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

by Alexander Heinz, PharmD Candidate, Roosevelt University College of Pharmacy; Julia Gilbert, PharmD Candidate, Roosevelt University College of Pharmacy; Gerald Cavanagh, PharmD Candidate, Roosevelt University College of Pharmacy; Abby A. Kahaleh, BPharm, MS, PhD, MPH, Associate Professor, Roosevelt University College of Pharmacy

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.[1] 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.[2] **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.[3,4] The incidence of heroin users is 19 times higher among those who use opioids for nonmedical reasons than those who report medical use.[3] 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.[4]

Figure 1: Contributing Factors to Opioid Abuse[2]

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.[1]

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 in inappropriately utilized, such as crushing, or with a route of administration that favors the opioid over the antagonist.[2]

III. *Aversive Excipients ADF's* The third category of abuse deterrent formulations consists of opioids with a particular aversive excipient, such as niacin.3 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.

Table 1. Technology-Based ADFs[5-13]

STUDY	AUTHORS/ REFERENCE	DESCRIPTION	FINDINGS/RESULTS	CONCLUSIONS	SR CONCLUSION
Comparing the effect of tampering on the oral pharmacokinetic profiles of two extended-release oxycodone formulations with abuse-deterrent properties, 2015	Gudin J, Levy-Cooperman N, Kopecky EA, Fleming AB[5]	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.	The intact study drug and crushed study drug had a Cmax (ng/mL) of 67.5 and 62.9, respectively, and a Tmax (hours) of 3.5 and 4, respectively. Crushed immediate release oxycodone had a Cmax of 79.4 ng/mL and a Tmax of 1.75 hours. Adverse events were not significantly different than immediate	The study found the ADF oxycodone maintains desired pharmacokinetics, lowering the likelihood of illicit use by modification	DETERx technology maintained desired plasma concentrations with modification and had few adverse events

			or extended-release oxycodone.		
A randomized, doubleblind, double-dummy study to evaluate the intranasal human abuse potential and pharmacokinetics of a novel extended-release abuse-deterrent formulation of oxycodone, 2016	Webster LR, Kopecky EA, Smith MD, Fleming AB[6]	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.	Intranasal DETERx oxycodone had a VAS score of -5.99 ($p < 0.5$) indicating a lower liking than oral DETERx oxycodone with a score of 14.7 ($p < 0.001$). Oxycodone immediate-release had a VAS score of 20.69 ($p < 0.001$), which is significantly greater than DETERx products.	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.	Intranasal oxycodone had lower plasma concentrations and lower drug liking than immediate-release oxycodone.
Oral human abuse potential of oxycodone DETERx: An abusedeterrent, extendedrelease formulation in recreational opioid users	Kopecky EA, Fleming AB, O'Connor M, Varanasi RK[7]	Evaluated drug liking, safety, and pharmacokinetic factors of DETERx using crushed and intact DETERx and crushed immediate release oxycodone	TEmax for both chewed and intact DETERx was significantly longer than that of crushed oxycodone ($p<0.0001$) and DETERx chewed did not change the PK profile compared with intact DETERx.	The study supported a lower abuse potential of either crushed or intact Oxycodone DETERx than immediate release oxycodone when taken orally.	The drug formulation DETERx may reduce the potential for abuse while achieving the desired pharmacokinetics over immediate release oxycodone
Long-term safety of Remoxy® (extended-release oxycodone) in patients with moderate to severe chronic osteoarthritis or low back pain	Friedmann N, Klutzaritz V, Webster L[8]	Studied the long term safety, tolerability, and efficacy of Remoxy® in patients with chronic lower back pain and chronic pain from osteoarthritis in the hip or knee	82% of patients reported Adverse reactions (AE's) similar to other opioid AE's such as constipation, nausea, and somnolence. One serious AE was probably due to remoxy and resulted in hospitalization. Pain was significantly lower in patients taking Remoxy® than those who we 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.	The long term use of remoxy is safe and efficacious in the treatment of pain from chronic osteoarthritis of the hip/knee and chronic lower back pain	Remoxy can be used to safely treat pain from chronic osteoarthritis of the hip/knee and chronic lower back pain
Efficacy and safety of an extended-release oxycodone (Remoxy®) formulation in patients with moderate to severe osteoarthritic pain	Friedmann N, Klutzaritz V, Webster L[9]	Studied the efficacy and safety of Remoxy® in patients with moderate to severe osteoarthritic pain	AUC change for pain intensity score was reduced by 30.4 in the placebo and 54.9 for Remoxy® ($p<0.007$). Significant reductions in pain intensity for each week also shown compared to the placebo group.	Remoxy® significantly improved pain intensity among patients with moderate to severe chronic osteoarthritic pain.	Remoxy is more efficacious in the treatment of pain from moderate to severe chronic osteoarthritic pain when compared to a placebo
Clinical outcomes during opioid titration following initiation with or conversion to Remoxy®, an extended-release Formulation of Oxycodone	Roland CL, Setnik B, Cleveland JM, Brown DA[10]	Evaluated long-term safety and efficacy in the titration of Remoxy® in relieving moderate to severe chronic pain.	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 by month 4 and maintained at this level through the end of the study.	Remoxy® is safe and efficacious in relieving moderate to severe chronic pain.	Remoxy® is safe and more efficacious in relieving moderate to severe chronic pain when compared to a placebo.
Correlation of subjective effects with systemic opioid exposure from fixed-dose combinations of oxycodone/acetaminophen in recreational users of prescription drugs. 2015	Morton TL, Devarakonda K, Kostenbader K, et al[11]	Studied drug liking in a randomized, double-blind, active- and placebo-controlled, 7way crossover study conducted in Montana, with 55 patients completing all aspects of the study	Results showed that intact immediate-release/extended release oxycodone/acetaminophen produced 50% lower oxycodone peak plasma concentrations than immediate-release oxycodone/acetaminophen ($P<0.001$) 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	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).	The formulation produces desired plasma concentrations whether intact or crushed and therefore decreased inappropriate drug liking.
A tale of 2 ADFs: differences in the effectiveness of abuse deterrent formulations of oxymorphone and oxycodone extended release drugs, 2016	Cicero TJ, Ellis MS, Kasper ZA[12]	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.	The survey consisted of both structured and open-ended questions and data showed that Oxycontin abuse deterrent formulation (ADF) was highly effective in reducing non-oral abuse (91.4% before the ADF, 47.9% afterwards) particularly with insufflation and intravenous injection of the active drug.	The conclusions of this study found that the ADF's effectiveness may be drug specific and each must be evaluated individually, even if the same foundational ADF technology is used.	Abuse deterrent formulations may play a role in decreasing non-oral abuse with oxycodone specifically.
A phase 3, multicenter, randomized, double-blind, placebo-controlled, safety, tolerability, and efficacy study of Xtampza ER in patients with moderate-to severe chronic low back pain. 2015	Katz N, Kopecky EA, O'Connor M, et al[13]	Evaluated the efficacy, tolerability and safety of Xtampza ER in patients with moderate to severe chronic low back pain. Xtampza ER is oxycodone formulated with DE-	Each subject was titrated on Xtampza ER and then randomized to two groups: active drug (N=193) and placebo (N=196) for 12 weeks. Efficacy results showed that there was a statistically significant difference in average pain intensity ($P<0.0001$)	Xtampza had similar adverse events to other oxycodone products and significantly reduced the pain of individuals.	Xtampza had similar adverse events to other oxycodone products and with abuse deterrent properties may be beneficial in reducing abuse.

		TERx technology for the prevention of opioid abuse. It was a phase 3, multi-center, randomized double blind, placebo controlled study with 389 subjects conducted in MA, IL	and also less need for a rescue medication (Acetaminophen) when using Xtampza ER rather than the placebo. The adverse event profile was similar to other opioid analgesics and the medication was well tolerated by the subjects		

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[14,15]

STUDY	AUTHORS/ REFERENCE	DESCRIPTION	FINDINGS/RESULTS	CONCLUSIONS	SR CONCLUSION
Abuse potential of intravenous oxycodone/naloxone solution in nondependent recreational drug users, 2014	Colucci S, Perrino P, Shram M, et al.[14]	Studied intravenous pharmacokinetics and drug liking of oxycodone and naloxone in nondependent recreational drug users in a double-blind, randomized, crossover study in Ontario, Canada with 24 participants.	Naloxone and oxycodone was not significantly different in drug liking from placebo and oxycodone alone. Naloxone and oxycodone had a VAS score of 49.5 vs 79.5 for oxycodone and 46 for placebo with p-values 0.46, 0.001, and <0.001, respectively.	Pharmacokinetics of the IV oxycodone with naloxone were not significantly dissimilar to IV oxycodone alone.	Intravenous oxycodone and naloxone had similar pharmacokinetic profiles with less drug liking than oxycodone alone.
Intranasal administration of crushed ALO-02 (extended-release oxycodone with sequestered naltrexone): A randomized, controlled abuse-potential study in nondependent recreational opioid users, 2015	Setnik B, Bramson C, Bass A, et al.[15]	Studied drug liking in the administration of crushed oxycodone with sequestered naltrexone in a randomized, double-blind, crossover study in North Carolina, U.S. with 28 subjects	The crushed study drug had significantly lower scores versus oxycodone IR on drug liking (60.5 vs 92.8, respectively) and high (25.2 vs 86.9, respectively).	The study found significantly lower drug liking/high VAS scales and lower adverse events with the oxycodone/naltrexone drug compared to immediate release oxycodone	The ALO-02 is efficacious in reducing drug/liking and high for patients taking oxycodone.

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.

Table 3. Aversive Excipient-Based ADFs[16]

STUDY	AUTHORS/ REFERENCE	DESCRIPTION	FINDINGS/RESULTS	CONCLUSIONS	SR CONCLUSION
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 nondependent, recreational opioid users, 2012	Webster LR, Rolleri R, Pixton GC, Sommerville KW[16]	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.	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 40.3, placebo 50.5, 40 mg oxycodone 65.9, and 80 mg oxycodone 75. Treatment emergent adverse events were occurred in 100% of 80/480 mg participants compared to 98% with 40/240 mg, 98% with 80 mg oxycodone, 77% with 40 mg oxycodone, and 13% with placebo.	Oxycodone HCl-niacin tablets may, in a dose dependent manner, decrease the potential for oral abuse of oxycodone without unexpected adverse events or clinically significant differences in safety parameters compared with oxycodone alone	Oxycodone 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 adherence.

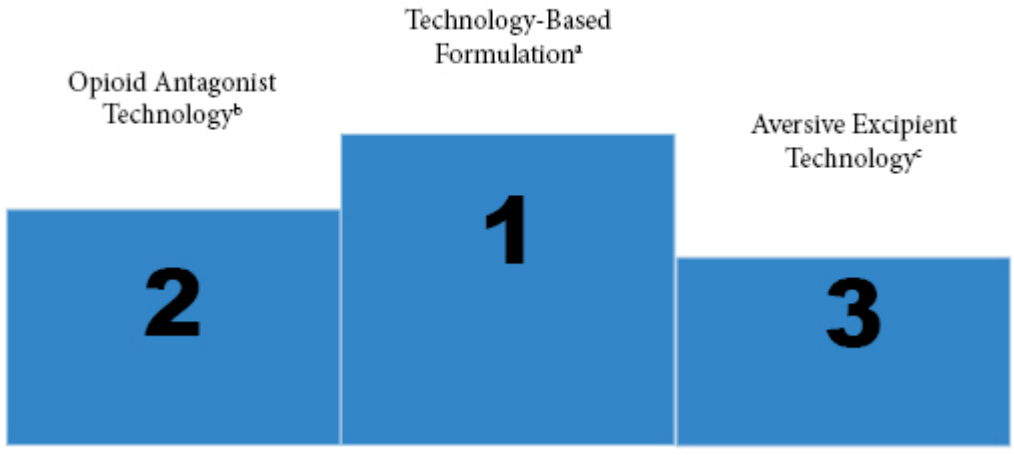
Aversive excipient formulations such as the use of niacin (**Table 3**) are effective in preventing opioid abuse. However, they have a high incidence of adverse effects in all patients. Studies showed that 98-100% of patients experienced treatment emergent adverse effects.

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.[4] **Figure 2** illustrates the efficacy ranking of the three categories of ADFs.

Figure 2. ADF Category Efficacy Ranking



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.[17] 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.[18] The American Pharmacists Association (APhA) indicated that ADFs are a potential strategy to complement education programs.[19] APhA encourages research into ADFs and encourages manufacturers to develop ADFs to combat opioid misuse and abuse.[20] Future studies should focus on current recommendations and guidelines offered by national associations on opioid deterrent formulations.

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