

# Safety of fentanyl initiation according to past opioid exposure among patients newly prescribed fentanyl patches

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See also [www.cmaj.ca/lookup/doi/10.1503/cmaj.160291](http://www.cmaj.ca/lookup/doi/10.1503/cmaj.160291)

## ABSTRACT

**Background:** Although a convenient opioid delivery system, transdermal fentanyl patches have caused several deaths and resulted in safety warnings reminding prescribers that fentanyl patches should be prescribed only for patients who have adequate prior exposure to opioids. We conducted a longitudinal analysis of the safety of fentanyl initiation by examining past opioid exposure among patients newly prescribed fentanyl patches.

**Methods:** We identified all patients in the province of Manitoba who were newly prescribed fentanyl patches between Apr. 1, 2001, and Mar. 31, 2013. We converted all prior opioid use to oral morphine equivalents and determined the average daily dose in the 7–30 days before initial fentanyl patch use. Fentanyl initiation was considered unsafe if the patient's pre-fentanyl opioid exposure was below the recommended level.

**Results:** We identified 11 063 patients who began using fentanyl patches during the study period. Overall, fentanyl initiation was deemed unsafe in 74.1% of cases because the patient's prior opioid exposure was inadequate. Women and patients 65 years of age and older were more likely than men and younger patients, respectively, to have inadequate prior opioid exposure ( $p < 0.001$  for each comparison). The proportion of patients who had unsafe prescriptions for fentanyl patches decreased significantly over the study period, from 87.0% in 2001 to 50.0% in 2012 ( $p < 0.001$ ).

**Interpretation:** The safety of fentanyl initiation improved over the study period, but still half of fentanyl patch prescriptions were written for patients with inadequate prior opioid exposure. Review of prior opioid exposure may be a simple but important way to improve the safe use of fentanyl patches.

**Competing interests:** None declared.

This article has been peer reviewed.

**Accepted:** Feb. 3, 2016

**Online:** Apr. 4, 2016

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*CMAJ* 2016. DOI:10.1503/  
cmaj.150961

Fentanyl is a high-potency opioid with a strength 100 times that of morphine.<sup>1</sup> Although available in a variety of forms, the most common form for outpatient use in Canada is the transdermal patch, which provides 3-day continuous delivery of the drug. Fentanyl was initially available in 25-, 50-, 75- and 100- $\mu\text{g}/\text{h}$  patches. A 12- $\mu\text{g}/\text{h}$  patch was introduced in 2006, recommended for dose titration rather than initiation.<sup>2</sup> The fentanyl patch is a convenient non-oral delivery system preferred by patients that may have fewer adverse effects than other sustained-release oral formulations of opioids.<sup>3</sup> As such, it has become a popular choice in the management of cancer-related and chronic non-cancer-related pain.<sup>4,5</sup> The replacement of OxyContin with the tamper-resistant OxyNeo and the accompanying regulatory changes concerning long-acting oxycodone products have been associated with an increase in the use of fentanyl in some jurisdictions.<sup>6,7</sup> Unfortunately, problematic fentanyl use is

increasing.<sup>8,9</sup> This rising level of use makes it an important time to assess safety issues related to the fentanyl patch.

One important safety issue, and a factor under the control of prescribers, is the recommendation that first-time users of the fentanyl patch have adequate prior exposure to opioids.<sup>2</sup> Fentanyl patches are not suitable for opioid-naïve patients. Only patients who have used the equivalent of 60 mg of morphine per day for at least 1 week should be prescribed a 25- $\mu\text{g}/\text{h}$  patch.<sup>2</sup> Failure to adhere to this recommendation has been associated with adverse effects of opioid overdose, including depression of the central nervous system, flaccid skeletal muscles, hypotension, bradycardia, respiratory depression and death.<sup>2,3</sup> Older patients are known to be at particular risk because of altered absorption and metabolism.<sup>2,10</sup> A number of safety warnings and advisories have been issued to ensure that prescribers confirm patients have sufficient opioid tolerance before prescribing a fentanyl patch.<sup>11–20</sup>

A study of reported opioid-related deaths in the province of Ontario found that 57 (2.7%) of the 3406 opioid-related deaths from 1991 to 2004 were related to fentanyl.<sup>21</sup> However, in this study, it is difficult to differentiate deaths related to problematic drug use or suicide from those associated with routine medical practice. There have been numerous case reports of deaths associated with inadequate opioid exposure before the initiation of fentanyl patches.<sup>11,12,14,17</sup> A Health Canada review found 11.5% of the 52 fentanyl-related deaths examined were associated with fentanyl patch initiation.<sup>18</sup> In a search of the Canada Vigilance Adverse Reaction Online Database for the period 1996–2015, after excluding cases related to the terms “intentional,” “abuse,” “suicide,” “dependence” and “diversion,” we found that health care professionals reported 284 deaths involving fentanyl patches to Health Canada.

We conducted a longitudinal analysis of the safety of fentanyl initiation by examining prior opioid exposure among patients newly prescribed fentanyl patches. The objective was to assess the potential influence of the various warnings and safety bulletins related to safe fentanyl prescribing and to determine the current level of risk in the Manitoba population.

## Methods

We examined the safety of fentanyl patch initiation among patients 18 years of age and older in the fiscal years from Apr. 1, 2001, to Mar. 31, 2013. We used data from the Population Health Research Data Repository maintained by the Manitoba Centre for Health Policy. Prescription records were obtained from the province’s Drug Programs Information Network database. This centralized system is used to process all outpatient prescriptions and submit claims to the province’s drug benefits plan (Pharmacare) and to third-party insurers. Using these prescription records, we examined pre-fentanyl opioid use to estimate whether the recommended guidelines for adequate opioid tolerance for safe fentanyl patch initiation had been met.

We constructed a cohort consisting of all patients who had 1 or more prescriptions for transdermal fentanyl filled. We excluded patients who had fentanyl prescriptions filled in the first 90 days of the study period, to avoid misclassifying prevalent use as fentanyl initiation. We used administrative data from hospital discharge abstracts to exclude patients admitted to hospital in the 30 days before their first fentanyl prescription, because no data were available on opioid use in hospital.

To determine opioid exposure before fentanyl patch use, we examined all opioid prescriptions filled more than 90 days before the start of fentanyl. We converted opioid doses to morphine equivalents using standard opioid conversion tables.<sup>22</sup> We calculated daily doses by multiplying the number of dispensed tablets by the strength of the morphine equivalent and dividing by the days supplied. For patients with concurrent opioid prescriptions, we summed the contributions from each prescription over the days of overlap. We calculated the average daily doses for the 7, 14, 30 and 60 days preceding the first fentanyl prescription and took the highest average daily dose. We classified fentanyl initiation as safe if the pre-fentanyl opioid daily dose met or exceeded the dosing guidelines in the manufacturer’s product monograph.<sup>2</sup>

We conducted a sensitivity analysis in which we defined fentanyl initiation as safe if there was any opioid use in the 60 days before the first fentanyl prescription. Patients with no prior exposure were considered to be fully opioid naive and at greatest risk of an adverse effect from fentanyl use. In addition, to ensure that most patients were not clustered close to the threshold of adequate opioid exposure, we stratified patients who had unsafe fentanyl initiation by the percentage of recommended opioid dose they received before starting fentanyl.

Use of the 12- $\mu\text{g}/\text{h}$  fentanyl patch was also examined to explore whether it was for dose titration or for fentanyl initiation. Each patient’s first prescription for the 12- $\mu\text{g}/\text{h}$  patch was classified as initiation if it was their first ever fentanyl patch, and as titration if otherwise.

## Statistical analysis

We performed all analyses using SAS software (version 9.4, SAS Institute). Univariate analysis was used to summarize our data. The proportion of prescriptions that were considered safe fentanyl initiations was calculated overall, by year, by sex and by age group (< 65, 65–74, 75–84 and  $\geq 85$  yr). The  $\chi^2$  test was used to examine the proportion of safe initiations for the categorical variables of sex, age group ( $\geq 65$  v. < 65 yr) and study year (first v. last). Rates of safe initiation were tabulated for each study year and, separately, by patient age (in years) at the time fentanyl was started. Ordinary linear regression models were constructed for each of these sets of data to determine the significance of trends present.

## Results

From Apr. 1, 2001, to Mar. 31, 2013, we identified 267 958 prescriptions for transdermal fentanyl patches dispensed to 17 102 distinct pa-

tients. The 744 patients given prescriptions in the first 3 months of the study were excluded as potentially prevalent users. We also excluded another 5295 patients admitted to hospital in the 30 days before fentanyl initiation. The final cohort of 11 063 patients included more women than men, and more older people ( $\geq 65$  yr) than younger patients (Table 1). The initial dose most commonly prescribed was 25  $\mu\text{g}/\text{h}$ ; in 18.4% of cases, the initial dose was 50  $\mu\text{g}/\text{h}$  or higher.

Fentanyl patch initiation was deemed unsafe in most cases overall, with 74.1% of new prescriptions written for patients with inadequate prior opioid exposure (Table 2). In 33.4% of cases, a combined formulation of acetaminophen/codeine or acetaminophen/oxycodone was the only opioid prescribed before the start of fentanyl (Table 1). Unsafe fentanyl initiation decreased over the study period, from 87.0% of prescriptions in 2001 to 50.0% in 2012 ( $p < 0.001$ ). The decrease was greater among men than among

women (by 40.4% v. 34.3%;  $p < 0.001$ ), and among older patients than among those less than 65 years old (by 37.7% v. 33.0%;  $p < 0.001$ ).

In the linear regression analysis in which the safety of fentanyl initiation was examined over time, we found a significant increase in the level of safe prescribing over the study period. The percent of new prescriptions that met the recommended pre-fentanyl opioid exposure levels increased by 3.9% each year (95% confidence interval [CI] 3.4%–4.5%). In the linear regression analysis by patient age, we found a significant trend toward decreased levels of safety with increasing age. Each additional year of life was associated with a 0.39% decrease in the mean rate of safe initiation (95% CI 0.32%–0.45).

In the sensitivity analysis in which fentanyl initiation was considered safe if any amount of opioid was used in the 60 days before the start of fentanyl, 26.3% of the prescriptions were to fully opioid-naïve patients. Again, older patients were at greater risk than those less than 65 years of age (32.3% v. 18.1%;  $p < 0.001$ ). The level of fentanyl patch initiation among opioid-naïve patients fell significantly over time, from 35.3% of all fentanyl starts in 2001 to 15.7% in 2012 ( $p < 0.001$ ). The levels of fentanyl initiation among the other patients, stratified by percent of recommended pre-fentanyl opioid dose, are shown in Figure 1.

The association between prior opioid exposure and the starting dose of fentanyl patch is examined in greater detail in Table 3. Although higher starting doses of fentanyl patch were generally associated with greater prior opioid exposure, all strengths of patch were at times initiated

**Table 1:** Characteristics of patients newly prescribed the fentanyl patch, 2001–2012

Characteristic	No. (%) <i>n</i> = 11 063
<b>Sex</b>	
Female	6884 (62.2)
Male	4179 (37.8)
<b>Age group, yr</b>	
$\leq 64$	4692 (42.4)
65–74	1894 (17.1)
75–84	2500 (22.6)
$\geq 85$	1977 (17.9)
<b>Initial dose of fentanyl patch, <math>\mu\text{g}/\text{h}</math></b>	
12	1293 (11.7)
25	7739 (70.0)
50	1459 (13.2)
75	363 (3.3)
100	209 (1.9)
<b>Prior opioid exposure*</b>	
Single-entity LA opioid	2956 (26.7)
Single-entity IR opioid	1889 (17.1)
Oxycodone/acetaminophen	1289 (11.7)
Codeine/acetaminophen	2406 (21.7)
No exposure	2523 (22.8)

Note: IR = immediate release, LA = long acting.  
\*Mutually exclusive groups of patients categorized by highest to lowest level of opioid used in the 90 days preceding the first fentanyl patch prescription (highest = single-entity LA opioid; lowest = codeine/acetaminophen combination).

**Table 2:** Safety of fentanyl initiation at the start and end of the study period, by sex and age

Characteristic	% (no.) of patients with unsafe fentanyl initiation*		
	2001 <i>n</i> = 866	2012 <i>n</i> = 574	Overall <i>n</i> = 11 063
<b>Sex</b>			
Female	87.4 (501/573)	53.1 (178/335)	76.3 (5 253/6 884)
Male	86.0 (252/293)	45.6 (109/239)	70.4 (2 943/4 179)
<b>Age group, yr</b>			
$\leq 64$	79.0 (233/295)	45.9 (119/259)	66.1 (3 100/4 692)
65–74	86.3 (126/146)	41.7 (48/115)	72.7 (1 377/1 894)
75–84	89.4 (210/235)	52.3 (58/111)	81.6 (2 039/2 500)
$\geq 85$	96.8 (184/190)	69.7 (62/89)	85.0 (1 680/1 977)
<b>All</b>	87.0 (753/866)	50.0 (287/574)	74.1 (8 196/11 063)

\*Unsafe = fentanyl patch newly prescribed to patient without adequate prior exposure to opioids.

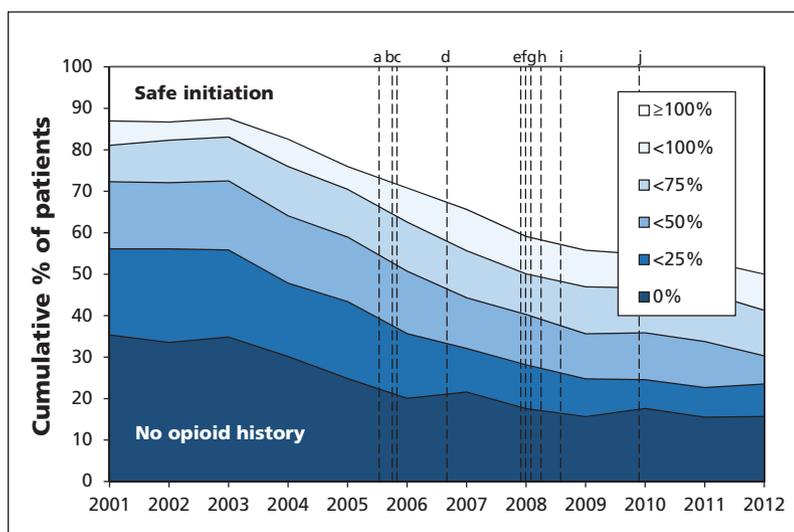
without previous opioid exposure. When we looked at the pattern of use for the 12- $\mu$ g/h fentanyl patch, we found that, in the first year of its use in Canada, 54% of first uses were for initiation rather than titration; by the end of the study period, this value increased to 65.5% of first uses. Because the 12- $\mu$ g/h patch has less opioid than the 25- $\mu$ g/h patch, it is easier to achieve adequate opioid tolerance with this strength of patch (30 mg v. 60 mg morphine equivalent per day). Even at this lower threshold, only 43.5% ( $n = 563$ ) of the 1293 initial prescriptions for the 12- $\mu$ g/h fentanyl patch would be considered safe. Of these safe starts, 54.7% ( $n = 308$ ) would have been classified as unsafe if the 25- $\mu$ g/h patch had been prescribed initially.

### Interpretation

Our analysis showed that the level of safety of fentanyl prescribing improved over the study period. However, by the end of the study, still only half of the initial prescriptions were issued to patients with adequate prior exposure to opioids. The sensitivity analysis of the distribution of patients relative to the percentage of the recommended pre-fentanyl opioid exposure allowed us to examine the different levels of prior opioid exposure, with the presumption that doses close to the recommended level would be associated with a lower risk of adverse effects. However, at the end of the study period, 15.7% of patients in the sensitivity analysis were receiving fentanyl patches without exposure to opioids of any kind in the 60 days before fentanyl was started. Of particular concern, patients 65 and older, who may be at the greatest risk, had higher levels of unsafe fentanyl initiation than younger patients. In the overall study population, there was considerable improvement, with a 37.0% decrease in unsafe prescribing over the study period. The use of the 12- $\mu$ g/h patch for fentanyl initiation increased over the study period. Although its use may reduce the risk of adverse effects, it does not eliminate the need for prior opioid exposure.

Absorption of fentanyl from patches varies widely between patients.<sup>23</sup> This variation, along with exposure of the patch to heat, improper use of the patch, use of multiple patches and a variety of other factors, combine with inadequate opioid exposure in cases that result in death.<sup>14,15,24,25</sup>

The systematic study of the quality of fentanyl patch prescribing has been limited. European studies of administrative data used different definitions of opioid tolerance but produced comparable results.<sup>26,27</sup> The largest study was in



**Figure 1:** Proportion of patients newly prescribed fentanyl patches, 2001–2012, by level of previous opioid exposure (% of recommended opioid dose in the 60 days before fentanyl initiation). Previous opioid use ranged from 0% (no opioid history) to  $\geq 100\%$  (safe initiation of fentanyl). The vertical dashed lines represent when warnings or advisories were issued by the US Food and Drug Administration (a and f),<sup>11,12</sup> Health Canada (b and i),<sup>13,18</sup> the Institute for Safe Medication Practices Canada (d, e, h and j)<sup>14–17</sup> and professional journals (c and g).<sup>19,20</sup>

Prior opioid exposure, mg/d of oral morphine equivalent	Initial fentanyl patch dose, $\mu$ g/h; no. (%) of patients*					
	12 <i>n</i> = 1293	25 <i>n</i> = 7739	50 <i>n</i> = 1459	75 <i>n</i> = 363	100 <i>n</i> = 209	Total <i>n</i> = 11 063
No exposure	301 (10.4)	2276 (78.3)	248 (8.5)	51 (1.8)	31 (1.1)	2907
1–29	429 (13.9)	2287 (73.9)	315 (10.2)	47 (1.5)	16 (0.5)	3094
30–59	308 (15.7)	1382 (70.4)	223 (11.4)	38 (1.9)	13 (0.7)	1964
60–179	215 (10.3)	1412 (67.6)	358 (17.1)	77 (3.7)	27 (1.3)	2089
180–269	18 (4.4)	191 (46.7)	134 (32.8)	43 (10.5)	23 (5.6)	409
270–359	9 (4.8)	71 (37.8)	57 (30.3)	40 (21.3)	11 (5.9)	188
$\geq 360$	13 (3.2)	120 (29.1)	124 (30.1)	67 (16.3)	88 (21.4)	412

\*Percentages are based on row totals. Values in blue screened cells represent inadequate prior opioid exposure.

Germany in 2004–2006 and found that 84.5% of fentanyl starts were in opioid-naive patients.<sup>26</sup> The authors defined opioid naive as receiving no high-potency opioids in the 3 months before fentanyl patch initiation. As in our study, they found a higher risk of unsafe fentanyl initiation among women than among men and a decreasing level of safe prescribing with increasing age. A small study in the United States examined fentanyl patch prescribing among nursing home residents.<sup>10</sup> As in our study, women and older adults were at increased risk of fentanyl patches and other long-acting opioids being started without prior exposure to short-acting opioids. In a recent US intervention study in a regional medical centre, McEvoy and colleagues<sup>28</sup> made use of electronic medical records to remind prescribers of the need for patients to be given 60 mg of morphine or equivalent before prescribing fentanyl patches. Before this intervention, only 46.7% of patients had received adequate opioid doses when fentanyl was prescribed. After the intervention, the value increased to 75.6%, which suggests that relatively simple interventions may substantially improve the safety of fentanyl prescribing. Despite the relatively low level of safe prescribing found in our study, we believe our results are generalizable, because similar levels of safety have been found in Europe and the United States.

### Limitations and strengths

This study has a number of important limitations. We estimated prior opioid use from pharmacy dispensing data for opioid prescriptions. Patients may not have used the medications, or they may have used more than initially prescribed based on verbal instruction from the prescriber for dose adjustment. However, the assumption of use based on pharmacy dispensations is common in administrative data studies.<sup>29</sup> We were not able to capture opioid medication use prescribed outside of the province. The study is also limited by not examining outcomes of fentanyl prescribing. We assessed the safety of fentanyl initiation as defined by the product monograph and safety warnings. The rate at which unsafe prescribing, as defined by dosing recommendations and warnings, translates into actual negative outcomes for patients is unknown, but case reports have shown that they occur.<sup>14–16,24</sup>

Despite these limitations, our study has a number of strengths. Our use of a fully linked population-level database leaves us confident that we captured most instances of community prescribing of opioids. The 12-year duration of

the study also allowed us to examine the safety of fentanyl prescribing before and after the release of safety warnings. We also used multiple definitions of opioid tolerance and used the most conservative result in our assessment of the safety of fentanyl prescribing.

### Conclusion

Considerable attention and effort have been placed into making prescribers aware of the need to ensure adequate opioid tolerance before prescribing fentanyl patches. Although we found evidence that the safety of fentanyl prescribing improved, by the end of the study period, still half of patients prescribed fentanyl patches had inadequate prior exposure to opioids. Special attention should be paid to older patients, who are at greatest risk of adverse outcomes but had the lowest level of safe prescribing. Opioid prescribing generally, and fentanyl patch prescribing in particular, has a number of inherent risks, many of which may be difficult to control fully. Ensuring adequate opioid tolerance before prescribing a fentanyl patch is one way this risk can be controlled by the prescriber.

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**Contributors:** Cornelius Woelk and Shawn Bugden were involved in the study conception. Kevin Friesen and Shawn Bugden were involved in the study design, and the acquisition, analysis and interpretation of data. Kevin Friesen and Shawn Bugden drafted the manuscript; all of the authors revised and critically evaluated the manuscript, approved the final version to be published and agreed to act as guarantors of the work.

**Funding:** This study was funded by a research grant (no. G00316138) from the University of Manitoba.

**Acknowledgement:** The authors acknowledge the Manitoba Centre for Health Policy for use of data contained in the Population Health Research Data Repository (HIPC file no. 2012/2013-08). The results and conclusions are those of the authors, and no official endorsement by the Manitoba Centre for Health Policy, by Manitoba Health, Healthy Living and Seniors, or by other data providers is intended or should be inferred. The authors thank Mara Creek for valuable review of the manuscript.