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Assessment of a formulation designed to be crush-resistant in prescription opioid abusers

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Abstract

Background—The extent of intranasal and intravenous prescription opioid abuse has led to the development of formulations that are difficult to crush. The purpose of the present studies was to examine whether experienced prescription opioid abusers (individuals who were using prescription opioids for non-medical purposes regardless of how they were obtained) were able to prepare a formulation of oxymorphone hydrochloride ER 40 mg designed to be crush-resistant (DCR) for intranasal (Study 1) or intravenous abuse (Study 2), utilizing a non-crush-resistant formulation of oxymorphone (40 mg; OXM) as a positive control.

Methods—No drug was administered in these studies. Participants were provided with DCR and OXM tablets in random order and asked to prepare them for abuse with tools/solutions that they had previously requested. The primary outcome for Study 1 was particle size distribution, and the primary outcome for Study 2 was percent yield of active drug in the extracts. Other descriptive variables were examined to better understand potential responses to these formulations.

Results—Fewer DCR than OXM particles were smaller than 1.705 mm (9.8% vs. 97.7%), and thus appropriate for analyses. Percent yield of active drug in extract was low and did not differ between the two formulations (DCR: 1.95%; OXM: 1.29%). Most participants were not willing to snort (92%) or inject (84%) the tampered products. Participants indicated that they found less relative value in the DCR than the OXM formulation across both studies.

Conclusions—Although there are safety issues associated with formulations that gel, these data suggest that the oxymorphone DCR formulations may be a promising technology for reducing opioid abuse.

Keywords

Abuse deterrent; tamper resistant; prescription opioid; oxymorphone; laboratory model

1. Introduction

The abuse of opioid analgesics is a public health problem in the United States. Estimates from the National Survey on Drug Use and Health reveal that non-medical use of narcotic pain relievers among persons aged 12 years or older was second only to that of marijuana in

2009 (SAMHSA, 2010). An estimated 5.3 million people aged 12 years or older (approximately 1.7% of the entire US population) are current, non-medical users of pain relievers, while 1.9 million individuals were classified with pain reliever abuse or dependence (SAMHSA, 2010). Estimates of prescription opioid related mortality have increased correspondingly (Maxwell, 2011). Cost estimates of prescription opioid abuse to the United States society have risen from \$8.6 billion in 2001 to \$55.7 billion in 2007 (Birnbaum et al., 2006, 2011; Hansen et al., 2011; Strassels, 2009).

Most nonmedical use of prescription opioids consists of ingesting the medication orally (Katz et al., 2008, 2011; TEDS, 2007; Webster, 2009). And yet, prescription opioid abusers also tamper with these medications in order to achieve a more rapid and robust drug effect (Budman et al., 2009; Cone, 2006; Farré and Camí, 1991; Hays, 2004; Katz et al., 2011; Oldendorf, 1992; Webster, 2009). The relationship between rate of drug delivery and drug preference has been demonstrated, although not extensively modeled, across multiple drug classes (Abreu et al., 2001; Comer et al., 2009; de Wit et al., 1992, 1993; Marsch et al., 2001; Mumford et al., 1995; Nelson et al., 2006; Roset et al., 2001; Volkow et al., 1995). With regard to prescription opioids, users may crush the pills into particles small enough for insufflation (“snorting”), or crush and dissolve the pills for injection (“shooting”) (Raffa and Pergolizzi, 2010). Administration of drugs in either manner is accompanied by increased health risks, such as overdose, or the transfer of communicable disease (Green et al., 2011; Scheinmann et al., 2007; Surratt et al., 2011; Martinez and Talal, 2008; Marcias et al., 2008).

To counter medication-tampering techniques that may lead to behaviors that are accompanied by such health risks, a great deal of attention is being paid to drug formulation technologies that may deter abuse (Coleman et al., 2005, 2010; Cone, 2006; Hamed and Moe, 2010; Katz et al., 2011). Examples of such opioid formulations are Suboxone®, which is buprenorphine combined with naloxone (Reckitt Benckiser; Johnson et al., 2003; Mendelson and Jones, 2003), and now produced in a film (Strain et al., 2011); Embeda®, an extended-release formulation of morphine containing sequestered naltrexone, that will only be released when the granules are crushed (King Pharmaceuticals/Pfizer; Johnson and Setnik, 2011; Smith, 2011); Remoxy™, a water-insoluble oxycodone extended-release formulation in a gelatin-capsule (Pain Therapeutics and King Pharmaceuticals/Pfizer; Friedmann et al., 2011a, b; Setnik et al., 2011); reformulated OxyContin®, an oxycodone extended-release formulation with a polymer coating that is difficult to crush and turns into a gel when mixed with water (Mannion, 2008); Nucynta® ER (Ortho-McNeil-Janssen Pharmaceuticals, Titusville, NJ; Tzschentke et al., 2007; 2009), which is tapentadol with a polyethylene oxide matrix that has been designed to be crush-resistant (INTAC™, Grünenthal GmbH, Aachen, Germany); and reformulated Opana®, which is oxymorphone HCl (Endo Pharmaceuticals Inc., Chadds Ford, PA) containing the same INTAC™ matrix as Nucynta® ER. It has been hypothesized that these formulations may be most likely to reduce the attractiveness of prescription opioids to abusers who snort, smoke, or inject them (Budman et al., 2009).

One specific strategy for abuse deterrence, as stated above, involves incorporating a physical barrier into tablets that is designed to render them crush resistant and therefore difficult to prepare for insufflation or injection (Coleman et al., 2010; Cone, 2006; Hamed and Moe, 2010; Webster and Fine, 2010; Wright et al., 2006). Tablets incorporating this technology have been marketed for reformulated oxycodone CR, tapentadol ER, and reformulated oxymorphone ER. Oxymorphone HCl is a semisynthetic μ -opioid agonist that is structurally similar to morphine. It is available for the relief of moderate to severe pain in patients requiring continuous opioid treatment for an extended period of time. Reformulated oxymorphone ER is the result of an extrusion process, with the composition of the

polyethylene oxide INTAC™ matrix conferring physical and physiochemical properties that theoretically lead to certain tamper-resistant properties. The tablet is difficult to crush, and will turn gel-like and viscous when combined with fluid.

Whether such tablets are able to withstand the efforts of experienced, intravenous and intranasal drug abusers is not known. Thus, the goal of the present studies was to examine the mechanical stability of oxymorphone ER tablets that have been designed to be crush-resistant (DCR), and to determine whether experienced abusers were able to convert the DCR tablets into forms that were amenable to intranasal or intravenous drug administration. Oxymorphone ER tablets formulated with the original polysaccharide hydrogel TimeRx® matrix (Opana® ER; (OXM), was used as a comparator. The 40 mg tablet was chosen for these studies because it is the highest ER formulation of Opana® ER, and was hypothesized to be the most likely to be abused by experienced users. No drug was snorted, injected, tasted, or otherwise consumed by the participants in these studies.

2. Methods

2.1 Study 1

2.1.1 Participants—Local newspapers and word of mouth were used to recruit healthy research volunteers between 21 and 60 years of age who were able to give informed consent. Participants had to be actively abusing prescription opioids intranasally (regardless of how the opioids were obtained) to participate in the study. Exclusion criteria were a history of significant violence or a current psychopathology that would interfere with study completion.

2.1.2 Design—This was a 1-day outpatient study with a repeated-measures design. Participants were provided with OXM 40 mg and DCR 40 mg tablets in random order. Tablets were referred to as Tablet A or Tablet B; the formulation of the tablets was not revealed. Tools that had been specifically requested by the participants were provided to them. After participants had received the requested tools and/or solvents, the investigator read scripted directions, instructing them to prepare the tablet for intranasal use. Participants were permitted to manipulate the tablet for as long as needed to turn it into a form suitable for snorting. Each session was monitored by a senior investigator and research assistant to ensure that no drug was taken, and to answer any questions that arose. After each attempt, investigators collected the tablet sample and packaged it for analysis; no drug was taken. This study was approved by the Institutional Review Board of the New York State Psychiatric Institute (NYSPI).

2.1.3 Procedure—Research volunteers came to the laboratory and, after signing a screening consent form, completed a brief screening procedure during which psychiatric and clinical interviews were conducted to ensure appropriateness for study participation. Participants then signed study consent forms describing the aims of the study and the potential risks and benefits of participation. Participants also completed a field sobriety test to ensure that they were not intoxicated. The field sobriety test included balancing on one foot, walking heel-to-toe in a straight line, and touching different parts of their face (nose, mouth, eyes) with their eyes closed. Once cleared for study participation, participants were seated at a desk in the laboratory with a large board in front of them upon which they were instructed to work. On the board was an 8½ × 11 inch piece of gray paper with illustrated rulers at right angles along the width and height of the paper to ensure the same scale was always depicted in photographs of the samples.

Participants were provided with test tablets (OXM or DCR) in a random sequence under direct supervision by the investigators. Tablets were referred to as Tablet A or Tablet B with

no further description. Approved tools that had been specifically requested by the participant prior to the onset of the session were provided to them. After receiving the requested tools and/or solvents, participants attempted to tamper with the tablet to turn it into a form suitable for intranasal abuse. Participants were encouraged to use as much time as they needed to tamper with the tablets. Investigators recorded the time spent manipulating the tablets with stopwatches. After the tampering procedures were completed, participants responded to questions concerning their impression of both formulations. Participants were subsequently paid for their study participation; they had been told that they would be paid \$75 for the session, and could earn an additional \$25 for putting forth their best efforts when tampering with the tablets. All participants were paid \$100, after which, they left the laboratory.

Upon the completion of each tampering attempt, investigators packaged the tampered samples into Nalgene cryogenic 15 mL vials, or Low Temp 3 mL freezer vials. Vials were labeled, and stored at ambient temperatures. Batch orders were shipped to Pharmaceutical Manufacturing Research Services, Inc (PMRS: Horsham, PA) for particle size analysis.

2.1.4 Outcome Measures—The primary outcome of the trial was particle size distribution. Secondary outcomes were the self-reported willingness to snort the tampered product, the actual time spent tampering with the tablets, and the self-reported maximum time participants would be willing to spend on a routine basis preparing the tablets for intranasal abuse. Additional data collected included the reasons participants gave for their decision as to whether or not they would be willing to snort the tablets, and the relative amount of money participants would be willing to pay for the DCR tablet if it contained the same amount of drug as the OXM, given what the participants had experienced during the laboratory session. Participants were also asked how often they took measures to prevent unwanted particles from ending up in the powder when they prepared a tablet for snorting (to estimate the degree of caution that exists in this population regarding insufflation of particles).

2.1.5 Data Analysis—The primary endpoint measure was the particle size distribution of the tampered tablets. Particle sizes were analyzed using a Sympatec Qicpic image analyzer (Clausthal-Zellerfeld, Germany), and summarized with descriptive statistics. Willingness to snort the formulations was a repeated proportional variable and analyzed with the Cochran's Q statistic. Continuous secondary endpoint measures, namely, the actual time spent tampering with the tablets and the self-reported maximum time participants would be willing to spend tampering with tablets were analyzed with paired t-tests. A mixed-model repeated measures ANOVA with the order of tablet presentation (OXM first or DCR first) as a between-groups factor revealed no differences in continuous outcome measures. Additional data were descriptively reported. Data analyses were performed with SPSS v. 20.0.0 (IBM).

2.1.6 Results—Twenty-five current intranasal prescription opioid abusers (17 men, 8 women: 13 Black, 8 White, 3 Hispanic, 1 Mixed), with a mean ($\pm$ SD) age of 44 ($\pm$ 11) years, and some college education (60%) completed this 1-day outpatient study. Participants had been abusing prescription opioids for 8 ($\pm$ 10) years, and were currently abusing OxyContin® (92%), Percocet® (20%), Dilaudid® (4%), or methadone (4%). Other current drug use included heroin (28%), cocaine (28%), marijuana (20%), alcohol (12%), Ecstasy (4%), and benzodiazepines (4%). The age of recreational prescription opioid use initiation was 37 ($\pm$ 13) years. Most (76%) had a favorite prescription opioid; favorites included OxyContin® (48%), morphine (20%), Roxicodone® (4%), and Dilaudid® (4%). Sixty-four percent began using prescription opioids to treat pain before recreational use was initiated.

Table 1 (left panel) presents the tools and solvents used by participants to prepare the tablets for insufflation. The most common tools used were hammers (92%), razors (56%), and wax paper (36%). Hammers were used for crushing the tablets, razors were employed for shaving or cutting the tablets, while wax paper was used to hold the tablets in place as they were being manipulated.

2.1.7 Primary Outcome Measure—The maximum cutoff for the Sympatec Qicpic image analyzer was 1.705 mm, meaning that only particles smaller than 1.705 mm could be analyzed with this technology. Most of the OXM samples submitted for analysis (19/25, 76%) contained 100% of the tampered tablets in particle sizes suitable for the Sympatec Qicpic analyzer, whereas 0% of the DCR samples consisted of 100% of the tablet. Of the 25 OXM samples, 97.7% (by weight) of particles were smaller than 1.705 mm, while of the 25 DCR samples, only 9.8% (by weight) of particles were smaller than 1.705 mm. The theoretical tablet weight of each tablet was estimated to be 221.45 mg.

Particle size distribution can also be described in terms of equivalent diameters where 10%, 50%, or 90% of the particles (d_{10} , d_{50} , or d_{90}), by volume, have a smaller diameter than the given value, which is akin to a percentile. Almost all of the OXM particles were small enough to be submitted for analysis (97.7% of the tampered particles from the sample). The OXM mean particle size distribution for d_{10} , d_{50} , and d_{90} was 60.5, 285.9, and 616.4 μm , respectively. Few of the DCR particles were small enough to be submitted for analysis (9.8% of the manipulated particles from the sample). From this set, the DCR mean particle size distribution for d_{10} , d_{50} , and d_{90} was 290.6, 335.9, and 375.1 μm , respectively.

Figure 1 depicts photographic samples from both OXM (A) and DCR (B) manipulated tablets following attempted preparation for intranasal abuse. As can be seen, OXM particles (A) were a fine powder, with small particles. However, DCR particles (B) were large and angular, with sharp edges.

2.1.8 Secondary Outcome Measures—Few participants (8%) stated they were willing to snort the tampered results from the DCR tablet, compared to most (96%) who stated they were willing to snort the powder from the OXM tablet (Cochran's $Q_{(1)} = 22.0$; $p < .001$). Participants spent more time tampering with the DCR (6 ± 5 min) than the OXM (3 ± 2 min), $t_{(24)} = -3.8$, $p = .001$. However, self-reported maximum time participants would be willing to spend tampering with the tablets did not differ between formulations (DCR: 10 ± 12 min, vs. OXM: 6 ± 7 min, ns).

Table 2 summarizes explanations participants provided when asked why they would (or would not) snort their tampered product. A few participants indicated they would snort the DCR powder because they believed it was possible (8%), however, the majority (92%) indicated that they would not snort the DCR powder, primarily due to the powder consistency (48%) or the tablet consistency (20%). The DCR particles were described as too big/large/chunky or not powdery, while the tablet simply did not crush. Other reasons for not wanting to snort the tampered DCR results were the anticipated nasal effects of the particles (12%). Some would simply take the tablet orally (8%), while others noted it was impossible (4%).

Most participants (96%) indicated that they would snort the results from manipulating the OXM tablet primarily because of the powder consistency, which was described as fine, light or fluffy (40%), or that the product was ready to sniff or familiar (32%). Another reason for snorting was the anticipated effect associated with doing so (noting the quick high, and feeling good, 24%). Some participants (4%) reported that they would not snort the product because they did not recognize the pill.

Table 3 summarizes the responses to the question how much participants would be willing to pay for the DCR (for snorting) if it contained the same amount of drug as the OXM. The majority of participants (72%) would pay "Less" for the DCR than OXM, due to the OXM tablet properties, namely, the ease of producing the OXM particles (easier to crush and snort, 48%), or the DCR tablet properties, namely, the difficulty of working with the DCR, such that it was too much trouble, taking too much time, or the presumption of not getting high from the particles (16%). Others indicated they would still pay something because they would figure out how to use it, or would be cautious and swallow (4% each). The remainder of participants (28%) indicated they would pay "Nothing" for the DCR because of the tablet properties (24%), or it was not recognized (4%).

Table 4 summarizes responses to the question addressing how often participants took measures to prevent unwanted particles from ending up in the powder when preparing a tablet for abuse. Approximately half of the sample "Always" (44%) or "Usually" (4%) removed unwanted particles prior to snorting, citing with equal frequency either wanting only the drug in the powder for the more immediate high (16%), or the dislike of the properties of the shell, such as being rubbery, irritating or burning the nose, or feeling like sand in the nose (16%). Some participants simply cited caution (8%). Twenty-four percent of participants said they "Sometimes" removed unwanted particles, primarily because they did not have a preference, i.e., they would do it if someone suggested they do it, they were not all that careful, or they sometimes needed to use quickly (16%). Also noted were the shell characteristics, and being cautious due to nosebleeds in the past (4% each). Participants who "Never" removed unwanted particles indicated they ground the shell up when they were preparing drug, and thought there was no point to removing them if the particles were small, or it took too much effort. Some noted that they generally worked in a clean area to avoid unwanted particles (28%).

2.2 Study 2

2.2.1 Participants—Healthy research volunteers between 21 and 60 years of age who were able to give informed consent were recruited. Participants had to be abusing prescription opioids intravenously (regardless of how the opioids were obtained) to participate in the study. Exclusion criteria were a history of significant violence or a current psychopathology that would interfere with study completion. Participants were recruited through local newspapers and word of mouth.

2.2.2 Design and Procedures—The design and procedures were similar to those employed in Study 1. The exception was that participants were instructed to tamper with the tablets in a manner that would render them into a form suitable for injection (shooting). After each tampering attempt, investigators packaged the tampered samples into Nalgene cryogenic 15 mL vials, or Low Temp 3 mL freezer vials if extract was produced. Vials were labeled; samples that did not involve extracts were stored at ambient temperatures, while extracts were frozen. Batch orders were shipped to PMRS for volume and concentration analyses.

2.2.3 Outcome Measures—The primary outcome of this study was the percent yield or the total percent of the 40 mg of active drug that was extracted. Secondary outcomes were the self-reported willingness to inject the tampered product, the actual time spent tampering with the tablets, and the self-reported maximum time participants would be willing to spend on a routine basis preparing the tablets for abuse. Additional data collected included the reasons participants gave for their decision as to whether or not they would be willing to inject the solution, the relative amount of money participants would be willing to spend for the DCR if it contained the same amount of drug as the OXM formulation, and the self-

reported willingness to inject the products of the tampering attempts. Participants were also asked how often they took measures to prevent unwanted particles from ending up in the solution when they prepared a tablet for injecting.

2.2.4 Data Analysis—The primary endpoint measure was the percentage of active drug in the solution that had been extracted from the tampered tablets. Percent yield of active drug was summarized with descriptive statistics. Continuous secondary endpoint measures, namely, the actual time spent tampering with the tablets and the self-reported maximum time participants would be willing to spend tampering with tablets were analyzed with paired t-tests. Willingness to inject the formulations was a repeated proportional variable and analyzed with the Cochran's Q statistic. A mixed-model repeated measures ANOVA with the order of tablet presentation (OXM first or DCR first) as a between-groups factor revealed no differences in continuous outcome measures. Additional data were descriptively reported. Data analyses were performed with SPSS v. 20.0.0 (IBM).

2.2.5 Results—Twenty-five current intravenous prescription opioid abusers (17 men, 8 women: 16 White, 5 Hispanic, 4 Black), with a mean ($\pm$ SD) age of 44 ($\pm$ 8) years, and some college education (60%) completed this 1-day outpatient study. Participants had been abusing prescription opioids 15 ($\pm$ 11) years, and were currently abusing OxyContin® (72%), Percocet® (16%), Vicodin® (16%), Dilaudid® (12%), Tramadol® (4%) or Suboxone® (4%). Other current drug use included heroin (64%), marijuana (32%), cocaine (24%), and benzodiazepines (12%). The average age of recreational prescription opioid use initiation was 29 ($\pm$ 11) years. All participants had a favorite prescription opioid; favorites included OxyContin® (72%), Dilaudid® (20%), Percocet® (4%), and Vicodin® (4%). Fifty-six percent began using prescription opioids to treat pain before recreational use was initiated.

Table 1 (right panel) presents the tools and solvents used by participants to prepare the tablets for injection. The most common tools and solvents employed were razors (80%), water (80%), spoons (72%), lighters (68%), hammers and syringes (both 56%), and cotton (48%). This reflects the standard procedure of crushing the tablets (with hammers or razors), mixing particles from the crushed tablet with a solvent in a spoon, heating the solution to a boil (with the lighter under the spoon), then drawing up the solution with a syringe using cotton as a filter.

2.2.6 Primary Outcome Measure—Only 13 samples contained enough extracted fluid to be analyzed; 6 from the DCR tablets, and 7 from the OXM Tablets. Volume (mL) and concentration of active drug (mg/mL) were used to calculate the percent yield of active drug with the following formula: % Yield = $100 * (a*b/c)$, where a=concentration (mg/mL), b=volume (mL), and c=total weight of the tablet (40 mg). Table 5 presents the volume, concentration, and percent active yield data. As can be seen, each formulation yielded approximately 2% or less active drug. There were no differences between the two formulations in percent yield of active drug. Figure 2 depicts photographic samples from both OXM (A) and DCR (B) tablets following attempted preparation for intravenous abuse. Both solutions were viscous and gelled. Little difference was observed between the two formulations.

2.2.7 Secondary Outcome Measures—Few participants were willing to inject the solution made from the DCR or OXM tablets (16% vs. 24%, Cochran's $Q_{(1)}=0.20$, ns). There was no difference in the actual time that participants spent tampering with the tablets (DCR: 8 ± 7 min, vs. OXM: 9 ± 6 min; ns). There was also no difference in self-reported maximum time participants would be willing to spend tampering with either tablet (DCR: 16 ± 14 min, vs. OXM: 14 ± 10 min; ns).

Table 6 summarizes the explanations provided by participants when asked why they would (or would not) inject the extract from their tampered product. Twenty-percent of the participants indicated they would inject the extract produced from the DCR tablet (but note that this was 83% of those who were able to produce a solution). Most (12%) indicated they would do so because they were curious, whereas the remainder said they would inject the extract because of the anticipated effects of the drug (8%). Of the 80% who would not inject the extract produced from the DCR, reasons cited were the inability to make an extract due to the tablet consistency (pill plastic, does not break up, 32%), the extract could not be drawn up through the needle (16%), or because the extract itself was described as too gooey, gummy, thick, or gelled (8%). An additional 20% provided no answer, or had no extract to inject. A small percentage indicated they would take the drug orally (4%).

Only 28% of the participants indicated they would inject the extract produced from the OXM tablets (but note that this was 100% of those who produced an extract). Reasons for doing so were curiosity (4%) or the anticipated drug effect (24%). Of those who would not inject the extract they derived from the OXM tablet, 4% indicated they could not generate an extract due to the consistency of the tablet, 8% had no answer nor an extract to inject, while 20% could not make an extract because they could not draw the solution up through the needle. Twenty-eight percent indicated they could not make an extract due to the consistency of the solution (it was too gooey, gummy, thick, or gelled), while 12% indicated they would simply eat the solution.

Table 7 summarizes the responses to the question how much participants would be willing to pay for the DCR tablet if it contained the same amount of drug as the OXM tablet. Responses were divided among the 4 possible responses ("Nothing," "Less," "More," or "The Same"), with most participants indicating they would pay "Nothing" (44%) or "Less" (40%) for the DCR tablet compared to the OXM tablet. The majority who would pay "Nothing" indicated this was due to frustration and not being able to do anything with the tablet (20%). Other reasons were the observation that neither formulation could be injected (12%), and the qualities of the actual pill, which were described as plastic by some, while the difficulty of removing the coating was cited by others (12%). Those who would pay "Less" for the DCR noted that the OXM formulation was more favorable, in that drug could be extracted from this tablet (or, ultimately sniffed, if not injected, 28%). Other reasons for paying "Less" included the pill qualities of not breaking up (in solution, 8%), or the general inability to inject solution from either formulation (4%). Some would pay "More" because they thought they could draw it up or inject it, perhaps with the help of a real lemon (8%), or noted that they could still ingest the drug (4%). Others would pay "The Same" amount for either tablet because they could not inject either (4%).

Table 8 summarizes the responses to whether participants would inject the remnants, or, what was left in the spoon, after the solution was drawn up. Of those who would inject the DCR remnants (8%), the rationale was to try to get as much drug as possible. Most participants (92%) would not inject the remnants from the DCR preparation. There were either no remnants, or no answer to this question (36%), the remnants were not possible to draw up due to the needle being clogged (28%), or the consistency of the remnants (described as residue, gel, paste, or gummed up, 12%). Others would not do it based upon their experience (4%). Participants would inject the remnants from OXM for the same reason as for the DCR, namely, to get as much drug as possible (20%). The majority of participants also would not inject the remnants from OXM (80%). The same reasons were cited as DCR, with the addition that 16% thought that the appearance of the remnants did not look right or they were impure.

Most of the sample "Always" (92%) or "Usually" (4%) removed unwanted particles prior to injecting (Table 9). Most did so with cotton (25%) or removed coatings prior to injection (13%). Some were not sure why they did so, but did it because that was how they had been taught to use the drug (8%). Others cited safety or cleanliness: to avoid infection/abscess (33%), they wanted the solution to be clean (17%), or to see the inside of the pill first (4%). Those who "Never" removed unwanted particles (4%) indicated that this process took too much time.

3. Discussion

Formulations that have been designed to be crush-resistant are being developed by the pharmaceutical industry as one manner by which to combat the public health problem of prescription opioid abuse (Webster et al., 2011). Deaths have been attributed to oxymorphone abuse in the academic literature (Garside et al., 2009; McIntyre et al., 2009; Vorce et al., 2010) as well as more popular sources (<http://community.discovery.com/eve/forums/a/tpc/f/655100142/m/21819967001>; accessed 4/23/12). The current studies were conducted to examine whether a formulation of oxymorphone ER that was designed to be crush-resistant (DCR) was able to withstand tampering efforts by experienced prescription opioid abusers. The data collected in the present studies characterize a number of tampering behaviors.

Neither intranasal nor intravenous abusers spent large amounts of time manipulating either OXM or DCR tablets. This was notable particularly because they were informed at the beginning of laboratory sessions that they could work as long as they liked. The maximum time spent preparing the OXM tablet for intranasal use was 7 minutes, whereas the maximum time manipulating DCR for intranasal use was 17 minutes. The maximum time spent manipulating either the DCR or the OXM tablets for intravenous use was 30 minutes. Although these studies occurred in a laboratory setting that may have influenced tampering behaviors, these data support the view that substance abusers do not spend unlimited amounts of time tampering with pills, as has been implicated in the literature (Budman et al., 2009; Coleman et al., 2005; Webster, 2009).

No particularly unique tools were requested for tampering purposes. Intranasal abusers worked primarily with a hammer, razor, and wax paper; while intravenous abusers primarily employed a razor, spoon, lighter, hammer, syringe and cotton, cookers, and water. This is consistent with observations gleaned from the internet regarding tampering, namely, complex procedures are not typically employed by substance abusers to alter medication formulations (Cone, 2006; Katz et al., 2006).

Most participants (92%) stated they were unwilling to snort powder produced from the DCR tablets, yet were willing to snort the powder produced from the OXM tablet (96%). The DCR particles were large and jagged, and most often had to be cut to size by hand, whereas OXM particles were produced quickly by crushing. In addition to the reasons cited for these choices, namely the favorable consistency of the OXM powder, and the lack of favorable powder consistency or difficulty with the DCR tablets; differences between the formulations were also captured with the particle size analyses. Particle size distributions for 10% (60.5 μm) and 50% (285.9 μm) suggest that the OXM formulation produced much smaller particles than the DCR. However, the estimate that 90% of the OXM particles were smaller than 616.4 μm whereas 90% of the DCR particles were smaller than 375.1 μm suggests that when considering the full distribution, the OXM particles were larger than those from the DCR. Yet the estimates cannot be interpreted independently of the amount of material that was submitted for analysis.

Approximately 90% of the DCR particles produced were too large to be analyzed by the present methods, and were not included in the particle size diameter estimates, whereas only 2% of the entire set of OXM particles were excluded from the analysis. It is a conservative estimate that at least 50% of the submitted OXM particles were suitable for insufflation, thus it seems reasonable to estimate that particles can be insufflated with diameters at least up to 285.9 μm , which is a value smaller than all DCR distribution estimates.

The relative value of the DCR tablets to prescription opioid intranasal abusers was clearly less than OXM, as evidenced by the finding that all participants would pay "Less" or "Nothing" for the DCR tablets. This was due to the complementary observations that either the OXM formulation was so much easier to prepare for abusers, or the DCR formulation was so much more difficult to prepare, suggesting that the majority of intranasal users are not interested in products that are difficult to prepare (Katz et al., 2006). This finding complements research being conducted with the goal of identifying factors that affect drug abusers' preferences for prescription opioids (Budman et al., 2009; Butler et al., 2006; 2010a, b). These studies have suggested that specific features of opioid formulations may affect the desirability or attractiveness of prescription opioids. The data herein support this notion.

Most intravenous prescription opioid abusers were not able to produce solutions, or stated they were unwilling to inject the solutions produced from both the DCR and the OXM tablets (80% and 72% respectively). The solutions that were produced were viscous. However, most of those who produced a solution from either formulation reported they were willing to inject it (DCR: 83%, OXM: 100%). Relative value was also assigned to the tablets, specifically, 16% would pay "More" or "The Same" for the DCR due to an estimation that the drug could still be used, or, even if it could not be injected, there was still drug available, so it was worth the same amount as a non-DCR tablet.

As 20% of participants stated they were willing to inject the solution from the DCR, or thought it had as much or more value than the current OXM formulation, a discussion of the injection of these formulations is in order. If prescription opioid abusers are willing to inject the extract, the health and safety implications of such behavior need to be researched. Controlled studies have not been conducted in humans for clear ethical reasons, therefore, the history of the tamper-resistant formulation of the benzodiazepine temazepam may be useful to consider.

Gel capsules (macrogols, or high molecular weight crystalline waxes called Gelthix; Launchbury et al., 1989; Scott et al., 1992) containing temazepam were manufactured in the UK in the late 1980s with the goal of deterring intravenous abuse, because it was hypothesized that benzodiazepine abusers would not inject a gel (Dobbin et al., 2003; Drake and Ballard, 1988; Farrell and Strang, 1988; Ruben and Morrison, 1992; Strang et al., 1994). However, the gel continued to be injected intra-arterially by abusers, resulting in reports of rhabdomyolysis; ischemia; thrombosis in arms, hands or legs; or intense pain, that often involved fasciotomy, debridement, or amputation of limbs (Adiseshiah et al., 1992; Bhabra et al., 1994; Blair et al., 1991; Ruben and Morrison, 1992; Russell et al., 1994; Scott et al., 1992).

The production of gelled temazepam was subsequently identified as being a counterproductive strategy for abuse deterrence, and there were multiple calls for the review of the product or the complete removal from the market (Farrell and Strang, 1988; Fox et al., 1992; Ruben and Morrison, 1992; Scott et al., 1992; Shaw et al., 1994). Notably, one physician was concerned about the advertising that suggested it was difficult to inject temazepam, when in his experience, individuals were injecting the medication. He was

reassured by the manufacturer that injection was not a problem because the solution contained so little active drug (Carnwath, 1993). Others noted that the problems were due to the active ingredient temazepam and not to the gel formulation per se (Launchbury et al., 1989; Launchbury and Drake, 1992; Russell et al., 1994). However, out of general concern for the problem, practitioners from multiple urban areas joined together in a voluntary ban of this formulation (Crompton, 1994; Moley et al., 1994).

The DCR oxymorphone formulation is not a gel capsule, but it quickly became a viscous gel after coming into contact with the liquid solvents that were employed in this study. Although most participants were unwilling to inject solutions from these formulations, and 60% could not produce an extract to inject, there were still individuals who could produce extracts and stated that they would inject them. It is not known what will happen when this occurs, however, it is reassuring that there was little intravenous abuse of both oxymorphone immediate release and extended release non-crush-resistant formulations reported in the 2009 Addiction Severity Index-Multimedia Version Connect assessments (Butler et al, 2011).

Data describing participants' opinions about remnant injection were promising in terms of participant safety. Namely, 92% would not inject the gelled remnants from the DCR, and 80% would not inject them from OXM. Nonetheless, the extent to which these formulations will be abused intravenously will not be known until they are readily available. As has been stated in the literature, ultimately the ability of any tamper-resistance strategy to deter abuse will have to be gauged by large, long-term data collection (Butler et al., 2011; Katz, 2008; Webster et al., 2011; Webster and Fine, 2010).

With regard to the present study, the findings must be considered in the context of the limitations. Four percent of intranasal users indicated they would not snort the powder they prepared because they did not recognize the drug. Although solely recruiting individuals with experience abusing oxymorphone would have avoided this outcome, oxymorphone abuse is rarely seen in this catchment area (Jones et al., 2011). Nevertheless, this information also supports the notion of prescription opioid preferences among these abusers (Budman et al., 2009; Butler et al., 2006, 2010a, b). Inclusion of a regularly abused prescription opioid, particularly one without any abuse-deterrent properties, such as the previous formulation of OxyContin®, would have enabled further comparisons to be made. Much of the data collected were self-report data, which leaves open the possibility that when faced with an immediate opportunity to snort or shoot a tampered product, a different decision would be made. Lastly, it is also possible that once participants had some time to think about the products after the sessions, they would have come up with new tampering strategies to attempt. To this end, follow-up phone calls the day after the session might have revealed more information.

This set of studies also leads to areas that could be considered for future DCR improvements. Intranasal and intravenous users who indicated that they would use the DCR employed razors when tampering with the tablets. Intranasal users reported that they would snort the tablet because they could cut the particles into sizes suitable for snorting. A tablet where this was not possible, either because of further hardness or a waxy consistency where small pieces could not be separated from the main tablet might address this perception. Intravenous users who were willing to inject the DCR solution reported confirming that the solution was cloudy and that it tasted strong and bitter before attempting to inject it. A solution that was viscous and looked unfamiliar without a strong, bitter taste might disrupt the opioid recognition that many abusers point to as a critical factor in their use. However, it should be noted that these formulations do not address the simultaneous ingestion of multiple intact doses. In addition to inducing greater positive subjective effects, use of

multiple tablets increases the risk of opioid overdose. A different approach may be needed for overdose prevention, such as a prescription opioid pro-drug, whereby the conversion to the active metabolite would be protective. To conclude, data from Study 1 suggest that a formulation of oxymorphone ER that has been designed to be crush-resistant (DCR) reduced the ability of intranasal abusers to quickly and successfully tamper with this medication when compared to the original formulation of oxymorphone ER (OXM). Data from Study 2 suggest that both formulations of oxymorphone ER are equally difficult to prepare for intravenous abuse.

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Figure 1.
Powders produced by intranasal abusers from the OXM (A) and DCR (B) tablets.

Figure 2.
Tampered solutions produced by intravenous abusers from the OXM (A) and DCR (B) tablets.

Table 1

Tools and Solvents Used for Intranasal (Left) and Intravenous (Right) Drug Preparation

Intranasal Tools	n (%)	Intravenous Tools	n (%)
Hammer	23 (92)	Razor	20 (80)
Razor	14 (56)	Spoon	18 (72)
Wax Paper	9 (36)	Lighter	17 (68)
Herb Grinder/D-ring		Hammer	14 (56)
Grinder/Spice Mill	6 (24)		
Spoon	5 (20)	Syringe	14 (56)
Strainer	5 (20)	Cotton/Q-tip	12 (48)
File	4 (16)	Mortar & Pestle	10 (40)
Metrocard	4 (16)	Bottle cap (cooker)	9 (36)
Mortar & Pestle	4 (16)	Pliers	9 (36)
Paper/Envelope/Magazine		Paper/Envelope/Magazine	
Page	4 (16)	Page	8 (32)
Pliers	3 (12)	Paper Towel/Napkin	7 (28)
Pill Crusher	3 (12)	Dollar Bill	6 (24)
Coffee Grinder	2 (8)	Wax Paper	6 (24)
Dollar Bill	2 (8)	File	5 (20)
Paper Towel/Napkin	2 (8)	Herb Grinder	4 (16)
Aluminum Foil	1 (4)	Metrocard	3 (12)
Knife	1 (4)	Strainer	3 (12)
Lighter	1 (4)	Tape	2 (8)
		Coffee Grinder	1 (4)
		Coins	1 (4)
		Credit Card	1 (4)
		Knife	1 (4)
		Paper Clip	1 (4)
		Pill Crusher	1 (4)
Solvents		Solvents	
Water	4 (16)	Water	20 (80)
		Lemon Juice	4 (16)
		Vinegar	1 (4)

Table 2

"If given the opportunity to snort the particles that you made, would you do it? Why?"

	DCR (%)	OXM (%)
Would snort the product	8	96
• Can snort: could get up nose/would try	8	
• Powder consistency: fine/ground nicely/enough there/small enough/light, fluffy powder/will hold and dissolve in nose		40
• Ready to sniff: snortable/crushed fast/what I'm used to		32
• Effects: quickest high/makes me feel good/enjoyment/need it		24
Would not snort the product	92	4
• Powder consistency: too big/large/chunky/not powdery/too hard/big chunks/too wide	48	
• Tablet consistency: can't turn into powder/can't crush/no powder/nothing to snort	20	
• Nasal effects: would stick in nose and not dissolve	12	
• Would take orally: would just eat it, get water and drink it	8	
• Impossible	4	
• Doesn't recognize pill		4

Table 3

"If you were planning to snort, how much money would you be willing to pay for the DCR if it contained the same amount of drug as the OXM?"

	%
Less	72
• OXM properties: easier to crush and snort/produced powder-broke when hit it/doesn't hurt hand	48
• DCR properties: hard to or doesn't crush/too much trouble/won't get me high/ takes too much time/can't snort	16
• Would have to figure out how to use	4
• Cautious: would only swallow DCR	4
Nothing	28
• DCR properties: hard to or doesn't crush/too much trouble/won't get me high/takes too much time/can't snort	24
• Don't recognize	4

Table 4

"When you prepare a tablet for snorting, how often do you take measures to prevent unwanted particles from ending up in the powder?"

	%
Always (44%) or Usually (4%)	48
• Only want drug: high more immediate w/o shell	16
• Shell: Coating is rubbery/irritates or burns nose/a waste/feels like sand in nose/don't want stuff in brain	16
• Caution: remove to be cautious/nose sensitive - had nosebleeds in past	8
• Save shell for later-can eat it	4
• No preference: Will do if someone suggests/not all that careful/if craving, doesn't bother to remove shell/sometimes needs to use quickly	4
Sometimes	24
• No preference: Will do if someone suggests/not all that careful/if craving, doesn't bother to remove shell/sometimes needs to use quickly	16
• Shell: Coating is rubbery/irritates or burns nose/a waste/feels like sand in nose/doesn't want stuff in brain	4
• Caution: remove to be cautious/nose sensitive - had nosebleeds in past	4
Never	28
• Crush & go: grinds shell up/no point if particles are small/too much effort/works in clean area	28

Table 5

Concentration, Volume and Percent of Oxymorphone in the Tampered Samples Prepared for Intravenous Use

	Concentration (mg/mL)		Volume (mL)		Yield (%)	
	M	(SD)	M	(SD)	M	(SD)
DCR (n = 6 samples)	4.93	3.60	.18	.15	1.95	1.89
OXM (n = 7 samples)	3.57	2.45	.16	.12	1.29	1.35

There were no significant differences between the two tablets.

Table 6

"If given the opportunity to inject the extract (the solution) that you made, would you do it? Why?"

	DCR (%)	OXM (%)
Would inject the extract	20	28
• Curious: to see what it does/would taste first/if I knew what it was	12	4
• Anticipated effect: Would make me feel better/got enough drug/want effect/want to get high	8	24
Would not inject the extract	80	72
• Can't make extract: tablet consistency - pill doesn't break up/pill plastic/not real/doesn't look safe	32	4
• No answer/no extract to inject	20	8
• Can't make extract: can't draw up	16	20
• Can't make extract: extract consistency - too gooey/ gummy/thick/gelled/no drug in water	8	28
• Would just eat it/would eat it if really sick	4	12

Table 7

"If you were planning to inject, how much money would you be willing to pay for the DCR if it contained the same amount of drug as the OXM?"

	%
Nothing	44
• Frustration: useless/no good/can't do anything with it/doesn't work	20
• Can't inject either OXM or DCR	12
• Pill qualities: Plastic/headache getting coating off/doesn't use anything with coating	12
Less	40
• OXM more favorable: easier to crush/dissolve/more familiar/could sniff/could get drug from	28
• Pill qualities: Doesn't break up	8
• Can't inject either OXM or DCR	4
More	12
• Can draw up and inject/with real lemon could have gotten more drug out	8
• Can still take orally	4
The Same	4
• Can't inject either OXM or DCR	4

Table 8

"If given the opportunity to inject the remnants left behind (i.e., the remains in the spoon), would you do it?"

	DCRM (%)	OXM (%)
Would inject remnants	8	20
• To get as much as possible: would feel better/2nd shot/would just keep adding water	8	20
Would not inject remnants	92	80
• No answer/no remnants to inject	36	28
• Can't draw up or inject: needle clogged/can't get anything out/won't go into syringe/too difficult	28	8
• Remnant consistency: Residue/gel/paste/gumming up/binder/won't travel through veins	12	20
• Would eat instead of trying to draw up	12	4
• Experience: don't inject remnants/would throw out/had bad experience with gel	4	4
• Appearance: Doesn't look right/impure/don't know what it is		16

Table 9

"When you prepare a tablet for intravenous injection, how often do you take measures to prevent unwanted particles from ending up in the extraction?"

	%
Always (92%) or Usually (4%)	96
• To avoid abscess/infection	33
• Use cotton	25
• Want solution to be clean	17
• Remove coating prior to injection	13
• Not sure why/was taught to do it this way	8
Never	4
• Takes too much time	4