The Effectiveness and Safety of Various Abuse Deterrent Formulations of Oxycodone: A Systematic Review

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Abstract

Introduction: Oxycodone is an opioid analgesic medication with a high risk for abuse. This systematic review examined and compared the effect of various opioid-deterrent formulations of oxycodone on their ability to reduce opioid abuse. Three types of abuse deterrent formulations (ADF) were studied: Technology-Based ADF’s, Opioid Antagonist ADF’s, and Aversive Excipient ADF’s.

Methods: Twelve randomized controlled trials that were published in English, conducted in North America within the past 5 years, and studied abuse deterrent formulations of oxycodone were included. Search methods for identification of studies were conducted through Pubmed and Cochrane Central Register of Controlled Trials (CENTRAL). The primary outcome was the effect of ADFs on oxycodone formulation manipulation and opioid abuse trends in patients prescribed ADFs. The secondary outcomes were adverse events, quality of life, adherence (primarily being used as prescribed), and patient experience of euphoria. All reviewers performed all data abstraction and quality assessment individually.

Results: Technology-based formulations were shown to be both effective in preventing opioid abuse and had a much lower incidence of adverse effects.

Conclusion: Although educating patients remains the most important step in reducing the epidemic of opioid abuse and overdose, studying additional ways to deter and reduce abuse can be extremely helpful in furthering the abuse potential.

Background

Description of the problem
Abuse of opioid analgesics is a major problem that has increased substantially in the United States throughout the past decade. In 2015, the total opiate-related overdose deaths was 33,091, which is nearly four-times the death rate in 1999.¹ Opioid abuse is contributed to a reduced quality of life and an increased risk of death from...
overdose. Opioids are primarily prescribed for pain management. However, they are easily accessible without a prescription.

Patient experience, resources, education, access, and drug properties are among the factors that influence substance abuse. Opioid analgesics are a treatment option for moderate to severe pain that are prescribed to millions of patients annually. Although opioids can be abused through oral ingestion, the frequency of abuse by injection or inhalation increases as the duration and severity of abuse increases. Figure 1 illustrates the contributing factors to opioid abuse.

There is a critical need to reduce the abuse potential of opioid medications. Studies indicate that abuse with prescription opioids is a strong risk factor for heroin use. The incidence of heroin users is 19 times higher among those who use opioids for nonmedical reasons than those who report medical use. Another study found that 50% of persons ages 18 to 33 years who had recently began using heroin reported having abused opioids in the past.

Figure 1: Contributing Factors to Opioid Abuse

Description of the intervention
Research over the past decade has extensively examined drug structures to address the emerging opioid pandemic. Opioid analgesics with abuse-deterrent properties can help prevent abuse via various routes of administration that require cutting, crushing, or other ways of manipulating the formulations. There are three methods utilized to create abuse-deterrent formulations (ADFs) are described below:

I. Technology-Based ADF’s: One category of abuse deterrent formulations is technology-based. These formulations use proprietary manufacturing that utilizes unique polymers, inactive beads, and excipients to maintain the original pharmacokinetic properties or “gel” upon crushing or dissolving, which prevents abuse in all routes of administration except the oral route.

II. Opioid Antagonist ADF’s Another category utilized is the addition of opioid antagonists, either naloxone or naltrexone to the formulation. Opioid antagonists compete and displace opioids at opioid receptor sites and can be formulated in dosage forms to release when a medication is inappropriately utilized, such as crushing, or with a route of administration that favors the opioid over the antagonist.
III. Aversive Excipients ADF’s

The third category of abuse deterrent formulations consists of opioids with a particular aversive excipient, such as niacin. This excipient gives the medication an unpleasant, unwanted side effect when used in excess and therefore, helps prevent abuse with the formulation.

**Objectives**

The primary objective of this study was to review the evidence for the safety and effectiveness of abuse deterrent formulations (ADF) of oxycodone. The secondary objective was to evaluate the potential of the ADF to prevent opioid abuse in American adults.

**Methods**

A systematic review method was utilized to conduct this research. The studies included in the systematic review were randomized controlled trials in adult participants who have a history of prescription and/or nonprescription opioid use. The interventions included the administration of various abuse deterrent oxycodone formulations compared to placebo and current non-abuse deterrent formulations.

The primary outcome was the effect of ADFs on oxycodone formulation manipulation and opioid abuse trends in patients prescribed ADFs. The secondary outcomes were adverse events, quality of life, adherence (primarily being used as prescribed), and patient experience of euphoria. Search methods for identification of studies were conducted through Pubmed and Cochrane Central Register of Controlled Trials (CENTRAL). All reviewers performed all data abstraction and quality assessment individually.

The inclusion criteria for the systematic review was inclusion of the terms “oxycodone,” “abuse deterrent,” “opioid,” “abuse resistant,” and “randomized.” The studies were all published in English and conducted in North America. Exclusion criteria were studies not published in English, conducted outside of North America, not relevant to the safety and efficacy of abuse deterrent formulations, and not evaluating oxycodone.

**Data Collection**

Three review authors independently assessed all the titles and abstracts identified as a result of the search strategy. Twenty-seven articles were collected on the search, 12 fit inclusion/exclusion criteria. Thirteen articles were not relevant to the study subject, as they were found to later fit the exclusion criteria and 2 publications were found to be published presentations. Three types of ADFs were evaluated in the data collected: opioid antagonist formulations, technology-based formulations, and aversive excipient-based formulations.

The three abuse deterrent formulation categories were ranked on an efficacy scale of 1-to-3, with 1 meaning highly effective and 3 meaning least effective. The efficacy was evaluated based on patient reported feeling, adverse events, and potential adherence. Of the studies included, nine were categorized as technology-based formulations, two as opioid antagonist formulations, and one as aversive excipient-based formulations. The previous drug effects were compared with adverse events to indicate how effective treatments were. In the rare occasions that the researchers disagreed on the ranking of the articles, they discussed the discrepancies until a consensus was reached.

**Results**

The following three tables describe the articles that were included in the systematic review. All three categories had similar efficacy results and were shown to prevent abuse. However, their safety profiles and types of abuse they prevented differed slightly.

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<tr>
<th>Study</th>
<th>Authors/Reference</th>
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<tr>
<td>Comparing the effect of tampering on the oral pharmacokinetic profiles of two extended-release oxycodone formulations with abuse-deterrent properties, 2015</td>
<td>Gudin J, Levy, Cooperman N, Kopecky EA, Fleming AB</td>
<td>Studied oral pharmacokinetic profiles of two extended release oxycodone products in a randomized, open-label crossover study in New Jersey, U.S. with 38 subjects.</td>
<td>The intact study drug and crushed study drug had a Cmax (ng/mL) of 67.2 and 62.9, respectively, and a Tmax (hours) of 3.5 and 4, respectively. Crushed immediate release oxycodone had a Cmax of 19.4 ng/mL and a Tmax of 1.75 hours. Adverse events were not significantly different than immediate.</td>
<td>The study found the ADF oxycodone maintained desired pharmacokinetics, lowering the likelihood of illicit use by modification.</td>
<td>DETERx technology maintained desired plasma concentrations with modification and had few adverse events.</td>
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<td>A randomized, double-blind, double-dummy study to evaluate the intranasal human abuse potential and pharmacokinetics of a novel extended-release abuse-deterrent formulation of oxycodone, 2016</td>
<td>Webster LR, Kopecky EA, Smith MD, Fleming AB</td>
<td>Studied intranasal pharmacokinetics and drug liking of abuse deterrent oxycodone in a randomized, double-blind, randomized controlled crossover trial in Utah, U.S. with 36 subjects.</td>
<td>Intranasal DETERx oxycodone had a VAS score of 5.99 (p &lt; 0.05) indicating a lower liking than oral DETERx oxycodone with a score of 14.7 (p &lt; 0.001). Oxycodone immediate-release had a VAS score of 20.69 (p &lt; 0.001), which is significantly greater than DETERx products.</td>
<td>Pharmacokinetics demonstrated lower plasma levels and abuse potential by VAS for the DETERx oxycodone vs immediate-release oxycodone with DETERx oxycodone having similar plasma concentrations by intranasal and oral routes.</td>
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<td>Oral human abuse potential of oxycodone DETERx: An abuse deterrent, extended-release formulation in recreational opioid users</td>
<td>Kopecky EA, Fleming AB, O’Connor M, Varanasi RK</td>
<td>Evaluated drug liking, safety, and pharmacokinetic factors of DETERx using crushed and intact DETERx and crushed immediate-release oxycodone &amp; TEmax for both chewed and intact DETERx was significantly lower than that of crushed oxycodone (p&lt;0.0001) and DETERx chewed did not change P4 profile compared with intact DETERx.</td>
<td>The study supported a lower abuse potential of either crushed or intact Oxycodone DETERx than immediate release oxycodone when taken orally.</td>
<td>The drug formulation DETERx may reduce the potential for abuse while achieving the desired pharmacokinetics over immediate release oxycodone.</td>
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<td>Long-term safety of Remoxy® (extended-release oxycodone) in patients with moderate to severe chronic osteoarthritis or low back pain</td>
<td>Friedmann N, Klutzaritz V, Webstler L</td>
<td>Studied the long term safety, tolerability and efficacy of Remoxy® in patients with chronic low back pain and chronic pain from osteoarthritis in the hip or knee</td>
<td>82% of patients reported adverse reactions (AEs) similar to other opioid AEs such as constipation, nausea, and somnolence. One serious AE was probably due to ramoxy and resulted in hospitalization. Pain was significantly lower in patients taking Remoxy® than those who were taking a placebo, (p=0.013) in the 5 week trial and (p=0.007) in the 12 week study as reported by pain intensity by the patients.</td>
<td>Remoxy® can be used to safely treat pain from chronic osteoarthritis of the hip/knee and chronic low back pain.</td>
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<td>Efficacy and safety of an extended-release oxycodone (Remoxy®) formulation in patients with moderate to severe osteoarthritis pain</td>
<td>Friedmann N, Klutzaritz V, Webstler L</td>
<td>Studied the efficacy and safety of Remoxy® in patients with moderate to severe osteoarthritis pain</td>
<td>AUC change for pain intensity score was reduced by 30.4% in the placebo group and 54.9% for Remoxy® (p&lt;0.007). Significant reductions in pain intensity for each week also shown compared to the placebo group.</td>
<td>Remoxy® significantly improved pain intensity among patients with moderate to severe chronic osteoarthritis pain.</td>
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<td>Clinical outcomes during opioid titration following initiation with or conversion to Remoxy®, an extended-release formulation of Oxycodone</td>
<td>Roland GL, Setnik B, Cleveland JA, Brown DA</td>
<td>Evaluated long-term efficacy and effectiveness of the titration of Remoxy® in relieving moderate to severe chronic pain</td>
<td>A stable steady state was achieved after an average of 2.2 titration steps. The average PI decreased from a baseline of 6.5 to 4.9 by month 4 and maintained at this level throughout the end of the study.</td>
<td>Remoxy® is safe and efficacious in relieving moderate to severe chronic pain.</td>
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<td>Correlation of subjective effects with systemic opioid exposure from fixed-dose combinations of oxycodone/acetaminophen in recreational users of prescription drugs, 2015</td>
<td>Morton TL, Devarakonda K, Kestenbader K, et al</td>
<td>Studied drug liking in a randomized, double-blind, active- and placebo-controlled, 2x2 crossover study-conducted in Montreal, Quebec, Canada with patients completing all aspects of the study</td>
<td>Results showed that intact immediate-release/extended-release oxycodone/acetaminophen produced 50% lower oxycodone peak plasma concentrations than immediate-release oxycodone/acetaminophen (p&lt;0.001) and median oxycodone time to maximum concentration was significantly longer for intact immediate release/extended release oxycodone/acetaminophen than immediate-release oxycodone/acetaminophen. It also showed that crushing did not shorten the median time to maximum concentration for immediate release/extended release oxycodone/acetaminophen.</td>
<td>The conclusions showed that the lower oxycodone concentrations seen in extended release formulations, particularly at earlier time points, were correlated with less positive subjective drug effects (drug high, drug liking).</td>
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<td>A tale of 2 ADFs: differences in the effectiveness of abuse deterrent formulations of oxymorphone and oxycodone extended release drugs, 2016</td>
<td>Cicero TJ, Ellis MS, Kasper ZA</td>
<td>The study was a structured survey of 12,124 individuals throughout the United States entering treatment for opioid use disorder followed by a more focused online survey with 129 of these patients.</td>
<td>The survey consisted of both structured and open-ended questions and data showed that Oxontic abuse deterrent formulation (ADF) was highly effective in reducing nonoral abuse (91.4% before the ADF, 47.9% afterwards) particularly with insufflation and intravenous injection of the active drug.</td>
<td>The conclusions of this study suggest that a combination of ADF’s effectiveness may be drug specific and each must be evaluated individually, even if the same foundational ADF technology is used.</td>
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<td>A phase 3, multi-center, randomized, double-blind, placebo-controlled, safety, tolerability, and efficacy study of Xampla ER in patients with moderate to severe chronic low back pain</td>
<td>Katz N, Kopecky EA, O’Connor M, et al</td>
<td>Evaluated the efficacy, tolerability, and safety of Xampla ER in patients with moderate to severe chronic low back pain. Xampla ER is oxycodone formulated with PF®.</td>
<td>Each subject was titrated on Xampla ER and then randomized to two groups active drug (N=1932) and placebo (N=1566) for 12 weeks. Efficacy results showed that there was a statistically significant difference in pain intensity (p&lt;0.001). Xampla had similar adverse events to other oxycodone products and significantly reduced the pain of individuals.</td>
<td>Xampla had similar adverse events to other oxycodone products and with abuse deterrent properties may be beneficial in reducing abuse.</td>
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<td>Abuse deterrent formulations may play a role in decreasing nonoral abuse with oxycodone specifically.</td>
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<td>Roland GL, Setnik B, Cleveland JA, Brown DA</td>
<td>Evaluated long-term efficacy and effectiveness of the titration of Remoxy® in relieving moderate to severe chronic pain</td>
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Technology-based formulations such as DETERx (Table 1) are both safe and effective. These formulations have been found to statistically significantly prevent opioid abuse. When these medications are crushed, they have been found to maintain similar pharmacokinetics as when intact, thus lowering the likelihood of illicit use by crushing. This formulation also allows these medications to be available for patients who have trouble swallowing or require a G-tube for medication administration. These medications were also not found to have significantly different adverse effects than immediate release or extended release oxycodone.

**Table 2. Opioid Antagonist ADFs**

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<th>CONCLUSIONS</th>
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<tr>
<td>Abuse potential of intravenous oxycodone and naloxone solution in non-dependent recreational drug users, 2014</td>
<td>Nafoxone and oxycodone were not statistically different in drug liking from placebo and oxycodone alone. Nafoxone and oxycodone had a VAS score of 45.5 vs 75.5 for oxycodone and 49 for placebo with p-values 0.46, 0.001, and -0.001, respectively.</td>
<td>Pharmacokinetics of the IV oxycodone with naloxone were not significantly dissimilar to IV oxycodone alone.</td>
<td>Intravenous oxycodone and naloxone had similar pharmacokinetic profiles with less drug liking than oxycodone alone.</td>
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<td>Intranasal administration of crushed ALO-02 (extended-release oxycodone with sequestered naloxone); A randomized, controlled abuse-potential study in nondependent recreational opioid users, 2015</td>
<td>The crushed study drug had significantly lower scores versus oxycodone IR on drug liking (62.1 vs 92.8, respectively) and high (25.2 vs 86.9, respectively).</td>
<td>The study found significantly lower drug liking/ high VAS scales and lower adverse events with the oxycodone/naloxone drug compared to immediate release oxycodone.</td>
<td>The ALO-02 is efficacious in reducing drug liking and high for patients taking oxycodone.</td>
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Medications formulated with opioid antagonists such as naloxone or naltrexone (Table 2) have been found to be relatively effective in preventing abuse, particularly by non-oral routes such as intravenous injection and insufflation. These formulations have similar safety effects as current FDA-approved opioid analgesics. However, adverse effects are common when they are crushed or chewed. This limits the use of these medications in patients who have trouble swallowing or require the use of a feeding tube for medication administration.
Aversive excipient formulations such as the use of niacin (Table 3) are effective in preventing opioid abuse. However, they have a high incidence of adverse effects in all patients. Studies showed that 98-100% of patients experienced treatment emergent adverse effects.

**Authors’ Conclusions, Discussion and Future Research**

In summary, technology-based formulations of oxycodone were shown to be effective in preventing opioid abuse and they have a much lower incidence of adverse effects compared to aversive excipient formulations of oxycodone. Opioid antagonists are effective in preventing abuse. However, these formulations are more successful in preventing abuse via non-oral routes, such as intravenous or insufflation. Formulation technology prevents opioid abuse by oral route and non-oral routes of administration and offer a safety profile similar to currently approved opioid analgesics. These medications can also be given to patients who have difficulty swallowing or require medication administration via G-tube routes.

By reducing the abuse potential from non-medical routes of administration, especially those seen with heroin use, rates of abuse may be reduced. Although educating patients remains the most important step in reducing the epidemic of opioid abuse and overdose, studying additional ways to deter and reduce abuse can be extremely helpful in furthering reducing the abuse potential. Figure 2 illustrates the efficacy ranking of the three categories of ADFs.

**Table 3. Aversive Excipient-Based ADFs**

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<tr>
<th>STUDY</th>
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<tr>
<td>Randomized, double-blind, placebo-controlled and active-controlled study to assess the relative abuse potential of oxycodone HCl-niacin tablets compared with oxycodone alone in non-dependent, recreational opioid users, 2012</td>
<td>Webster LR, Rollin R, Rotlink GC, Sommerville KWM</td>
<td>Studied deterrent excipients with immediate release oxycodone on relative abuse potential in a randomized, double-blind, crossover study in Utah, U.S. with 49 participants.</td>
<td>The study drug had a Visual analog scale (VAS) score less than the placebo: 40/240 mg had a VAS of 47.2, 80/480 mg 46.5, placebo 50.5, 40 mg oxycodone 65%, and 80 mg oxycodone 75%. Treatment emergent adverse events were occurred in 100% of 80/480 mg participants compared to 56% with 40/240 mg, 96% with 80 mg oxycodone, 77% with 40 mg oxycodone, and 13% with placebo.</td>
<td>Oxycodeone HCl-niacin tablets may, in a dose dependent manner, decrease the potential for oral abuse of oxycodone without unexpected adverse effects or clinically significant differences in safety parameters compared with oxycodone alone</td>
<td>Oxycodeone and niacin produced significant reduction in drug liking with a high degree of adverse reactions. Although aversion is high, the adverse event profile of oxycodone and niacin is a barrier to adoption.</td>
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4 Figure 2 illustrates the efficacy ranking of the three categories of ADFs.

Opioid Antagonist Technology

Technology-Based Formulation

Aversive Excipient Technology

a. Technology-based formulations had the highest efficacy, safety, and overall ability to be used by patients. It can prevent opioid abuse by oral route and non-oral routes of administration and has a safety profile similar to currently approved opioid analgesics.
b. Opioid antagonists are effective in preventing abuse, however, these are more successful in preventing abuse via non-oral routes such as intravenous or insufflation.

c. Although oxycodone and niacin produced significant reduction in drug liking, the adverse event profile is a barrier to adherence.

At the time the study was conducted, the authors searched several national association websites to identify recommendations on ADFs and found that there was no consensus on the use of abuse deterrent formulations. The Centers for Disease Control and Prevention (CDC) did not currently have recommendations on abuse-deterrent formulations. The American Society of Health-System Pharmacists (ASHP) supported formulation development of abuse deterrent narcotics as one of a collection of strategies to address opioid abuse. The American Pharmacists Association (APhA) indicated that ADFs are a potential strategy to complement education programs. APhA encourages research into ADFs and encourages manufacturers to develop ADFs to combat opioid misuse and abuse. Future studies should focus on current recommendations and guidelines offered by national associations on opioid deterrent formulations.

References