In healthy volunteers, morphine sulfate with embedded naltrexone 100 mg (Embeda) showed bioequivalence with ER morphine.<sup>77,78</sup> In a randomized, double-blind, crossover study, treatment with Embeda for 14 days provided similar pain relief to that provided by ER morphine in patients with osteoarthritis of the knee or hip and exhibited an AE profile typical of opioid analgesics.<sup>78</sup>

In a phase III, enriched-enrollment trial,<sup>79</sup> 547 patients with moderate to severe osteoarthritis of the knee or hip were given a dose of Embeda (20-160 mg/d) that was titrated in a flexible, individualized fashion to be most effective. During double-blind treatment, Embeda was associated with significant improvements in average daily pain compared with placebo ( $P=.045$ ). Three patients in the placebo group experienced moderate withdrawal, which led to discontinuation in 1 patient, indicating that the differences between Embeda and placebo were actual treatment effects and not withdrawal effects. As in previous trials, Embeda was associated with typical opioid AEs.

Unsurprisingly, even with flexible, individualized titration, in a substantial proportion of patients enrolled in the enriched-enrollment, randomized-withdrawal trial of Embeda, titration was not successful to reach an effective, generally well-tolerated Embeda dose. Patients vary in the response to different opioids with ostensibly the same mechanisms of action.<sup>49</sup> Factors contributing to this variability are not clearly understood but may include differences among opioids and among patients.<sup>80</sup> Opioids differ with respect to how they bind to  $\mu$ ,  $\kappa$ , and  $\delta$  opioid receptors,<sup>81</sup> and several genetic factors have been identified that influence response to individual opioids.<sup>82,83</sup> The reasons for this variability are not clearly understood, and most patients require trials of several opioids before finding an agent that provides adequate analgesia and is tolerable.<sup>84-86</sup> It is therefore important to have multiple opioids available to find a tolerable agent that works.<sup>49</sup>

This is also true for tamper-resistant opioids. As stated previously, the availability of a single opioid in a tamper-resistant formulation may simply divert abusers to opioids for which no such formulations are available. If Embeda and reformulated oxycodone remain the only tamper-resistant opioids, then patients not responding to treatment with one or both of these formulations will have limited tamper-resistant options.

Compared with ER morphine, Embeda taken intact or chewed was associated with fewer positive subjective effects, including euphoria, and participants indicated they would be willing to pay less for it.<sup>87</sup> During clinical trials, Embeda has not been associated with severe withdrawal symptoms when

taken as intended<sup>79,88</sup> or after chewing.<sup>87</sup> However, it should be noted that in clinical practice, Embeda has been associated with at least 2 published case reports of acute opioid withdrawal after either accidental or deliberate chewing.<sup>73,74</sup> This suggests that when working as designed, opioids with embedded naltrexone may produce serious AEs, whether the patient intends to abuse the drug or mistakenly chews or crushes the tablet.

## SUMMARY

There are 3 main approaches to deter tampering with opioids, each based on a presumption that abusers will tamper with intact tablets. These include agents with physical barriers to crushing, chewing, and extraction; agents with sequestered aversive agents; and agents with sequestered opioid antagonists.

There are no tamper-resistant formulations directed at preventing abuse of intact tablets by taking them when they are not prescribed or in amounts that exceed the prescribed dose, although agents with sequestered aversive agents may have dosage ceilings imposed by the AEs precipitated by the noxious component (eg, niacin) when the product is taken as intended. For this reason, it may be advantageous to prescribe opioids that cause less euphoria compared with other formulations.

Although all 3 approaches have the potential to deter tampering, only opioids presenting physical barriers to crushing or chewing seem to provide additional benefit to nonabusers. Physical barriers prevent accidental crushing or chewing, providing a benefit to patients who may do this without intent of tampering. Moreover, physical barriers to chewing or crushing do not add to the risk of AEs for abusers or nonabusers.

In contrast, opioids with mechanisms of action based on precipitating AEs as a means of deterring inappropriate use have risks, regardless of the patient's level of compliance. Sequestered aversive agents will cause AEs in patients who chew or crush tablets accidentally without intent of abuse, and even intact tablets with sequestered aversive agents may produce AEs from the aversive component in some fully compliant patients. The extent of deterrence with these agents is unclear because individuals who intentionally abuse opioids may be willing to endure the discomfort of the aversive agent's AEs. Although sequestered opioid antagonists may represent a more effective approach to pharmacologically deterring abuse by rendering the opioid ineffective, there is evidence of sudden opioid withdrawal in patients who chewed their tablet, even accidentally.

None of the current approaches to deterrence has been validated by long-term postmarketing data



**TABLE 2. Recommendations for Selecting a Tamper-Resistant Opioid Formulation**

Population	Recommendation
Patients at risk of abuse	Consider prescribing a crush-resistant opioid or one with a sequestered antagonist or aversive component
Elderly patients	Consider a crush-resistant opioid for older patients at risk of accidental chewing or misguided crushing (eg, for dissolution in orange juice or apple sauce) to facilitate swallowing Avoid opioids with sequestered antagonists or aversive components in older patients because these may precipitate withdrawal symptoms or AEs It is better to prevent chewing/crushing by an older patient than to deny analgesia or cause AEs for a nonabusing patient who makes a mistake
Patients who may be targeted for theft	Prescribe any available tamper-resistant opioid to patients who may be targeted for theft; this will protect the compliant patient and create a barrier to the abuser, who will have to go elsewhere for an opioid supply

AE = adverse event.

as actually succeeding in deterring abuse. Such data are essential to a proper risk-benefit analysis. If one approach to formulation proves more successful than others in deterring abuse, a low incidence of AEs in compliant, nonabusing patients may be acceptable. In the meantime, it may be prudent initially to restrict the prescription of these putatively tamper-resistant opioids to patients with a high risk of abuse, misuse, or diversion and to cautiously weigh the risks they may present to low-risk patients. We would propose several recommendations for the use of tamper-resistant opioids in several key populations, including patients at risk for abusing opioids, patients who may be targeted for theft, and the elderly (Table 2). However, one could argue that the same level of scrutiny and precaution be placed on all patients, because some patients formally assessed to be low risk may use medications inappropriately.

Risk management changes proposed by the FDA, including REMS proposed for a list of certain long-acting or modified-release opioid preparations, could have formidable effects on prescribing and possible long-term influences on misuse, abuse, and diversion. Many of the more recently approved and reformulated long-acting and ER opioid formulations have been approved with “interim REMS” and have delivery systems and pharmacokinetic properties that may make them more difficult to tamper with at some level, which may decrease the ease of misuse and abuse compared with that for older formulations. In the future, extending a class-wide REMS to include short-acting formulations (branded and generic) may even the playing field for all prescribed products and may further help to deter misuse, abuse, and diversions of prescription opioids.

## CONCLUSION

The attractiveness of an opioid for abuse is in large part dependent on characteristics of the tablet formulation, particularly the ease with which it can be crushed or dissolved in fluids. Drug manufacturers have been developing opioid formulations that resist these common forms of tampering, but these formulations do not prevent abuse of intact tablets. It is hoped that in the near future, clinicians will have at their disposal a sufficient number of tamper-resistant options to effectively meet the clinical needs of patients with legitimate pain indications while simultaneously presenting some obstacles to opioid abuse.

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**Abbreviations and Acronyms:** AE = adverse event; CR = controlled release; ER = extended release; FDA = Food and Drug Administration; REMS = Risk Evaluation and Mitigation Strategy

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**Correspondence:** Address to Steven P. Stanos, DO, Rehabilitation Institute of Chicago, Center for Pain Management, 980 N Michigan Ave, Ste 800, Chicago, IL 60611 (sstanos@ric.org).

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