Routes of Opioid Abuse and its Novel Deterrent Formulations

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Abstract
This review aimed to investigate the abuse patterns of common prescription opioids currently on the market by collecting large-scale surveys of different abuser populations. Furthermore, we aimed to analyze the efficacy and properties of currently implemented abuse-deterrent formulations (ADF) for these compounds. Our investigation showed that while oxycodone and oxymorphone are primarily abused by oral ingestion and insufflations, respectively, their ADF products (reformulated OxyContin and Opana ER) show some encouraging results to deter their abuse. Tapentadol is not popular amongst abuser populations, its ADF are difficult to tamper with, and it does not produce significantly desirable effects in noncompliant patients when compared to other opioids. Hydromorphone is predominantly abused by injection, and any effective abuse-deterrent strategy must specifically prioritize and target this route. Current formulations have successfully conferred aversive properties onto the drug in the event of preparation for injection, yet overall rates of hydromorphone abuse remain high, suggesting that more innovative steps need to be taken. Despite novel deterrent technologies that collectively offer deterrence by insufflations, injection and co-ingestion with alcohol, more priority needs to be given to deterring the most common and accessible route of abuse, i.e., oral ingestion of multiple doses.

Keywords: Tapentadol; Hydromorphone; Opioid formulation

Introduction
Despite the development and approval of abuse deterrent medications aiming to decrease the misuse of prescription opioids, abuse remains prevalent in the United States (U.S.) and abroad. Additionally, abusers have refined their tampering methods in order to bypass the advanced deterrent mechanisms of these novel formulation technologies [1,2]. Tampering with a medication can be done to assist in the separation and harvesting of the active ingredient, allow for administration by alternate routes, destroy controlled release mechanisms, or for a combination of these reasons. Due to their prevalence, these forms of tampering are often done to oral opioid products, allowing for administration via nasal insufflation, smoking (inhalation by vaporization), rectal, and intravenous injection. These alternate routes of administration (ROA) may vary depending on the abusable medication and a particular product formulation type. Additionally, the likelihood to use non-oral routes of abuse can be dependent on age, ethnicity, and substance abuse dependence [3].

The primary purpose of this paper was to determine differences in tampering methods and alternate ROA based on the individual opioid or specific opioid formulation. This was accomplished by reviewing published sources and collecting available surveys examining diverse populations of abusers. This review is organized by drug and focuses solely on prevalent opioids currently being abused (i.e., oxycodone, oxymorphone, tapentadol, and hydromorphone). For each drug, details of our results regarding alternate ROA and abuse methods are summarized. Furthermore, when such opioids are included in an abuse deterrent formulations, product specific information regarding alternate ROA and reduced abuse potential are discussed where available.

Opioid Tampering and Abuse

Oxycodone hydrochloride

Oxycodone is consistently ranked amongst the most attractive and highly abused prescription pain medications in the U.S. and abroad [4,5]. In the U.S., oxycodone is only approved for oral administration and is supplied in both immediate- and extended-release formulations. The drug is available in many generic formulations, with OxyContin and Oxydoo (formerly Oxecta) (Figure 1) being examples of formulations having abuse deterrent properties. OxyContin had no deterrent features until it was reformulated (Figure 1) in August of 2010.

A large scale study conducted across the U.S. involving patients enrolled in treatment for substance abuse disorders showed oxycodone administration and tampering occurred at different rates based on formulation [6]. For example, abusers of immediate release formulations (n=3279) mostly preferred to swallow the medication intact (81.4%) over alternate ROA; insufflation (28.4%) chew and swallow (19.8%), or intravenous injection (6.3%). It was also reported that 7.3% performed multi-step preparation procedures involving a combination of tampering methods. In contrast, abusers of extended-release formulations (n=3271) reported less frequently to swallow the medication intact (62.1%) or chew before swallowing (18.4%). The more preferred methods were reported to be crushing and snorting (45.9%), injecting (24.5%), or using multi-step preparation procedures (10.5%). Even with differences in tampering and alternate ROA between formulations, the most popular administration route still remained oral ingestion of intact or tampered product. It should be noted, study respondents were allowed to choose more than one preferred ROA for both formulations, resulting in a total counts greater than 100%.

Another study of opioid abusers (n=212) was conducted in the U.S. in order to determine if there were disparities between the preferred ROA of opioids (including oxycodone) among abusers of urban and rural populations [7]. Results determined that for urban participants, swallowing a tablet whole was the preferred ingestion method for
of the IR. Among those surveyed, 96% reported being able to abuse the IR formulation by at least one alternate ROA on an average of 19.5 days per month. The most preferred administration routes (more than one could be chosen) were insufflation (70%), and injection (51%). When compared to the IR product, the abuse deterrent ER product showed markedly lower reported abuse rates. Only 33% of respondents reported being able to abuse the ER formulation through any ROA at an average frequency of 1.9 days per month. Nasal insufflation was reported in only 5% of responders followed by injection at 0.5%.

A larger study on the abuse deterrence of reformulated OxyContin was conducted in over 357 treatment centers across the U.S. who provided care for 140,496 patients undergoing substance abuse therapy for opioid dependence [11]. The study determined prevalence of oxycodone abuse before and after the introduction of the abuse-deterrent ER reformulation. Patients were surveyed on their preferred ROA for each formulation, as well as their prevalence of abuse in the past 30 days both before and after the introduction of the reformulated product. There was a significant, 41% general reduction in observed abuse potential for the reformulated product compared to the original. Abuse via swallowing the tablet whole was 17% lower and non-oral routes were 66% lower for the reformulated product. These observations were promising as a testament to the potential efficacy of tamper resistant formulations for opioids, and encouraged continued research and innovation in the matter. However, these results could also suggest that abusers are simply willing to switch to other opioids for abuse if they are not achieving desired results with a given formulation. To study this effect, 19 healthy male drug abusers were exposed to both an IR and the reformulated oxycodone [12] product. The respondents were asked to determine whether or not they liked the drug and whether or not a given formulation got them “high.” It was determined that intact, orally ingested reformulated oxycodone was less desirable, and gave a less euphoric “high.” Some participants responded that they needed to take double the dose of reformulated oxycodone to produce comparable effects to the IR formulation.

Abuse of specific medication formulations, particularly reformulated OxyContin (Figure 1), has also been investigated. One such study interviewed 189 prescription opioid abusers from December of 2010 through September of 2011 [10]. In this sample, the abuse potential and preferred ROA of reformulated extended-release oxycodone (i.e., OxyContin) were compared to an immediate-release (IR) non-abuse deterrent formulation. In general, the prevalence and frequency of abuse for the ER formulation was low compared to that of all opioids studied. In contrast, rural participants were much more likely to use a variety of alternate ROA depending on the drug being abused. Specifically, rural participants were more inclined to inject hydromorphone and morphine, and were also more inclined to snort oxycodone, methadone, and hydrocodone.

This preference for snorting oxycodone formulations could also be seen in other sample populations. In a study of adolescents ranging from 16-19 years of age, individuals including both males (n=16) and females (n=8) indicated that their preferred ROA across all oxycodone formulations was insufflation, with 83% of surveyed abusers prefer this method for immediate release tablets and 69% prefer this method for the extended release (ER) formulations [8]. Around half of those surveyed preferred to ingest the drug orally and fully intact, 25% of those who reported ingesting whole tablets preferred to use single-entity (SE) oxycodone, and 38% preferred extended-release (ER) formulations. Only 13% of those who preferred to orally ingest ER oxycodone and 17% of those who preferred SE preferred to chew the pill first before swallowing. About 13% of ER users and 0% of SE users indicated that they preferred ingestion via smoking, while injection and snorting were largely unreported amongst the survey sample. This study suggests that adolescents, amongst other high abuse profile populations, have a relatively higher attraction for snorting oxycodone when compared to the general population of abusers. This may be due to a perceived and circulated notion of higher efficacy. However, other studies suggest that injection of oxycodone is higher in young males due to their tendency to be more risk-tolerant and more willing to utilize aggressive forms of administration than other demographics [9].

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use commonly available supplies to prepare samples of both original OxyContin and reformulated OxyContin for abuse [13]. At the conclusion, participants were surveyed regarding the attractiveness of their prepared sample in relation to other opioid products. In every case, original OxyContin produced the most attractive results for abusers amongst all opioids. In contrast, reformulated OxyContin was evaluated as the least desirable and least susceptible to tampering.

Studies outside the U.S. also give reports of decreased abuse potential of reformulated OxyContin. For example, one study involved 522 Australian subjects who routinely tampered with prescription opioids [14]. These participants were surveyed regarding their preferred method of ingesting the reformulated tamper-resistant version of oxycodone introduced into the Australian market. The results of the study showed that 81% of subjects claimed to have previously tampered with the original formulation and 29% continued to abuse the tamper-resistant oxycodone after its introduction into the market. The most popular ROA reported following the introduction of the reformulated product were swallowing a whole tablet (15%), isolated instances of successful injection (6%), chewing (2%), dissolving in a solution and drinking (1%), and smoking (<1%). In every case, reformulated oxycodone was more difficult to abuse than the original formulation, with only 19% of respondents having reported successful tampering.

Studies comparing other oxycodone formulations utilizing different technologies for abuse deterrent can also be found. One example is a randomized, open-label study involving reformulated OxyContin, an IR product, and another ER oxycodone formulations having abuse deterrent properties [15]. It was shown that the crushed reformulated OxyContin displayed a pharmacokinetic profile similar to IR oxycodone formulations, whereas the other deterrent product (DETERx formulation) retained its extended-release profile even after tampering via crushing. ER formulations resistant to rapidly releasing (DETERx formulation) retained its extended-release profile even after tampering via crushing. ER formulations resistant to rapid releasing postulated levels of abuse still persist and abusers may preferentially choose formulations without abuse deterrent features.

Studies evaluating abuse deterrence to specific ROA have also been conducted, specifically in the case of intranasal administration. A randomized, single-blind, single-dose, triple-period crossover study of 83 healthy adults ranging from 18-55 years evaluated the tolerability and pharmacokinetics of nasally insufflated original OxyContin versus the reformulated product [16]. The new formulation was generally less attractive than the original oxycodone product and generated lower Cmax and higher Tmax values. Furthermore, the reformulated product had an 80% lower calculated Abuse Quotient (Cmax/Tmax) than finely crushed original OxyContin tablets, as well as producing a much higher degree of discomfort upon insufflation.

The above finding suggests that the reformulated OxyContin is capable of achieving its intended purpose of curtailing abuse and can create a sharp initial drop in abuse rates amongst participants [17]. However, because the effectiveness of deterrent technologies is imperfect, a residual level of abuse still persists and abusers may preferentially choose formulations without abuse deterrent features. In a survey study of 88 opioid abusers familiar with tampering the reformulated OxyContin, 34% were able to bypass the abuse deterrent features and prepare a solution for snorting or injection. Furthermore, some abusers may migrate to non-prescription and illegal opioids such as heroin [14].

1In the end, we see that oxycodone is a highly desirable medication for abuse. Our literature investigation showed that a wide range of population’s abuse this drug and its patterns of abuse vary depending on factors such as age, demographics, and setting. Literature studies found on oxycodone abuse were more abundant than any other opioid studied in this review. This further highlights its popularity and need for resources to be invested in enhancing abuse-deterring properties of formulations containing oxycodone. Currently implemented ADFs containing these drugs, such as reformulated OxyContin ER, have been shown to overall reduce its abuse profile in the current market. However, these formulations fail to sufficiently deter abuse via simple oral ingestion for over-administration; the most popular ROA across the majority of studied abuser populations.

Oxymorphone hydrochloride

Oxymorphone is a semi-synthetic opioid analgesic that was first introduced to the U.S. in 1959, and is now one of the most popular drugs for abuse. In a study sample of over 12,000 opioid abuse forum posts occurring online, oxymorphone was ranked as the most highly endorsed pain medication for abuse [5]. Oxymorphone is available orally in both an immediate release and ER products. The ER formulation (i.e., Opana ER) is now manufactured to have deterrent properties (Figure 1), predominantly crush resistance. This may be beneficial as its abuse by nasal insufflation has been reported to be the most popular alternate ROA based on a study of patients being treated for abuse disorders across 464 facilities in the U.S. [6]. Other, less preferred routes included swallowing intact tablets (47%), injecting (20%), chewing (13%), and via multi-step tampering methods (13%). Again, participants were allowed to choose more than one preferred ROA, resulting in a responder count greater than 100%. Of these routes, parental administration could be the riskiest in that there have been numerous reports of induced thrombotic microangiopathy and acute kidney injury resulting from injection of Opana ER [18].

When compared to oxycodone, oxymorphone has similar abuse potential when given at higher doses. In a double-blind, placebo-controlled inpatient study, healthy opioid users were given IR formulations of both oxymorphone and oxycodone in order to compare their abuse liability to one another across numerous parameters. Results showed that at lower doses, oxymorphone was generally less potent than oxycodone across several pharmacodynamics measures, and produced less adverse effects. However, when dosage amounts were increased to around 40 mg, the abuse liability of the two drugs were largely similar [19].

2Current abuse deterrent formulations of oxymorphone (i.e., Opana ER) appear to target crush resistance and help deter nasal insufflation, the drug’s most popular reported alternate ROA. However, more attention still needs to be focused on deterring the drug’s abuse by ingestion and over-administration as these methods still remain as most popular amongst abusers. Furthermore, deterring abuse by intravenous injection should also be of high priority since this form of abuse has been shown to induce potentially fatal adverse effects.

Tapentadol

Tapentadol is a synthetically-derived opioid analgesic which is currently distributed in the U.S. by Depomed Inc. An immediate release formulation was first introduced in 2008, followed by an ER formulation almost 3 years later. Each product is branded under the trade name Nucynta and Nucynta ER (Figure 1). The frequency of reported abuse of tapentadol is significantly less than most other opioid formulations, with the exception of hydromorphone when adjusted for prescription volume [20]. Additionally, internet discussions amongst regular opioid users from numerous online forums showed that the proportion of posts dedicated to tapentadol endorsement and abuse were significantly lower than all other comparator products [21]. Furthermore, abusers who initiate opioid abuse with tapentadol were shown to be less likely to develop advancing dependent behaviors, such as collecting overlapping prescriptions from more than one prescriber in different pharmacies (i.e., doctor shopping) [22].

Our inquiry into published reports showing methods and routes of abuse for tapentadol revealed such results were sparse. However,
one large study surveying college students showed that of the 1626 respondents reporting nonmedical usage of prescription opioids, 101 reported abusing tapentadol IR [23]. Of this sample, the most popular ROA was swallowing intact (49.5%), chewing (41.6%), and nasal insufflation (20.8%). This study concluded that the abuse rates of tapentadol IR were already low upon the introduction of the medication, and has only decreased over time. Furthermore, the extended release formulation of tapentadol was shown to be resistant to physical manipulation, pulverization, and required extensive effort to release even 50% of its active ingredient by mechanical stress [24]. This coincides with a study where current opioid abusers were asked to tamper with an original OxyContin and an ER tapentadol tablets for up to one hour [25]. Participants were told they could use any methods they deemed necessary in order to prepare the product for either snorting or injection. Very few participants were willing to snort or inject the preparation they recovered from the tapentadol tablets. Furthermore, the actual amount of active ingredient that could be recovered was significantly lower as well.

**Hydromorphone hydrochloride**

Hydromorphone is a highly potent opioid agonist of the phenanthrene class. Due to its low oral, rectal, and intranasal bioavailability yet relatively high solubility in aqueous solutions [26], hydromorphone is commonly given parenterally in the clinical setting. One oral formulation of ER hydromorphone (Exalgo) uses an osmotic delivery system to precisely control the rate at which active ingredient is released from the tablet. This type of formulation also provides crush resistance and can induce aversive responses upon tampering [27-29]. Nonetheless, hydromorphone remains a very highly abused and popular opioid [5].

In a large scale study of patients who were entering treatment for opioid abuse disorders across the U.S., the most popular method of administration across all hydromorphone formulations was injection (57.6%). Additionally, swallowing intact tablets (33.2%), snorting (24.4%), chewing (7.8%), and administration via individually formulated, multi-step ROAs (8.3%) were reported [3]. Regarding hydromorphone abuse, no additional information was found in the literature, with the exception of those no longer considered relevant to current abuse trends (i.e., before 2009).

Of the overwhelmingly predominant ROA for hydromorphone abuse was intravenous injection, any effective abuse-deterrent formulation strategy must specifically prioritize and target this route. It appears the current oral formulation of hydromorphone has conferred little aversive-type properties onto the drug, particularly during the preparation for injection as overall rates of abuse remain high. This suggests that more innovative steps need to be taken to decrease the ease of its abuse by alternate ROA.

**Current abuse deterrent formulations**

Research into abuse deterrent formulations (ADF) is continuing to grow, and is largely focused on preventing common tampering methods to oral formulations in preparing them for alternate ROA [1,30-32]. For example, nasal insufflation and injection are popular alternate ROA for tablet formulations. For both these routes, the product is first crushed to a fine powder. For snorting, crushing allows reduction in particle size to produce particles small enough to be aerosolized and comfortably insufflated into the nasal cavity. Furthermore, a crushed tablet formulation will have greater total surface area and be more conducive to faster absorption in the nose. Additionally, the crushed powder will likely display more rapid dissolution in liquids intended for extraction and injection purposes. As such, formulations of many currently available products offer some type of crush resistance/crush deterrence into their design by enhancing mechanical strength and resist physical manipulations such as chewing, cutting, and grinding.

Likewise, another formulation approach may be to develop a product that does not lend itself to being reduced to fine particles, such as a semisolid product inside a capsule. This approach was used in the formulation of an extended release oxycodone product (Remoxy) which delivers the drug from a dissolution-resistant matrix. Although this product is still seeking regulatory approval in the U.S., preliminary studies showed that when compared to IR oxycodone and controlled-release oxycodone, Remoxy was consistently evaluated amongst abusers and their counselors as a less attractive product for abuse [33]. Furthermore, the formulation was still able to provide significant pain management without being susceptible to alcohol “dose-dumping” (no significant deviations of Cmax in the presence of alcohol) [34]. The drug has finished Phase III studies, however the new drug application has yet to be approved by the Food and Drug Administration [34].

Approaches using more traditional dosage forms such as tablets appear to have gained more popularity. For example, reformulated OxyContin (Figure 1) is produced as a solid polymer tablet matrix which provides physical resistance to crushing and chewing, and deters injection by turning into a viscous gel upon contact with water [35,36]. The new formulation resists tampering to a larger extent while also inducing a significantly higher degree of aversive effects when ingested via unintended methods such as chewing or snorting [14,16,37]. Furthermore, when this formulation was successfully crushed and snorted, studies showed that it yielded markedly lower Cmax and increased T1/2 as well as decreased drug liking and intranasal tolerability compared to the crushed original formulation [38]. It also appeared to gain greater attention in online drug forum posts after its introduction to the market [39].

Many ADFs gain resistance to crushing and form viscous gels in aqueous solutions by incorporating high amounts of polyethylene oxide (PEO) in their formulations. For example, ER oxymorphone is currently distributed in such a formulation under the brand name Opana ER (Figure 1). The PEO matrix is specifically designed and proven to be largely crush resistant in response to forces that the human body is not capable of producing via biting or chewing [40]. This formulation has also been shown to be less attractive to abusers when compared to tablets of controlled-release oxycodone [41].

A promising field of abuse deterrent technologies involves the inclusion of opioid antagonists into the formulation (Figure 2). When antagonists have good oral bioavailability, they have to be sequestered to prevent legitimate users from being exposed to the antagonist after oral ingestion. This exposure can result in aversive effects such as quick-onset of withdrawal symptoms in the user. An example of an antagonist with low oral bioavailability used in ADFs is naltrexone, which is a pure opioid antagonist given parenterally to counter the effects of opioid overdose. However, it has also shown potential for deterring and diminishing the rewarding effects of opioid abuse. In a study of recreational opioid abusers who had previously tampered with ADFs, subjects were asked to rate the appeal of an intravenous dose of both untreated oxycodone solution and an oxycodone/naltrexone formulation [42]. The results showed that there was a marked decrease in drug appeal and rewarding effects of the naltrexone containing
solution compared to the untreated solution. However, oxycodone/naloxone solutions have been reported to induce acute withdrawal syndrome amongst certain groups when taken orally [37,43].

Orally active opioid antagonists, such as naltrexone, can be used in ADFs to address abuse by oral ingestion [44]. For instance, when naltrexone hydrochloride was coated and sequestered in a morphine sulfate ER product, sufficient pain management was achieved when swallowed, yet produced adverse physiological responses such as nausea and vomiting when physically tampered before ingestion [37,45].

Seeing that oral administration is the predominant method of ingestion amongst opioid abusers [46], this appears to be the most relevant new frontier for novel ADFs. No approved opioid product has yet to claim effective deterrence against multiple administrations (overdose), though attempts to produce such a product have been undertaken (Figure 3). One example of such an attempt was to use low dose niacin in a short-acting oxycodone formulation. Niacin was used as an aversive agent designed to deter against multiple ingestion by inducing symptoms such as itching, sweating, dizziness, nausea, or flushing sensation when high doses are taken. A survey of 40 recreational drug users who self-administered both oxycodone and oxycodone with niacin reported that the niacin product was up to 30% less desirable than the IR formulation [34]. Other studies showed that the implementation of niacin as an aversive agent induced responses such as dizziness or nausea when tablets were ingested after crushing and chewing, or when fully intact tablets were taken in large amounts [35]. It is important to note that in a separate study, this formulation also produced side effects in compliant patients similar to the aversive effects intended at higher doses [47]. This raises an important concern.

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**Figure 2:** Agonist/antagonist technology to deter opioid abuse.

**Figure 3:** Use of aversive agents to deter opioid abuse.
in that aversive agents used to deter abuse via over-administration may also produce undesirable effects in legitimate, compliant patients requiring relatively high doses of pain medication [35].

Closing Remarks

Many abuse-deterrent technologies have been shown to be effective in terms of deterring abuse via alternative ROA, including intravenous injection and nasal insufflation. However, more attention needs to be given to deterring the most prevalent form and route of abuse; i.e., over-ingesting intact tablets by oral ingestion. In the future, other less common forms of abuse, such as smoking or "parachuting", or never imagined ROA and oral ingestion. In the future, other less common forms of abuse, including intravenous injection and nasal insufflation. However, be effective in terms of deterring abuse via alternative ROA, and tampering methods may rise in precedence and lead the science of abuse deterrence towards a different direction. For now, ADFs addressing crush resistance, injection, and snorting need to show a larger impact on reducing abuse to become more relevant from the perspective of clinicians, third party payers, regulatory agencies, and pharmaceutical manufacturers as a whole.

References


