

# Validity testing of patient objections to acceptance of tamper-resistant opioid formulations

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**Background:** Tamper-resistant formulations (TRFs) of oral opioid drugs are intended to prevent certain types of abuse (eg, intranasal, intravenous). Patients raising objections to receiving a TRF may have valid concerns or may be seeking a formulation that can be more easily misused.

**Methods:** US clinicians experienced in pain management met in October 2011 to discuss common patient objections to being switched from a non-TRF opioid to a TRF of the same opioid. Retail pharmacy, health insurance, and scientific data were used to assess the potential validity of these patient objections.

**Results:** Clinical experience switching patients from a non-TRF to a TRF opioid was limited to oxycodone controlled release (CR), as it was the only TRF available at that time; knowledge of other TRFs was limited to the scientific literature. Common objections from patients included “costs more,” “not covered by insurance,” “can’t feel it working,” and “causes adverse events.” Objective retail pharmacy and insurance coverage information for oxycodone CR was accessible and indicated that patient objections were based on cost and coverage varied by insurer. Unpublished trial results (ClinicalTrials.gov) revealed that TRF oxycodone CR has a slower initial release than the non-TRF formulation, which may reduce positive subjective effects. The complaint “I can’t feel it working” may reflect lessened positive subjective effects rather than reduced analgesic efficacy. Most tolerability complaints lacked objective support.

**Conclusion:** The general process used to assess the validity of patient objections to TRF oxycodone CR may be applied to other TRFs once they become available. Publication of clinical data on TRFs would help clinicians to appropriately weigh patient concerns.

**Keywords:** opioid analgesics, chronic pain, substance abuse, tamper-resistant formulations

## Introduction

The authors met on August 11, 2011, in Chicago, Illinois, USA, to discuss their experience with tamper-resistant formulations (TRFs) of opioid medications and their impact on chronic pain therapy. The topic considered was whether patients had expressed objections to being switched to a TRF opioid from a non-TRF, and how these objections had been addressed. The authors considered it important to distinguish between legitimate objections to a TRF opioid versus drug-seeking objections from recreational drug users intended to facilitate a switch back to a non-TRF opioid, which would be more easily misused. The validity of each identified objection was tested by investigating appropriate resources, including product prescribing labels and manufacturer medical information; published scientific literature; trial results posted on ClinicalTrials.gov;<sup>1–5</sup> Internet searches; public and private health insurance formularies and press releases; and pharmacies.

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At the time of the meeting, oxycodone controlled release (CR; OxyContin®; Purdue Pharma, Stamford, CT, USA) was the only marketed opioid to have been reformulated as a TRF, and was therefore the only TRF with which the authors had any direct clinical experience with patient objections. Nonetheless, the authors believe that their process of investigation can be extrapolated to new TRFs being introduced to the market, particularly TRFs which replace an existing, non-TRF opioid. This expert opinion piece, which is based on the clinical experience of the authors, will discuss common objections made by their patients to being switched to a tamper-resistant opioid and describe their approach to investigating the validity of such patient objections.

## Patient objections to tamper-resistant oxycodone CR

TRFs are only one tool for minimizing risks of opioid abuse and must not be considered a substitute for other measures intended to prevent or detect abuse. TRFs do not prevent the abuse of intact tablets, and early postmarketing data for TRF oxycodone CR suggest that patients who formerly abused oxycodone may simply migrate to other prescription opioids or illicit substances such as heroin.<sup>6-8</sup> It is therefore essential that clinicians continuously assess all opioid-treated patients for signs of abuse and conduct regular urine drug monitoring. As part of patient assessment, clinicians who prescribe TRFs must learn to distinguish between a patient with a legitimate objection to a TRF and a patient who is trying to obtain a preferred drug of abuse.

Among the three clinicians, four common patient objections to switching to TRF oxycodone CR from the previous non-TRF oxycodone CR emerged, including reported tolerability problems not experienced with the previous formulation, reduced efficacy compared with the previous formulation, lack of formulary coverage for TRF oxycodone CR, and that the TRF oxycodone CR was considerably more expensive than the previous formulation.

## Objection validity testing

### Tolerability objections

Some patients have reported difficulty swallowing the reformulated TRF oxycodone CR tablet. The manufacturer issued a "Dear health care professional" letter citing reports that the TRF oxycodone CR tablet may swell and gel when exposed to saliva in the mouth, resulting in difficulty swallowing, especially when not swallowed immediately or taken with enough water to ensure complete swallowing.<sup>9</sup>

This issue with swelling/gelling was not the case with the previous oxycodone CR formulation. No other objective evidence was found for patient complaints of increased rates of adverse events with TRF oxycodone CR compared with the previous formulation. Thus, other patient complaints related to tolerability generally had no objective support.

### Efficacy objections

Some patients whose treatment was switched from the previous formulation to TRF oxycodone CR reported they could not "feel" the new drug working. No information on the pharmacokinetics, efficacy, or safety of TRF oxycodone CR was found in the published scientific literature because the manufacturer did not publish these data in peer-reviewed journals. However, clinical trials evaluating the bioequivalence of reformulated oxycodone CR and the previous formulation have been posted (with results) on ClinicalTrials.gov (NCT01101165; NCT01101178; NCT01100086; NCT01099709; NCT01101191; NCT01100320).<sup>1-5</sup>

In addition, an Internet search (Google) located a presentation by Purdue Pharma to the US Food and Drug Administration (FDA) Advisory Committee, which included pharmacokinetic data (mean concentration versus time graphs) indicating that TRF oxycodone CR has a less rapid early release phase, with a slightly higher peak maximal concentration than the previous formulation.<sup>10</sup> Positive subjective effects of opioids are accentuated by rapid drug release and increase the attractiveness of a drug for misuse.<sup>11,12</sup> A recent head-to-head comparison of the previous formulation of oxycodone CR with oxymorphone extended release (ER) suggested that the initial rapid release phase of the previous formulation of oxycodone CR may have contributed to reports of increased positive subjective effects with oxycodone CR compared with equianalgesic doses of oxymorphone ER, which shows a slower initial release.<sup>12</sup> Consequently, patients who complain that since switching to TRF oxycodone CR they could not "feel it working" may be experiencing lower initial positive subjective effects rather than reduced analgesia. There is no clinical reason to believe reformulated oxycodone CR would be less effective as an analgesic than the previous formulation. Asking the patient to describe his or her pain level after the initial onset period (eg, from 2 hours postdose) to the end of dose (eg, 8–12 hours postdose) may help the clinician to tease out the subjective effects associated with onset from the analgesic effects during sustained release.

## Insurance coverage objections

The TRF of oxycodone CR is carried on large private insurance formularies as a brand-name drug.<sup>13,14</sup> Some Medicare formularies may include TRF oxycodone CR,<sup>15,16</sup> but others may not,<sup>17</sup> or, if they do, may restrict patient access to the higher dose tablets of oxycodone CR.<sup>18</sup> The Ontario (Canada) Drug Benefit Formulary discontinued coverage of oxycodone CR when the TRF formulation was introduced. The decision to do so was based on the high rate of abuse of the previous formulation.<sup>19</sup> In summary, testing the validity of this objection will require contacting the patient's insurer or checking the formulary of the patient's plan.

## Cost objections

The wholesale price of oxycodone CR did not change with the introduction of the TRF. However, oxycodone CR is only available as a brand-name drug, which means it will be more expensive than an opioid available as a generic. For example, in Vermont, USA, the average wholesale price for a 1-month supply of TRF oxycodone CR 80 mg tablets may be as much as \$1500.<sup>20</sup> Participants in Medicare Part D may have to bear up to 25% of the cost of branded drugs,<sup>21</sup>

which would be >\$350 for a 1-month supply of 80 mg tablets at the Vermont average wholesale price.<sup>20</sup> Testing the validity of complaints about cost may require a call to the pharmacist to inquire whether a given patient is actually incurring greater out-of-pocket costs since switching to a TRF opioid.

## Protocol for testing validity of patient objections

A summary of our process of investigating the validity of patient objections to switching to a TRF is presented in Table 1. Obvious starting points are the product prescribing label, manufacturer medical information resources, and FDA updates. Searching the medical literature may reveal scant information about efficacy and tolerability of the TRF opioid.

The approval process for replacing an existing product with a TRF may require only proof of bioequivalence; randomized, controlled studies of efficacy and safety will not be repeated. In this regard, ClinicalTrials.gov may become a valuable resource. For example, Purdue posted their bioequivalence trials with data for TRF oxycodone CR on ClinicalTrials.gov rather than publishing the clinical

**Table 1** Protocol for testing validity of objections to tamper-resistant opioids

Objection	Response
Causes more adverse events than my previous opioid	<ul style="list-style-type: none"> <li>• Check the product label, manufacturer/FDA updates, and manufacturer medical information</li> <li>• Search PubMed for published reports of AEs</li> <li>• Check ClinicalTrials.gov for unpublished trial results</li> <li>• Conduct an informal Internet search to determine what recreational drug users/abusers are saying about the drug</li> <li>• Attempt to switch a patient reporting AEs with one TRF opioid to a different TRF opioid</li> </ul>
Less effective than my previous opioid	<ul style="list-style-type: none"> <li>• Check the product label, manufacturer/FDA updates, and manufacturer medical information</li> <li>• Search PubMed for published reports on efficacy and subjective effects</li> <li>• Check ClinicalTrials.gov for unpublished trial results</li> <li>• Conduct an informal Internet search to determine what recreational drug users/abusers are saying about the drug</li> <li>• Continue treatment long enough to confirm that the complaint is actually due to reduced analgesia</li> <li>• Switch a patient reporting reduced efficacy with one TRF opioid to a different TRF opioid</li> </ul>
Not covered in my formulary	<ul style="list-style-type: none"> <li>• The formulary status of a medication can be easily determined</li> </ul>
More expensive than my previous opioid	<ul style="list-style-type: none"> <li>• Check with the patient's pharmacy about the patient's out-of-pocket expense with the drug</li> <li>• Because all TRF opioids are branded products, patients who cannot afford the out-of-pocket costs may require a switch to a generic non-TRF opioid</li> <li>• Medicare recipients with limited resources or experiencing coverage gaps may have access to buying assistance programs</li> </ul>

**Abbreviations:** AE, adverse event; FDA, US Food and Drug Administration; TRF, tamper-resistant formulation.

trials used to support FDA approval in peer-reviewed journals.<sup>1–5</sup>

## Current tamper-resistant opioid formulations

Currently available TRFs and their tamper-resistance mechanisms are summarized in Table 2. Among available TRFs, oxymorphone ER is the only product similar to oxycodone CR in having been previously marketed as a non-TRF that has now been replaced with a formulation designed to resist crushing. Because of its recent introduction, the authors have limited experience switching patients to reformulated oxymorphone ER.

However, unlike oxycodone CR, the manufacturer of oxymorphone ER has published clinical trial results in peer-reviewed publications comparing previous and reformulated oxymorphone ER with respect to bioequivalence and bioavailability when coingested with ethanol.<sup>22,23</sup> Clinical trials comparing the efficacy and safety of the previous and reformulated versions of oxymorphone ER have not been performed. Nonetheless, there is no reason to expect differences in efficacy or tolerability between the two formulations.

Tapentadol ER (Nucynta® ER; Ortho-McNeil-Janssen Pharmaceuticals, Titusville, NJ, USA) and immediate release (IR) oxycodone with aversive technology (Oxecta®; King Pharmaceuticals, Bristol, TN, USA, and Acura Pharmaceuticals Inc, Palatine, IL, USA) were initially introduced with TRFs; thus, it will not be possible to gauge patient objections relative to a previous non-TRF version. Tapentadol ER does not disclose in its prescribing information that it has a hardened matrix designed to resist crushing,<sup>24</sup> but in its New Drug Application to the FDA it is described as a TRF.<sup>25</sup> As with reformulated oxycodone CR, the formulary status and

costs of reformulated oxymorphone ER, tapentadol ER, and oxycodone IR with aversive technology are easily obtained from insurance plans and pharmacies. In reviewing a cross section of insurers, tapentadol ER is available in private formularies but oxycodone IR with aversive technology is typically not covered.<sup>13,14</sup> Either tapentadol ER or oxycodone IR with aversive technology may be available in some Medicare formularies but not others.<sup>16–18</sup>

Oxymorphone ER, tapentadol ER, and oxycodone IR with aversive technology are all available as brand-name drugs, making them more costly than opioids available as generic formulations. However, both tapentadol ER and oxycodone IR with aversive technology are new drugs and have no previous, non-TRF formulation to permit a cost comparison. Reformulated oxymorphone ER has the same price as the previous oxymorphone ER formulation; hence, switching a patient from one to the other should not create new cost concerns.

It should be stated that following the introduction of reformulated oxycodone CR, postmarketing data indicated that many abusers switched to other substances for abuse, including heroin and oxymorphone ER.<sup>8,26</sup> However, these data were gathered prior to the introduction of reformulated oxymorphone ER. The reformulation of oxymorphone ER has been fortified with mechanical barriers to tampering that are similar to those incorporated into reformulated oxycodone CR;<sup>27</sup> it is not yet known how this will affect its use by abusers. Unfortunately, heroin will continue to be available and may present an even greater public health risk than abuse of prescription opioids because there is no certainty about its purity or the presence of adulterants.

The reported shift in opioid usage patterns highlights the importance of using urine toxicology tests to ascertain

**Table 2** Available tamper-resistant opioid formulations

Formulation	Mechanism
OxyContin® (oxycodone controlled release; Purdue Pharma, Stamford, CT, USA)	<ul style="list-style-type: none"> <li>Resists crushing and chewing</li> <li>Turns into a viscous gel in liquids that resists intravenous abuse</li> </ul>
OPANA® ER (oxymorphone extended release; Endo Pharmaceuticals Inc, Chadds Ford, PA, USA)	<ul style="list-style-type: none"> <li>Formulated in a hard polyethylene oxide matrix (INTAC™, Grünenthal GmbH, Aachen, Germany) designed to resist crushing</li> <li>Turns into a highly viscous gel in liquids</li> </ul>
Nucynta® ER (tapentadol extended release; Ortho-McNeil-Janssen Pharmaceuticals, Titusville, NJ, USA)	<ul style="list-style-type: none"> <li>Formulated in a hard polymer (INTAC®, Grünenthal GmbH, Aachen, Germany) designed to resist crushing</li> <li>Turns into a highly viscous gel in liquids</li> </ul>
Oxecta® (oxycodone immediate release; King Pharmaceuticals, Bristol, TN, and Acura Pharmaceuticals Inc, Palatine, IL, USA)	<ul style="list-style-type: none"> <li>Aversive ingredients cause irritation if the product is crushed and inhaled</li> </ul>

**Abbreviation:** ER, extended release.

whether a patient complaining about a tamper-resistant opioid formulation has migrated to another drug obtained from an alternate source, such as another doctor, a street dealer, or by theft. It may not be easy to determine if a patient who has been prescribed oxycodone CR has begun abusing illicitly obtained oxymorphone because oxycodone produces oxymorphone as a metabolite; thus, the presence of oxymorphone in the urine of a patient prescribed oxycodone does not necessarily indicate that the patient has been consuming oxymorphone illicitly.<sup>28</sup> A quantitative analysis must be ordered, and only if the ratio of oxymorphone to oxycodone exceeds that expected relative to the time of dosage is the test indicative of oxymorphone abuse.<sup>29</sup> Thus, monitoring compliance in opioid-treated patients will remain essential (and complicated) even when a TRF is prescribed.

At the time of the last literature search performed before submission of this manuscript (July 26, 2012), no data on the epidemiology of abuse of reformulated oxymorphone ER, tapentadol ER, or oxycodone IR with aversive technology had been published.

## Conclusion

Patient objections about the tolerability, efficacy, and cost of reformulated oxycodone CR may have validity. Objections about insurance coverage and costs were insurer specific but easily verified. Objections based on efficacy or tolerability could not be checked against published peer-reviewed articles. However, in some instances, non-peer-reviewed (unpublished) data are available on the Internet; these data suggest that changes associated with the new TRF of oxycodone CR may alter a patient's perception of "response" because of the slower time to maximal concentration, which could reduce the drug's subjective effects.

Generally, it may be difficult to distinguish legitimate objections from drug-seeking behavior with tamper-resistant opioids. Cost and availability objections should be easy to address. However, objections based on lack of efficacy or poor tolerability may be difficult to confirm if the patient is switched to a TRF opioid from a non-TRF of a different opioid molecule. It is well known that patients vary in their response to individual opioid molecules, making lack of efficacy or intolerable adverse events commonplace following a switch from one molecule to another.<sup>30</sup> The availability of multiple tamper-resistant opioids would allow for multiple opioid rotations in patients reporting poor outcomes; this would help address objections based on poor efficacy or tolerability without reverting to a non-TRF.

It may seem ironic that Ontario Drug Quality and Therapeutics Committee recommended discontinuing coverage of

TRF oxycodone CR because of the high rate of abuse with the previous, non-TRF formulation.<sup>19</sup> However, studies of substance abuser preferences indicate that drug formulation is only one of several factors that influence the attractiveness of a substance for abuse.<sup>31</sup> Factors such as media attention, peer preferences, availability, and cost may cause a drug to retain some value for abuse after tamper-resistant reformulation, particularly because abuse of intact tablets is not addressed by any of the available TRF strategies.

A limitation of this review is that it presents the authors' opinions, based on their experience in clinical practice. These opinions cannot be extrapolated to all physicians treating other pain populations. However, in the absence of hard data in the early days of TRF availability, it is important for clinicians to share their experience in ways that may guide future research.

Despite the lack of a substantial body of postmarketing data, the authors believe that the presence of opioid formulations that are designed to resist tampering (eg, crushing, extraction), such as oxycodone CR, oxymorphone ER, tapentadol ER, and IR opioids, could possibly lessen recreational misuse of these drugs, along with the associated costs to the healthcare system. Inclusion of tamper-resistant opioids as preferred drugs on private and public formularies will require post-marketing data to indicate that they reduce misuse and requires recognition on the part of payers that drug acquisition costs will be offset by reduced costs related to poor outcomes and abuse.

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