Effect of tamper-resistant/abuse deterrent formulations on the abuse potential of opioids

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Introduction

The medical use of opioids has led to a parallel increase in the non-medical use of prescription opioids.[4] Every year, over five million Americans engage in the non-medical abuse of opioids, burdening the United States with over 100 billion dollars a year in opioid-related healthcare costs.[2,3] Efforts to curtail opioid abuse are of great economic and societal interest. To address the addictive nature of prescription opioids tamper-resistant formulations have been created. The primary mechanisms of tamper-resistant formulations include combination formulations with deterrent agents such as naloxonone, pro-drug formulations, and crush-proof tablets. [3]

Single-entity oxycodone has a fast onset when taken orally and has contributed greatly to the oral abuse of opioids. In 1995, oxycontin OC was approved as an extended-release version of oxycodone; however, many users learned to crush the tablets to elicit fast acting effects.[2] Subsequently, opioid overdose rates increased from about 2,700 deaths per year in 1997 to 11,700 in 2011.[5] As a result of this dramatic increase in opioid-related mortalities, in 2010, oxycontin OCF was approved as a tamper-resistant form of oxycontin.[2] Currently, tamper-resistant opioid formulations are an active area of research. Our literature search explores the effect that tamper-resistant opioids have on a clinical and societal level.

Methods

A literature search was performed using the following search terms: abuse potential of tamper-resistant OR abuse deterrent opioid formulations. Additional filters included: English only, date range from 2010 to present, and free full text. This search yielded 15 articles, 7 of which were not considered as they were reviews, and 4 that were not applicable to the PICO question. The remaining four articles included two randomized, double-blind, positive- and placebo- controlled studies, a retrospective cohort study, and a randomized, repeated measures study.

- **P** = opioid abuse
- **I** = tamper-resistant/abuse deterrent opioid formulations
- **C** = non-tamper-resistant/abuse deterrent opioids
- **O** = reduction in abuse potential of opioids

Results

The retrospective cohort study eliminated selection bias, experimenter bias, and repeated testing bias with the use of a national data archive and objective measures. One limitation of this study is that it only includes data from reported abuse; there may be many cases of abuse exposure that go unreported to local poison centers and would thus decrease internal validity. Confounding variables like prescription monitoring, overdose prevention, and drug take-back programs may contribute to the reduction in abuse exposure and are, therefore, threats to internal validity.

The RCT's eliminated selection bias and experimenter bias. With similar control and study groups, within each study and between the two, there were few confounding variables. All these factors strengthen the internal validity of the studies. In addition, the RCT's used both objective and subjective measures to assess their hypotheses which helps to strengthen the internal validity and avoid repeated testing bias. However, both studies used surrogate measures that may not translate to a decrease in the rate of abuse in the overall population. Both RCT's had participants that were lost for various reasons, which may decrease the internal validity of the study. Both RCT's were financed by drug companies, which could have a negative effect on the internal validity of the study.

The repeated measures study eliminated selection bias and experimenter bias which helps to strengthen internal validity. Internal validity is also strengthened because the study used objective data and subjective data from participant's experience with the different formulations. Participants in the study were oxycodone abusers and, therefore, may have preferred non-tamper-resistant formulations more so than the average population; this possible confounding variable may decrease internal validity.

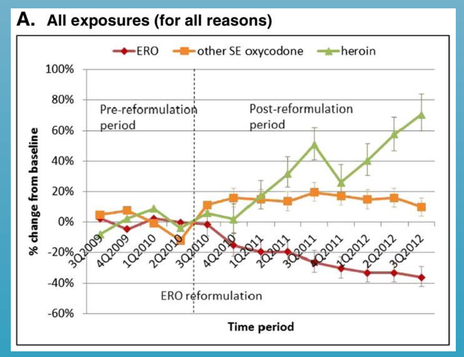
Reference	Study Design	Significance
Coplan et al.[1]	Retrospective cohort study	This study demonstrated that when tamper-resistant oxycodone ORF was introduced, there was a decrease in prescription opioid abuse. However, there was a marked increase in heroin and single entity oxycodone poison control calls. Abuse exposures decreased by 36% for patient using reformulated extended-release oxycodone (tamper-resistant form), increased 20% for single-entity oxycodone, and increased 42% for heroin users.
Harris et al.[2]	Randomized controlled trial	This study was used because it showed that Reformulated OxyContin (ORF) tablets have a lower potential for abuse than standard OxyContin tablets. Compared to the 84.0% of participants who liked finely crushed standard OxyContin tablets, only 59.8% of participants liked the finely crushed ORF tablets and 49.6% of participants liked the coarsely crushed ORF tablets. Only 26.7% of participants liked the placebo. This evidence is corroborated by pharmacokinetic profiles of each drug that indicated less potential for abuse. Data was taken using a bipolar visual analog scale, in which patients only have three options - like, dislike, neutral. Data was reported by like rate.
Webster et al.[4]	Randomized controlled trial	This study was used because it showed that the combination formulation oxycodone HCl-niacin tablets have a lower potential for abuse than standard oxycodone tablets. Compared to the 15% (40 mg dose) and 4% (80 mg dose) of participants who disliked standard oxycodone tablets, 60% (40/240 mg) and 64% (80/480 mg) of participants disliked the oxycodone HCl-niacin tablets. Data was taken with the same bipolar visual analog scale as above, and was reported by dislike rate, rather than like rate.
Vosburg et al.[3]	Repeated measures study	This study compared non-tamper resistant OxyContin(OXY40) with a tamper-resistant formula called tapentadol (TAP50 and TAP250). The experiment consulted experienced oxycodone abusers to see if they would choose to use the tapentadol over the oxycontin. Repeated intranasal abuse was reduced to 24% for TAP50 and 16% for TAP250, whereas non-tamper–resistant formulation was chosen for repeated abuse at a rate of 100%. Participants were only able to extract 3.5% of drug from TAP50 as opposed to 37.0% for standard OxyContin. The OxyContin was preferred for abuse over the tamper-resistant formulations.

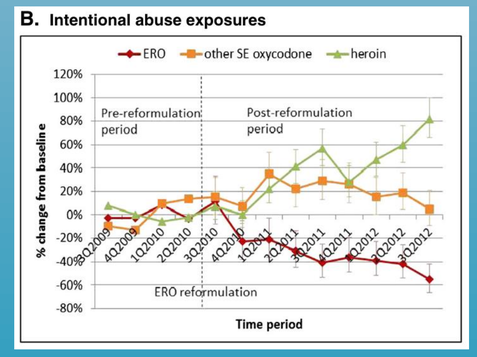
Conclusions/Recommendations

Tamper-resistant and abuse deterrent opioid formulations, such as tapentadol and reformulated oxycontin, have proven to reduce the abuse potential of prescription opioids. Our recommendation is to replace the current highly addictive opioids with tamper-resistant formulations. The development of these formulations is costly and time-consuming; however, the reduction in overdose fatalities related to opioids is worth the cost.

With their slow onset of action and mechanisms resistant to physical manipulation, tamper-resistant formulations have made it more difficult to abuse prescription opioids. As a result, many opioid abusing patients in the post-oxycontin formulation era have begun switching to heroin as an alternative. Among the subpopulation of patients who abuse prescription opioids, there has been a sharp rise in the rate of heroin abuse as evidenced by the increase in heroin related calls to US Poison Control centers.[1] The increased rate of heroin use among opioid abusing patients has important medical and societal ramifications.

Despite their promise and demonstrated effectiveness, tamper-resistant prescription opioid formulations are not a silver bullet to end opioid abuse. In summary, we recommend tamper-resistant formulas mainly to reduce the influx of new patients into the opioid abusing pool. Regarding the current pool of prescription opioid abusers, public health measures must be implemented in order to most effectively obtain a net reduction in overall opioid abuse.





Changes in calls to poison centers reporting problems from exposure to brand extended release oxycodone (ERO), other single-entity (SE) oxycodone products, and heroin by exposure type between 2009 and 2012.[1]

Citations

1. Coplan, P., Kale, H., Sandstrom, L., Landau, C., & Chilcoat, H. (2013). Changes in oxycodone and heroin exposures in the National Poison Data System after introduction of extended-release oxycodone with abuse-deterrent characteristics. *Pharmacoepidemiology and Drug Safety, 22*, 1274-1282.
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3. Vosburg, S., Jermaine, J., Jeanne, M., Ashworth, J., Shapiro, D., & Comer, S. (2013). A comparison among tapentadol tamper-resistant formulations (TRF) and OxyContin® (non-TRF) in prescription opioid abusers. *Addiction,108*(6), 1095-1106.
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5. www.cdc.gov/nchs/data/databriefs/db166.htm