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Relative abuse potential of opioid formulations in Canada: A structured field study

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ABSTRACT

Introduction: *While prescription opioids can improve quality of life through pain relief, they are susceptible to misuse. This field study characterizes the relative susceptibility and attractiveness of a new analgesic patch, with fentanyl embedded in a matrix material, compared to other opioid dose formulations.*

Methods: *Recreational opioid abusers (N = 42; 31 male, 11 female) from three Canadian sites participated in structured interviews. They were presented with nine products, some of which were hypothetical (fentanyl [F], hydromorphone [H], and oxycodone [O] in each of three formulations: matrix patch [M], reservoir-type gel patch [G], and tablet [T]). The attractiveness and tampering potential of each product was ranked using two 7-point Likert scales (Value of Product and Likelihood to Tamper), an index representing the product of the two scales, a 17-item Opiate Attractiveness Scale (OAS), relative street value, and rank order of overall desirability. Non-parametric analyses were used to compare each product to the FM.*

Results: *The FT, HT, and FM were highly valued and most likely to be tampered with. The products were ranked in decreasing order of desirability as follows: FT > HT > FM > FG > OT > HM > HG > OM > OG. On the OAS, FM was more attractive than all gel-patch products ($p < 0.001$), and OT was most attractive overall. FM was statistically similar to OT, FT, OM, and HT. Of the 42 subjects, 25 (60 percent) preferred the matrix patch to the gel patch. Of the 17 subjects who preferred the gel patch, 10 (59 percent) were from a region generally unfamiliar with that formulation.*

Conclusions: *Fentanyl is attractive to opioid abusers regardless of formulation. In Canada, a fentanyl matrix patch may be at higher risk for diversion, tampering, and abuse than other transdermal opioid formulations. These findings should be confirmed by epidemiological studies. Comparative risk management programs should be part of the development of any new narcotic delivery system.*

Key words: opioid, abuse, risk, matrix patch, formulation, tampering

INTRODUCTION

Prescription opioids bring important quality-of-life improvements to patients suffering pain.[1] Most opioid medications, however, have the potential to be abused. The challenge is to maintain the availability of opioid medications for therapeutic use while minimizing the risk of diversion for abuse.[2]

Tampering persists despite the incorporation of tamper-resistant features into several opioid products. A slow-release formulation of oxycodone (OxyContin®) was intended to have low abuse potential due to its lower peak concentrations and slower rate of entry into the brain.[3] However, abusers either crushed the tablets before ingestion or dissolved them in water for injection, thereby bypassing the slow-release mechanism. Similarly, the currently available transdermal fentanyl reservoir gel patch (Duragesic®) is designed to provide sustained pain relief with reduced likelihood of abuse, but abusers have extracted fentanyl from the hydroxyethyl cellulose gel for intravenous use[4,5] or chewed the patch for transmucosal delivery.[6-8]

A new analgesic patch has fentanyl dissolved directly into a polyacrylate copolymer adhesive layer in a flexible matrix material, creating a simplified transdermal system. The currently available form-and-seal patch has a reservoir containing the drug formulation in a hydroxyethyl cellulose gel, and it utilizes permeation enhancers and a rate-limiting diffusion membrane.[9] The newer matrix design results in a simplified two-layer drug-in-adhesive system. Hypothetical methods of tampering may include cutting the patch into smaller pieces for buccal use, or the use of readily available solvents (e.g., water, alcohol,

Table 1. Nine drug-formulation combinations presented to subjects		
Drug	**Formulation**	**Product status**
Fentanyl	Reservoir gel patch	Existent
	Matrix patch	Hypothetical*
	Controlled-release tablet	Hypothetical
Hydromorphone	Reservoir gel patch	Hypothetical
	Matrix patch	Hypothetical
	Controlled-release tablet	Existent
Oxycodone	Reservoir gel patch	Hypothetical
	Matrix patch	Hypothetical
	Controlled-release tablet	Existent
* Hypothetical for Canadian opioid users; formulation exists outside of Canada.		

vinegar) or heat to extract fentanyl for intravenous injection. These types of tampering methods are commonly employed by recreational drug users, who often share knowledge over the Internet.[10,11] This is in contrast to the reservoir gel patch, where the drug is neither readily soluble nor easily separated from the hydroxyethyl cellulose components, and where cutting the patch into smaller, more portable pieces results in complete gel extrusion. Therefore, the likelihood of tampering with the new matrix patch may be increased compared to the fentanyl gel patch, creating a new public health concern. Individuals intent on abusing drugs go to great lengths and take great risks to obtain and use opioids. It is imperative that new opioid formulations be carefully evaluated for abuse potential.[12]

Patterns of drug abuse and tampering methods vary among countries and regionally within a country.[13,14] The present study gathered Canadian data from recreational drug users and reviewed them in order to better understand the relative abuse risk of a proposed fentanyl matrix patch in Canada.

METHODS

The study protocol, consent form, amendments to the protocol, and advertisements for subject recruitment received Institutional Review Board approval (IRB Services, Aurora, Ontario).

Subject population

Prior to any study procedures, written informed consent was obtained from each subject. Subjects were excluded if they displayed positive breath alcohol or indication of intoxication at the study session or inability or unwillingness to complete study procedures in a useful and timely manner, or if study staff had concerns about the subject's reliability.

A total of 42 adults (31 male, 11 female; mean age 40.1 years, range 22 to 60 years) were enrolled from three sites across Canada: Toronto, Ontario (n = 18); Winnipeg, Manitoba (n = 12); and Dartmouth, Nova Scotia (n = 12). Each participant confirmed having engaged in recreational drug use in the last six months. Abuse of, or dependence upon, prescription opioids was confirmed by DSM IV criteria. All participants had knowledge of fentanyl, hydromorphone, and oxycodone and were required to provide specific, correct information about each drug. Participants were required to demonstrate that they had tampering experience by providing two specific examples of prescription pharmaceutical product tampering. Recent or current drug users were enrolled to prevent cue-induced relapse in recovering users. Each participant completed the study as per protocol.

Study design

This was a multicenter, noninterventional, single-session study. Each subject attended a three-hour session consisting of a structured interview, evaluation of choice procedures, and estimation of monetary street values comparing three opioid drugs in each of three formulations (Table 1). It is important to note that some of these formulations were hypothetical or not currently available in the Canadian marketplace. The interview format was finalized following a Toronto-based pilot study (n = 5, data not shown).

Table 2. Subject demographics, overall and by study site				
Parameter	**All subjects (N = 42)**	**Toronto (n = 18)**	**Winnipeg (n = 12)**	**Dartmouth (n = 12)**
Age (years)				
Mean	40.1	43.0	35.2	40.8
Range	22-60	31-60	22-54	26-51
Sex (n [percent])				
Male	31 (73.8)	15 (83.3)	7 (58.3)	9 (75.0)
Female	11 (26.2)	3 (16.7)	5 (41.7)	3 (25.0)
Race (n [percent])				
Caucasian	40 (95.2)	17 (94.4)	11 (91.7)	12 (100.0)
Black/African American	1 (2.4)	1 (5.6)	–	–
American Indian	1 (2.4)	–	1 (8.3)	–

Testing

Choice procedures. Subjects were required to assign a score for each product on two 7-point Likert scales, each anchored by "Strongly Disagree" and "Strongly Agree." The Value of Product scale (VPS) stated, "This drug would be highly valuable to me"; the Likelihood to Tamper scale (LTS) stated, "I would definitely tamper with this drug." Subjects also completed a validated 5-point scale (the 17-item Opiate Attractiveness Scale [OAS])[15,16] which presented specific drug features related to abuse attractiveness for each of the nine products (some hypothetical). Subjects then ranked the products according to overall desirability.

Street value. Subjects were asked to give a subjective street-sale dollar value to 13 reference drugs (both illicit and prescription, based upon a study assessing street values in Vancouver[1]); these were then ranked in descending order. Without assigning a specific street value to the test products, subjects were asked to rank each of the nine test products within the ranking of the 13 reference drugs. The street value for each test product was derived as the midpoint between the dollar values for the two closest reference drugs (i.e., the drug ranked immediately higher and the drug ranked immediately lower than the test product).

Product presentation. Samples of the three different formulations were available for subjects to view and/or handle. Multiple sizes of matrix and reservoir patches (containing no active ingredients) and photos of different tablets were used to illustrate different dosages of each compound; no actual tablets were presented. Each formulation was documented for the subject on a board along with basic information including the drug's brand name, street name(s), active ingredient, available doses, drug solubility, and potency relative to morphine.

Placebo reservoir (gel) and matrix patches were supplied by Janssen-Ortho, Inc. Existent tablet formulations used were OxyContin®, Purdue Pharma, and Dilaudid®, Abbott Laboratories. Triphasil® 28, Wyeth Pharmaceuticals, was used as a basis for the hypothetical fentanyl tablet formulation.

Data analysis

No formal sample-size calculation was performed. The Type I error for all hypothesis testing was set at 0.05 (two-sided). Two-sided 95 percent confidence intervals were used. No multiplicity adjustments were made for multiple testing because no primary endpoint was specified. Each of the following endpoints was considered equal: VPS, LTS, Value of Product-Likelihood to Tamper Index (VP-LT index, a product of the VPS and LTS), OAS, relative desirability of opioid formulations, monetary street value of opioid formulations relative to local street drugs, and description of potential tampering methods.

Nonparametric methods (Wilcoxon Rank-Sum test) were used to compare the derived street value of the fentanyl matrix patch to the values derived for each of the test products. Descriptive analysis was used to identify

Table 3. Description of opioid use history and preferences				
Opioid	**Subjects using in past six months (n = 42) N (percent)**	**Subjects with tampering experience (percent of subjects using opioid in past six months) n (percent)**	**First opioid of choice n = 40* n (percent)**	**Second opioid of choice n = 38** n (percent)**
Methadone	40 (95.2)	14 (35.0)	0 (0)	0 (0)
Morphine	30 (71.4)	24 (80.0)	7 (17.5)	14 (36.8)
Codeine	27 (64.3)	11 (40.7)	3 (7.5)	0 (0)
Oxycodone	26 (61.9)	20 (76.9)	7 (17.5)	5 (13.2)
Hydromorphone	22 (52.4)	21 (95.5)	14 (35.0)	10 (26.3)
Fentanyl	14 (33.3)	13 (92.9)	0 (0)	5 (13.2)
Heroin	13 (31.0)	6 (46.2)	6 (15.0)	2 (5.3)
Hydrocodone	7 (16.7)	2 (28.6)	1 (2.5)	2 (5.3)
Oxymorphone	5 (11.9)	4 (80.0)	2 (5.0)	0 (0)

* Missing data for two subjects; ** Missing data for four subjects.

the mean price ± standard deviation for each opioid drug and formulation combination.

Data for the three opioid drugs, in each of three formulations, were categorized into relevant groupings prior to analysis. The VP-LT Index was analyzed as for Likert scales. Nonparametric analysis was used to evaluate rankings.

In the structured interview and open-ended questions, the respondents also provided narrative descriptions of tampering methods.

Data were keyed into PDS Express, version 3.4 (Phoenix Data Systems, Inc., King of Prussia, PA). All statistical analyses were performed using SAS version 8.2 (SAS Institute, Inc., Cary, NC).

RESULTS

Subject demographics were similar across study sites (Table 2). All subjects reported using opioids within the six months prior to the study, including at least one of the following: methadone (95 percent), morphine (71 percent), codeine (64 percent), oxycodone (62 percent), hydromorphone (52 percent), fentanyl (33 percent), heroin (31 percent), hydrocodone (17 percent), or oxymorphone (12 percent). Tampering experience was highest among heroin and fentanyl users (96 percent and 93 percent, respectively) (Table 3).

Value of Product and Likelihood to Tamper scales

Overall, and independent of formulation, fentanyl was statistically similar to hydromorphone in its perceived value and likelihood to be tampered with, but it was significantly more valued ($p < 0.001$) and more likely to be tampered with ($p = 0.01$) than oxycodone. When formulation type was considered independent of drug, tablets were most valued (tablet vs. matrix: $p = 0.01$) and were more likely to be tampered with, although the probabilities for tampering with tablet, matrix, and gel products were not significantly different. The matrix and gel patches were not ranked significantly differently on either the VPS or LTS.

On the VPS, the fentanyl matrix patch was statistically similar to the three tablets, the fentanyl gel patch, and the hydromorphone matrix patch. The fentanyl matrix patch was perceived as being more valued than the hydromorphone ($p = 0.02$) and oxycodone ($p < 0.001$) gel patches and the oxycodone matrix patch ($p < 0.001$). A similar trend was observed for the LTS (data not shown).

Table 4. Rank, from highest to lowest, of products on the Value of Product-Likelihood to Tamper (VP-LT) Index		
Product	**All subjects (N = 42)**	
	p value	**Rank**
Fentanyl tablet	0.02	1
Hydromorphone tablet	ns	2
Fentanyl matrix	–	3
Oxycodone tablet	ns	4
Hydromorphone matrix	0.03	5
Fentanyl gel	ns	6
Hydromorphone gel*	0.002	7
Oxycodone matrix	< 0.001	8
Oxycodone gel**	< 0.001	9
* Indicates three missing data points; ** Indicates two missing data points; ns = not significant; p value based on comparisons to the fentanyl matrix patch (bolded).		

The VP-LT Index for the fentanyl tablet was significantly higher than for the fentanyl matrix patch (p = 0.02) (Table 4). The fentanyl matrix patch was ranked similarly to the other tablet formulations and the fentanyl gel patch and was of more interest to subjects than were both of the matrix patches and the hydromorphone and oxycodone gel patches.

Overall desirability

The overall desirability of each of the three drugs, three formulations, and nine products is provided in Table 5, in decreasing order of desirability. Independent of the drug involved, the tablet was the most desirable dosage form, followed by the matrix patch and then the gel patch. Regardless of formulation, fentanyl was significantly more desirable than both hydromorphone and oxycodone. As a result, the (hypothetical) fentanyl tablet was ranked consistently as the most desirable product and was significantly more desirable than the fentanyl matrix patch. The fentanyl matrix patch was statistically similar in terms of desirability to the hydromorphone and oxycodone tablet formulations and to the fentanyl gel patch, and it was significantly more desirable than both types of (hypothetical) hydromorphone and oxycodone patches.

Opiate Attractiveness Scale

Mean scores for the OAS are presented in Table 6. Results were similar among study centers (not shown). The oxycodone tablet ranked as the most attractive formulation. The fentanyl matrix patch was significantly more attractive than all three gel-patch products, and it was statistically similar in attractiveness to all three tablet formulations and the oxycodone matrix patch.

Estimation of street value

The mean subjective street values of reference drugs and study products are presented in Table 7. Of the 13 reference street drugs presented to subjects, ketamine, *d*-amphetamine, Hycodan®, and Demerol® could not be assigned dollar values due to a lack of experience in the majority of subjects; these have been excluded from Table 7.

The range of mean dollar values for the reference drugs was large and, on average, the values assigned were either "low" (< $20) or "high" (> $70). Each of the nine study products ranked intermediately between the "low" and "high" value categories of the reference drugs.

Overall, the fentanyl matrix patch had the highest derived dollar value of the test products, followed by the fentanyl tablet and fentanyl gel patch; however, the difference between fentanyl formulations was not statistically significant.

Table 5. Overall desirability of drug, formulation, and product			
		All subjects (N = 42)	
		p value	Rank
Drug	**Fentanyl**	–	1
	Hydromorphone	< 0.001	2
	Oxycodone	< 0.001	3
Formulation	Tablet	< 0.001	1
	Matrix	–	2
	Gel	0.03	3
Product	Fentanyl tablet	0.001	1
	Hydromorphone tablet	ns	2
	Fentanyl matrix	–	3
	Fentanyl gel	ns	4
	Oxycodone tablet	ns	5
	Hydromorphone matrix	0.002	6
	Hydromorphone gel	< 0.001	7
	Oxycodone matrix	< 0.001	8
	Oxycodone gel	< 0.001	9
Products are ranked from most to least desirable, using fentanyl, a matrix patch, and the fentanyl matrix patch as comparator references (bolded).			

Feedback on matrix and gel formulations

Subjects were asked for feedback on any safety concerns, as well as how they might tamper with and share the formulations to get high (data not shown). In addition, subjects were asked which fentanyl product they would prefer to use to get high.

Of the 42 subjects interviewed, 25 (60 percent) said they would prefer to use the matrix patch, as it was perceived to be easier to prepare for intravenous use (soluble in water and without hydroxyethyl cellulose gel, making it "cleaner" to use).

More than half of the subjects preferring to use the gel patch over the matrix patch (10 of 17, or 59 percent) were from Dartmouth. The most common reason for Toronto and Winnipeg subjects' preference for the gel patch was familiarity; the most common reason for Dartmouth subjects was that they could see the gel (i.e., the drug).

DISCUSSION

This study compared the likelihood and potential for tampering with a fentanyl matrix patch to that of other

Table 6. Mean scores for the Opiate Attractiveness Scale				
Product	**N**	**Mean score**	**p value**	**Rank**
Oxycodone tablet	42	4.01	ns	1
Fentanyl tablet	42	3.93	ns	2
Oxycodone matrix	42	3.85	ns	3
Fentanyl matrix	42	3.82	–	4
Hydromorphone tablet	42	3.68	ns	5
Hydromorphone matrix	42	3.57	0.03	6
Fentanyl gel	42	3.30	< 0.001	7
Oxycodone gel	42	3.29	< 0.001	8
Hydromorphone gel	42	3.22	< 0.001	9
Ranked from most to least attractive; p value based on comparison to the fentanyl matrix patch (bolded).				

opioid formulations among Canadian recreational opioid users. Based on self-reported histories, hydromorphone was the preferred opioid and was the one with which subjects had most often tampered.

Regardless of dosage form, fentanyl is highly sought by abusers. The theoretical fentanyl tablet was the most preferred product on all scales except the OAS, where it ranked second after the oxycodone tablet.

In general, tablet formulations were preferred, followed by matrix patches and then gel-patch formulations. The preference for tablet formulations may reflect the subjects' previous experience with opioids that are available in tablet formulations (i.e., hydromorphone and oxycodone). Many commonly abused prescription drugs are available in tablet formulations, and tampering by chewing, crushing, or dissolving for oral, intranasal, or intravenous administration is fairly routine among recreational drug users.[10] In addition, tablets may have been perceived as easier to obtain in greater quantities due to the number of tablets per prescription compared to patches, making them easier to divert, divide, and resell. Subjects considering such aspects may also have weighed the perceived familiarity or preferences of potential buyers. Of the matrix-patch formulations, the fentanyl matrix was most desired and ranked comparably to tablet formulations. The fentanyl gel patch was ranked higher than the hydromorphone and oxycodone gel formulations, and it was consistently ranked lower than the fentanyl matrix patch. The exception was in overall desirability by Dartmouth subjects (Eastern Canada), who tended to prefer the gel-patch formulations (primarily because they could see the gel). This regional difference may reflect unfamiliarity with the gel patch and limited experience tampering with this formulation, as those who expressed knowledge of the extraction process with gel patches generally preferred other formulations.

The few inconsistencies in the ranking of products among scales may reflect differences in scale properties, form, and instructional control. For example, the OAS measures the effect of individual product characteristics on attractiveness; the other scales measure choice or attractiveness based upon the subject's baseline knowledge. Additionally, the results appear to have been influenced by product familiarity and experience.

Given the choice to tamper with either a matrix or gel-patch formulation, 60 percent of subjects chose the matrix patch, primarily because it was perceived as being easier to extract opioids from for intravenous use. Of those choosing the gel patch, 59 percent were from

Table 7. Mean subjective street values of reference and study products			
Drug (unit)	**n**	**Mean dollar value/unit (± SD)**	**p value**
Heroin (g)	33	216.06 (96.28)	
Cocaine (g)	41	85.96 (28.19)	
Fentanyl matrix (patch)	42	61.68 (42.17)	–
Fentanyl tablet (pill)	42	61.47 (51.77)	ns
Fentanyl gel (patch)	42	57.65 (45.02)	ns
Hydromorphone matrix (patch)	42	45.21 (32.79)	0.04
Hydromorphone gel (patch)	42	41.46 (30.89)	0.01
Oxycodone gel (patch)	42	35.54 (26.48)	0.001
Oxycodone matrix (patch)	42	34.70 (23.61)	< 0.001
Hydromorphone tablet (pill)	42	27.20 (21.54)	< 0.001
Oxycodone tablet (pill)	42	24.27 (21.96)	< 0.001
MDMA (pill)	33	18.44 (7.88)	
MS Contin (pill)	40	16.55 (12.26)	
Methadone (20 mg)	39	14.20 (18.17)	
Fiorinal $C_{1/2}$ (pill)	22	4.08 (5.14)	
Percodan (pill)	42	3.97 (1.32)	
Tylenol 4 (pill)	36	2.06 (1.27)	
Valium (pill)	40	1.66 (2.07)	
Note: Drug names in italics are reference drugs; p value based on comparison to the fentanyl matrix patch (bolded).			

Dartmouth and, as discussed, were less familiar with the fentanyl gel patch than subjects from Toronto (Central Canada) and Winnipeg (Western Canada). The fentanyl matrix patch had the highest derived street value compared to the other eight products, a value lower than those of only heroin and cocaine. The high estimated value, plus overall desirability, suggests a higher incentive for diversion of the fentanyl matrix patch than for the existing gel patch and other currently marketed products (hydromorphone and oxycodone tablets). However, the differences between street values derived for fentanyl formulations were not statistically significant.

Our data suggest that the risk for misuse of various formulations may differ regionally and that drug users' preferences may be based on past experience. There was a tendency for subjects to prefer drugs with which they were familiar. However, the highly rated desirability and attractiveness of the matrix patch (a hypothetical product

not yet marketed in Canada) raises concern regarding the abuse potential of such a product in Canada. With availability and tampering experimentation, baseline knowledge of the fentanyl matrix patch would increase, perhaps substantially increasing its attractiveness to opioid users. The relevance of the current data to other global regions or countries is unknown.

Despite differences in what the scales measured and the confounding influence of comparing hypothetical to existing products, all scales consistently showed the fentanyl matrix patch to be more valued, more likely to be tampered with, more desired, and more attractive than the fentanyl gel patch. This suggests that the fentanyl matrix patch may have greater abuse potential than the existing reservoir gel patch.

Fentanyl in any form is highly attractive to opiate abusers, even in a tamper-resistant formulation. Although not conclusive, these results suggest that a fentanyl matrix formulation has characteristics indicating an increased risk of diversion and tampering in Canada. Such risk should be evaluated by prospective epidemiological studies or comparative risk management programs (RMPs). RMPs should be part of the development of any new narcotic delivery system.

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