



AN INTERNATIONAL NETWORK OF SAFE MEDICATION PRACTICE CENTRES

**Medication incidents related to the use of fentanyl
transdermal systems:
An international aggregate analysis**

Contributing countries: Canada, Ireland, United Kingdom, United States

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Executive Summary

Over the past several years, there have been reports in the medical literature and from medication safety centres around the world concerning adverse events with fentanyl transdermal systems (also referred to as fentanyl “patches”). Many of these incidents have been reported to result in harm and in some cases, even death. To date this information has been scattered and sporadically reported, making it difficult to discern trends or patterns.

In order to gain a better understanding of the nature of transdermal fentanyl-related incidents and what factors contribute to them, the International Medication Safety Network undertook the research described in this report. This is the first study of its kind to collect and analyze fentanyl transdermal system incident report from multiple jurisdictions, in this case Canada, Ireland, the United Kingdom and the United States. The creation of a larger and more comprehensive aggregate database of incidents has made possible more detailed quantitative and qualitative analysis.

A sequential, mixed methods approach was adopted, in which quantitative analysis was conducted on the categorical data fields using customary medical use systems (n=3271 cases), followed by qualitative analysis on the narrative data fields (n=1076 cases). (The analysis methodology is described in Appendix I.)

The quantitative analysis provided a “snapshot” of the data (e.g., 8.3% of cases resulted in harm or death, with 0.3% being death). The quantitative analysis also suggested potential areas of focus. For example, wrong dose, strength or quantity and dose omission were found to account for more than two-thirds of incidents resulting in harm or death. Administration and supply of the medication from a clinical area was the most common stage at which error occurred (66.4% of errors resulting in harm or death).

The qualitative analysis identified four major themes containing 21 potential contributing factors:

- too much medication or administered too soon;
- too little medication or administered too late;
- patient didn’t need or should not have received the medication; and
- other.

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In order to better address systems issues, a second classification scheme was developed which focused on six potential areas of medication system improvement:

- Critical information: Health care practitioners' lack of awareness of critical information regarding transdermal fentanyl
- Patient education
- Complexity of transdermal fentanyl administration
- Communication pertaining to the prescribing and transcription of orders for transdermal fentanyl
- Product design
- Interfaces of care: Use of transdermal fentanyl not identified or recognized through interfaces of care

Many recommendations have been suggested in the literature as well as in numerous newsletters and alerts from various patient and medication safety centres and regulatory agencies in different countries. A summarized list of selected recommendations is contained in the section "Recommendations" and a comprehensive list is provided in Appendix II. Two key areas for action are highlighted as applicable for global implementation:

- Greater efforts must be focused on safeguards to ensure healthcare practitioners have adequate knowledge and training in the proper use of transdermal fentanyl.
- Effective strategies are needed to ensure patients and their families are well informed and educated about the use of transdermal fentanyl. Emphasis should be made on their clear understanding of the complexity of the dosing regimen, proper disposal of used patches as well as monitoring any side effects from this potent analgesic.

In order to achieve success in these areas, five specific recommendations are proposed:

- Require mandatory education on transdermal fentanyl as part of regulated entry to practice and continuing education programs for physicians and pharmacists (e.g., labelled indications and appropriate dosing as well as the potential for harm);
- Require pharmacists to counsel patients at the time of dispensing of transdermal fentanyl and specifically discuss:
 - i. the appropriateness of the dose ordered (i.e., confirm opioid tolerance and indication for use);
 - ii. signs and symptoms of toxicity; and
 - iii. when to seek immediate medical attention.
- Request that software vendors build automated alerts requiring acknowledgement of opioid tolerance for all new transdermal fentanyl orders.
- Request all manufacturers of transdermal fentanyl to provide clear, legible and easy to understand warnings in patient education materials, using pictograms as applicable. (A sample patient information brochure, developed by the Institute for Safe Medication Practices (United States) illustrating these principles is provided in Appendix III).

- Request all manufacturers of transdermal fentanyl to make coloured patches, to increase visibility on the body and to reduce the likelihood of duplicate application or failure to remove.

Continued efforts will be necessary for the further development of effective systems-based solutions targeting the various areas of medication system improvements identified in this analysis.

Background

This analysis was initiated by the International Medication Safety Network (IMSN) to examine and analyze data from multiple jurisdictions (Canada, the US, the UK and Ireland) on medication incidents involving fentanyl transdermal systems. The fentanyl transdermal system is a topically applied patch providing continuous, 72-hour delivery of fentanyl, a potent synthetic opioid agonist. It is indicated for management of “persistent, moderate to severe chronic pain that requires continuous, around the clock opioid administration for an extended period of time, and cannot be managed by other means such as non-steroidal analgesics, opioid combination products, or immediate-release opioids.”¹ There have been a number of reports in several countries of medication incidents, some of which have resulted in patient harm or even death.

Pharmacology / pharmacokinetics

An understanding of the pharmacologic and pharmacokinetic properties of fentanyl transdermal systems can provide a foundation for understanding appropriate or safe use of this potent medication (see Table 1).

Table 1: Summary pharmacologic and pharmacokinetic of transdermal fentanyl parameters

Pharmacologic / pharmacokinetic parameter	Characteristics of transdermal fentanyl	Practical implications
Potency	75 to 100 times more potent than morphine ²	<ul style="list-style-type: none">• Contraindicated in opioid-naïve patients• Dose titration should not be made abruptly
Structure	<p>Reservoir patch: 4 layer structure including a protective strip, a rate control membrane and a fentanyl reservoir³</p> <p>Matrix patch: Consists of a drug-in-adhesive matrix layer (covered by a protective liner) and a backing layer.⁴</p>	<ul style="list-style-type: none">• Protective strip needs to be removed prior to application• Patches should not be cut, since drug reservoir may leak out • Protective strip needs to be removed prior to application• Cutting or damaging the matrix fentanyl transdermal patch is against the approved labelling from FDA.²⁸

Pharmacologic / pharmacokinetic parameter	Characteristics of transdermal fentanyl	Practical implications
Onset	After application of the first patch, it may take 12 to 18 hours to reach peak of pain relief ⁵	<ul style="list-style-type: none"> • Dosage adjustments should not be made sooner than recommended
Duration	A newly applied patch will maintain steady state fentanyl concentrations with minimal fluctuations for 72 hours ¹	<ul style="list-style-type: none"> • Patches must be changed according to schedule to maintain pain control
Effect of heat sources	Temperature-dependent increase of fentanyl release ¹	<ul style="list-style-type: none"> • Patients on transdermal fentanyl should not be exposed to direct heat sources (e.g., heating pads, sun exposure, hot compresses etc.)
Metabolism	Cytochrome P450 3A4 isozyme ¹	<ul style="list-style-type: none"> • Drug interactions with P450 3A4 inhibitors (e.g. ritonavir)⁶
After 72 hours of application	Approximately 40% fentanyl still left in patch ⁷	<ul style="list-style-type: none"> • Important to remove old patches when new one is applied • Importance of the proper disposal of used fentanyl patches to avoid accidental application by others.
After removal	Serum fentanyl levels fall to 50% approximately 17 hours after patch removal ¹	<ul style="list-style-type: none"> • Extended period of monitoring in cases of toxicity (at least 24 hours or until the adverse event has subsided)¹

With its unique pharmacologic and pharmacokinetic profile, fentanyl transdermal systems represent an alternative to oral opioids. Their advantages compared to oral opioids include convenience and the relatively constant fentanyl concentrations throughout the dosing period; they may also be beneficial for patients with difficulties swallowing oral medications.

Medication incidents involving transdermal fentanyl

Despite their potential benefits, inappropriate or incorrect use of transdermal fentanyl can lead to significant patient harm. In fact, there has been a steady stream of reports of adverse events, including fatalities, caused by inappropriate prescribing, dispensing and administration.⁸ As a result, a number of alerts and warnings have been issued world-wide by various patient and medication safety centres and regulatory agencies.^{9, 10, 11, 12, 13} These alerts have highlighted a number of different issues related to the inappropriate utilization of transdermal fentanyl.

“A patient was found to have new patches on their [sic] right upper arm, and old patches still on the left arm. The patient was responsive, but sluggish, with pinpoint pupils...”¹⁰

“...a 15 year old girl was prescribed Duragesic 25 for chronic headache. She was discovered unresponsive with respiratory depression 21 hours after the first and only application. She was resuscitated but suffered severe anoxic brain injury and died 2 days later.”³

Need for coordinated, system-based solutions

Coordinated, systems-based solutions are needed to ensure the safe use of transdermal fentanyl. The first step in the development of effective solutions is to understand the circumstances, conditions and contributing factors associated with inappropriate or incorrect use. This can be achieved by the analysis of medication incident reports involving fentanyl transdermal system. There are two main approaches to this type of analysis: (a) the study of individual or a small number of case reports and (b) aggregate analysis of large number of cases.

In the past, aggregate analyses of local data have been conducted^{13, 28} but this report is the first to combine data from multiple jurisdictions: the UK, US, Canada and Ireland. The inclusion of data from multiple jurisdictions has made possible a more complete and robust picture of issues and challenges in the safe use of this potent opioid.

Overall Goal:

The primary goal of this analysis is to gain an in-depth understanding of transdermal fentanyl incidents. The work conducted to address this goal includes:

- a) an aggregate analysis of fentanyl transdermal system incidents received by the participating medication and patient safety centres in the UK, US, Canada and Ireland; and,
- b) a review of the medical literature.

The intent of this report is to raise awareness of the risks associated with transdermal fentanyl and potential contributing factors; as well as to present recommendations for medication systems enhancements to ensure the safe use of this product.

Methodology

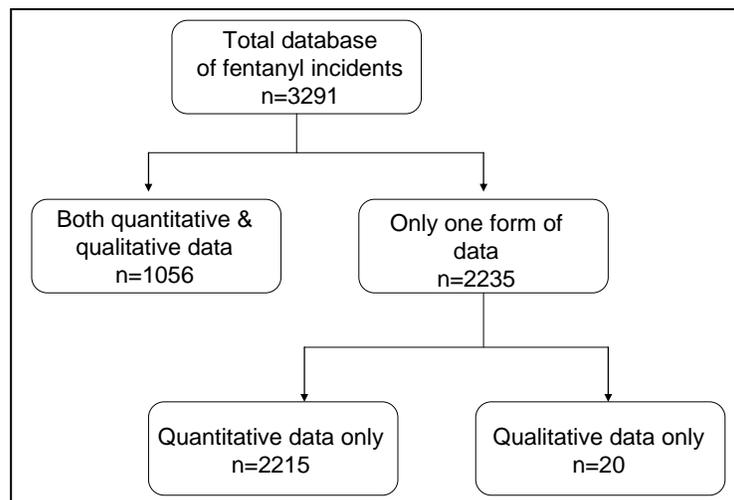
Data for this study consisted of fentanyl incident reports submitted by safe medication practice centres in the UK, US, Ireland and Canada. As shown in Figure 1, incident reports contained both quantitative and qualitative data fields (n=1056), quantitative fields only (n=2215) or qualitative data fields (incident narrative) only (n=20), for a total of 3291 reports. Appendix I outlines how medication incident data was collected, prepared for analysis and analyzed.

The analysis utilized a sequential mixed methods approach. First, quantitative analysis was conducted. This enabled the classification of reports according to severity, type and medication stage (i.e., *what* type of errors and *where* in the medication use process they occurred).

Second, qualitative analysis was conducted on narrative data fields to gain more in-depth insights regarding the underlying contributing factors associated with different types of incidents (i.e., *why* errors occur). Two analysts worked independently to refine and confirm emerging patterns and main themes. To illustrate the themes, data from the incident reports was supplemented with a literature search and review of case reports and articles describing transdermal fentanyl medication incidents.

Both the quantitative and qualitative analyses were conducted using an iterative process of analysis, review and reflection, and re-analysis.

Figure 1: Fentanyl Incident Data Collection (n=3291)



i) Quantitative Data Analysis

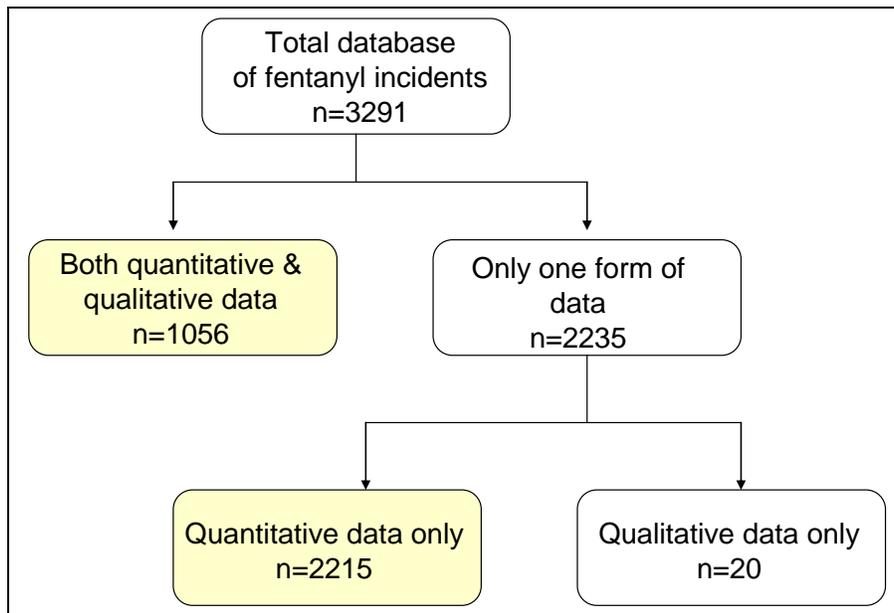
Figure 2 illustrates the number and type of reports included in the quantitative analysis (n=3271).

For this analysis, transdermal fentanyl incidents were classified according to:

- Severity/outcome
- Type of incident:
 - All incidents
 - Incidents resulting in harm or death
- Medication system stages involved:
 - All incidents
 - Incidents resulting in harm or death

As described in Appendix I, mapping schemes were developed for each of the relevant classifications; corresponding frequency tables from each set of data were combined according to the mapping scheme in order to produce combined frequency tables.

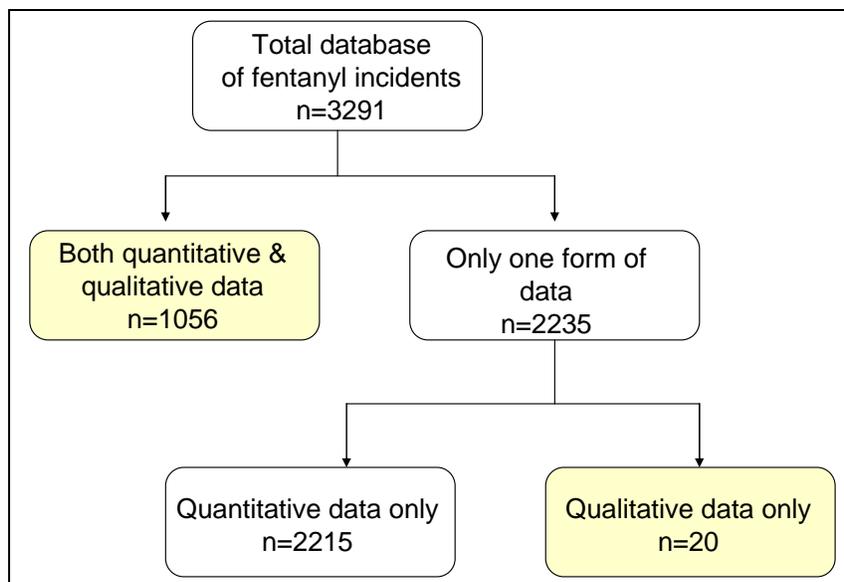
Figure 2: Data for Quantitative Analysis (n=3271)



ii) Qualitative Analysis

Data for this analysis included the event description data field (a narrative data field which allows the reporter to type in a summary of the medication incident) and other narrative data fields of transdermal fentanyl incident reports. Figure 3 shows the data included in the qualitative analysis (n=1076). The qualitative analysis was conducted to gain more in-depth insights regarding the underlying factors contributing to transdermal fentanyl incidents.

Figure 3: Data for Qualitative Analysis (n=1076)



Reports were reviewed by two independent analysts to identify the main themes. Four patient-focused themes emerged as reports were reviewed. Each incident was classified under one of the four theme areas. Within each theme, incidents were further classified under sub-categories until clusters of incidents were achieved that were relatively homogeneous in nature. Incidents within each subgroup were studied to identify potential contributing factors. The contributing factors were categorized into two classification schemes:

- a) the four patient-focused themes mentioned above (i.e., patient-focused analysis)
- b) six areas of medication system improvements (i.e., medication system oriented analysis)

iii) Literature search

A literature search was performed to identify case reports and articles describing transdermal fentanyl medication incidents. The information was used both in the qualitative analysis, to help support the formation of analytic categories, and as a source of information on proposed solutions. A summarized list of existing solutions from the current literature was compiled. More information on the search is included in Appendix I.

Analysis Findings

Results of the quantitative analysis

Quantitative analysis was conducted on 3271 incident reports, focusing on severity, type and medication stage.

Incident severity

As shown in Table 2, the majority (91.7%) of incidents did not result in harm. 8.0% (n=263) of incidents resulted in harm while 0.3% (n=8) of incidents resulted in death.

Table 2: Transdermal fentanyl medication incidents classified by severity of outcome

Severity of Outcome	Number of Medication Incidents (%)
No error	161 (4.9%)
No harm	2839 (86.8%)
Harm	263 (8.0%)
Death	8 (0.3%)
TOTAL	3271 (100.0%)

Incident types

From the incident reports received, the two most common types of incidents were associated with wrong dose, strength or quantity (32.8% of all incidents and 37.6% of those resulting in harm or death) and dose omission (30.5% of all incidents and 32.1% of those resulting in harm or death). (See table 3.)

Table 3: Transdermal fentanyl medication incidents classified by type of incident

Type of incident	All incidents (n=3271)		Incidents resulting in harm or death (n=271)	
	Number	Percent*	Number	Percent **
Wrong dose, strength or quantity	1073	32.8%	102	37.6%
Dose omission	998	30.5%	87	32.1%
Prescribing error	281	8.6%	12	4.4%
Incorrect time	278	8.5%	7	2.6%
Incorrect drug	183	5.6%	13	4.8%
Wrong frequency	95	2.9%	11	4.1%
Incorrect patient	72	2.2%	6	2.2%
Incorrect administration technique	67	2.1%	6	2.2%
Wrong storage	37	1.1%	-	***
Contraindication	-	***	4	1.5%
Incorrect dosage form	34	1.0%	-	***
Expired or deteriorated drug	33	1.0%	3	1.1%
Drug prepared incorrectly	-	***	3	1.1%
Wrong/omitted verbal patient directions	-	***	3	1.1%
Other / unknown***	261	8.0%	25	9.2%
Total types identified:	3412	104.3%	282	104.0%
Total incidents:	3271	100.0%	271	100.00%

* For all incidents, the percentage is calculated based on the total number medication incident reports (n = 3271). Since a medication incident may involve more than one type of incident, the total percentage is greater than 100%.

** For incidents resulting in harm or death, the percentage is calculated based on the total number of medication incident reports (n = 271). Since an incident report may involve more than one type of incident, the total percentage is greater than 100%.

*** For all incidents, "other" categories with percentages less than 1% were: drug prepared incorrectly, wrong / transposed / omitted medicine label, incorrect duration, unknown, contraindication, incorrect route of administration, incorrect rate, patient allergic to treatment, wrong / omitted verbal patient directions, adverse drug reaction, wrong / omitted patient information leaflet, drug therapy monitoring problem, drug-drug interaction, drug therapy monitoring problem: clinical.

For incidents resulting in harm or death, "other" categories with percentages less than 1% were: wrong storage, patient allergic to treatment, adverse drug reaction, drug therapy monitoring problem: drug-drug interaction, incorrect dosage form, wrong / transposed / omitted medicine label, incorrect duration, incorrect route of administration, incorrect rate, wrong / omitted patient information leaflet, drug therapy monitoring problem: clinical.

Medication stage involved

Table 4 presents the medication incidents received classified by the medication system stage involved. 66.4% of the incidents resulting in harm or death were from the “administration and supply of a drug from a clinical area” stage.

Table 4: Transdermal fentanyl patch medication incidents classified by medication system stage involved

Stage involved	All incidents (n=3271)		Incidents resulting in harm or death (n=271)	
	Number	Percent*	Number	Percent **
Physician ordering (prescribing)	419	12.8%	38	14.0%
Order entry & transcription	417	12.8%	16	5.9%
Preparation, dispensing and delivery of drugs	397	12.1%	17	6.3%
Administration and supply of a drug from a clinical area	1692	51.7%	180	66.4%
Monitoring / follow-up of drug use	185	5.7%	22	8.1%
N/A	168	5.1%	1	0.4%
Other	41	1.3%	6	2.2%
Total selections:	3319	101.5%	280	103.3%
Total incidents:	3271	100.00%	271	100.00%

* Percentage is calculated based on the total number of medication incidents (n = 3271). Since a medication incident may involve more than one stage selection, the total percentage is greater than 100%.

** Percentage is calculated based on the total number of medication incidents with outcome of harm or death (n = 271). Since a medication incident may involve more than one stage selection, the total percentage is greater than 100%.

Results of the qualitative analysis

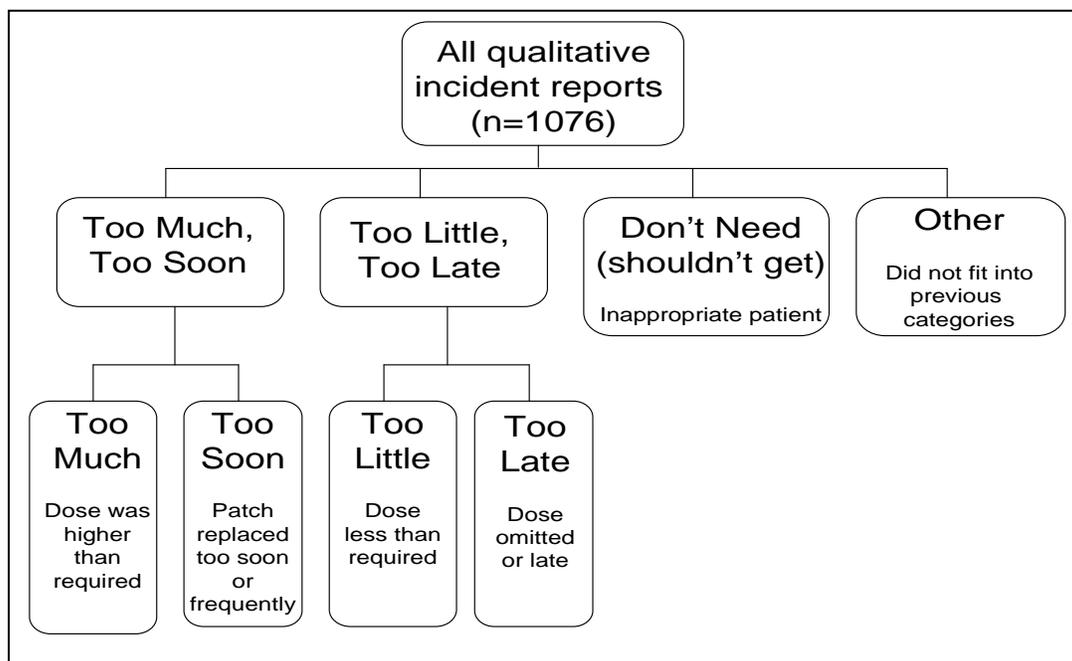
a) Patient-focused analysis

After reviewing the narrative data fields of incidents (n=1076), four main themes emerged that represented the medication administration outcomes for patients resulting from these incidents:

1. doses that were too high (“too much” or “too soon”);
2. doses that were too low (“too little” or “too late”);
3. treatment of people who should not receive transdermal fentanyl (don’t need (shouldn’t get)); and
4. other.

These themes are illustrated in Figure 4.

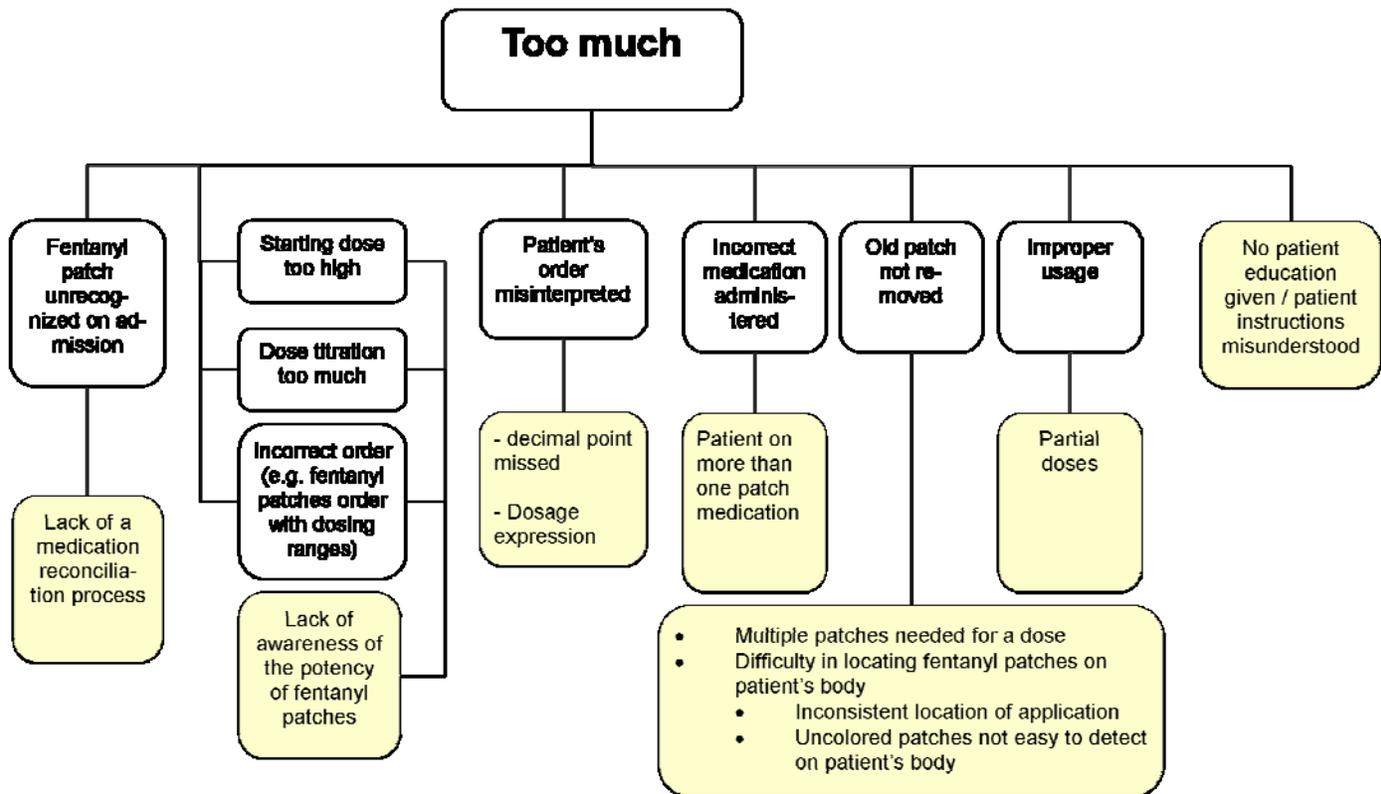
Figure 4: Qualitative analysis of transdermal fentanyl patch incidents: Main themes



1. “Too Much” or “Too Soon”

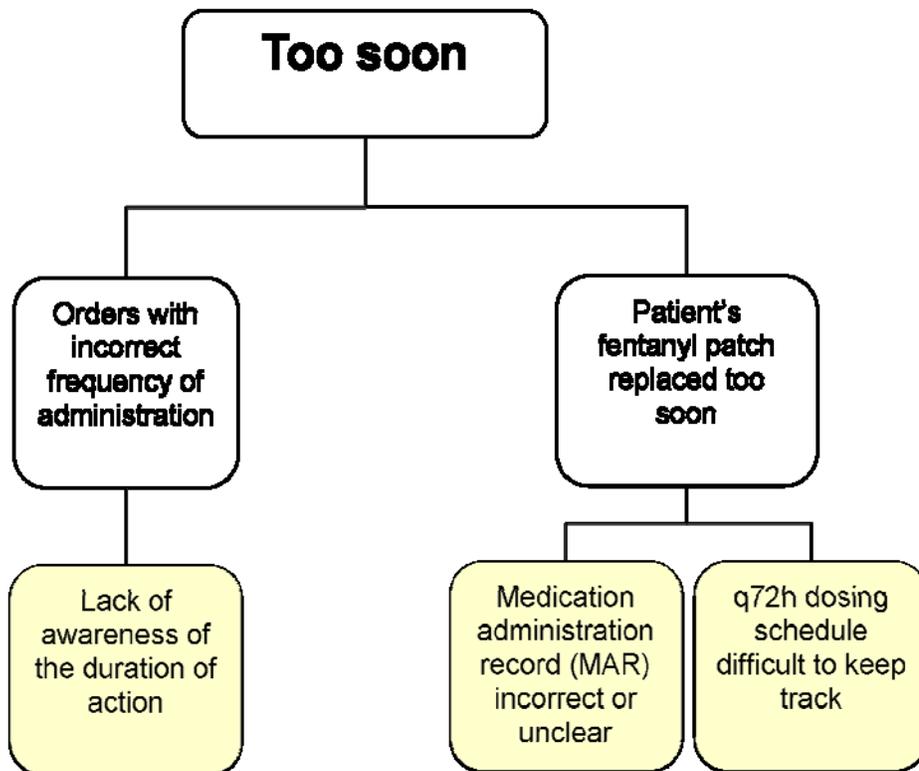
This includes incidents in which transdermal fentanyl was prescribed, dispensed or administered at a higher dose or frequency than required by the patient (i.e., according to the patient’s previous opioid usage). Figures 5 and 6 summarize the subcategories and potential contributing factors (in coloured boxes) within the themes “too much” and “too soon”.

Figure 5: “Too much”: Subcategories and potential contributing factors



(Colored boxes indicate potential contributing factors)

Figure 6: “Too Soon”: Subcategories and potential contributing factors

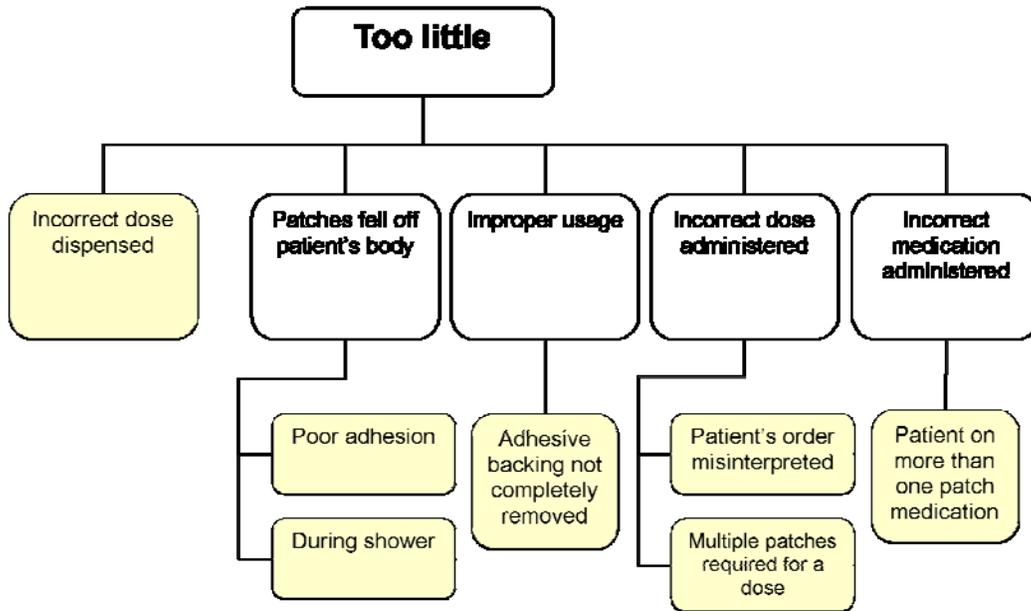


(Coloured boxes indicate potential contributing factors)

2. “Too Little” or “Too Late”

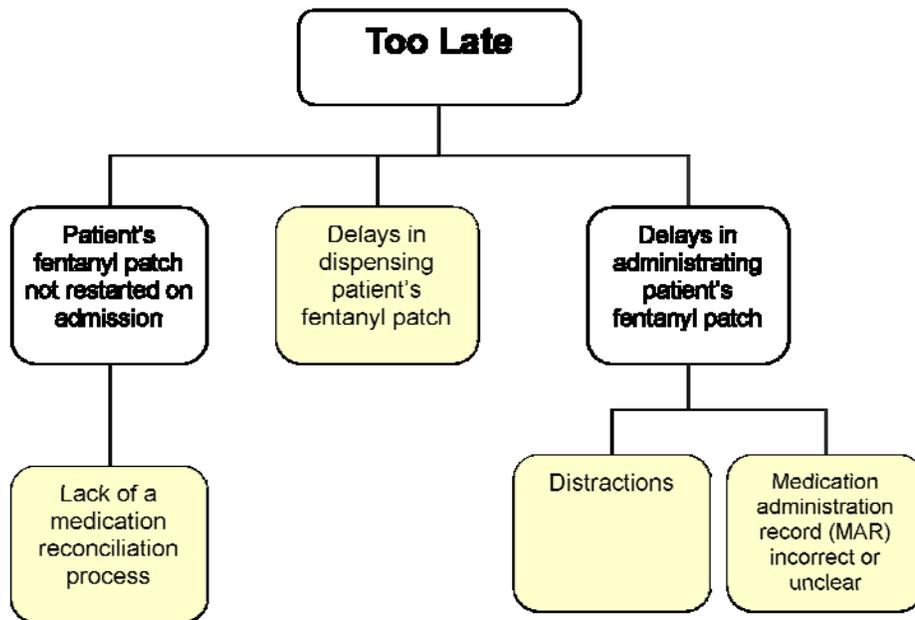
This includes incidents in which transdermal fentanyl was prescribed, dispensed or administered at a lower dose (too little) or frequency (too late) than required by the patient. The “too late” theme also included incidents where the fentanyl dose was omitted. Figures 7 and 8 summarize the subcategories and potential contributing factors (in coloured boxes) within the themes “too little” and “too late”.

Figure 7: “Too little”: Subcategories and potential contributing factors



(Colored boxes indicate potential contributing factors)

Figure 8: “Too Late”: Subcategories and potential contributing factors

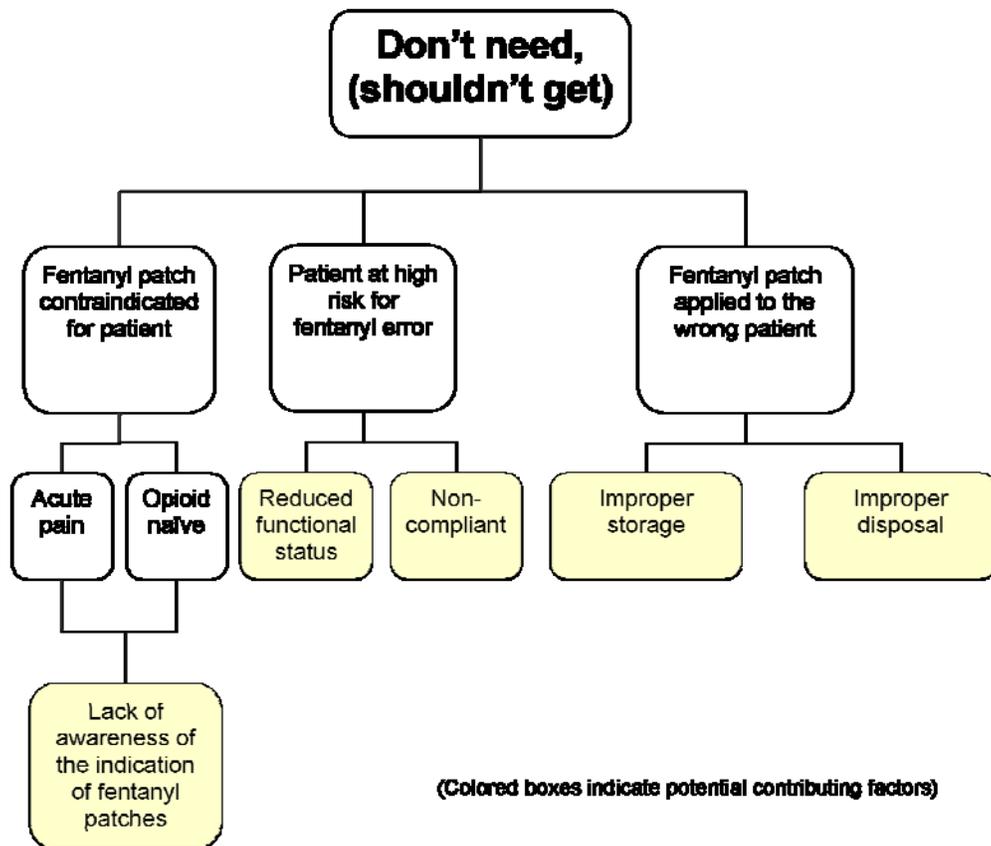


(Colored boxes indicate potential contributing factors)

3. “Don’t need (shouldn’t get)”

This theme consisted of cases in which patients were prescribed a transdermal fentanyl system without an appropriate indication. (See figure 9.)

Figure 9: “Don’t need (shouldn’t get)”: Subcategories and potential contributing factors



4. “Other”

The majority of the incidents in the “other” category concerned non-patient specific situations in which transdermal fentanyl patches were improperly stored. Another type of error identified among the “other” incidents was “narcotic discrepancy”.

Summary of Potential Contributing Factors

Table 5 summarizes the 21 potential contributing factors (i.e., the coloured boxes) identified via the patient-focused analysis.

Table 5: Potential contributing factors identified

- Lack of medication reconciliation process
- Lack of awareness of the potency of transdermal fentanyl
- Decimal point missed in interpreting the order
- Inconsistent dosage expressions used in ordering transdermal fentanyl
- Patient on more than one transdermal medication
- Multiple patches needed for a fentanyl dose
- Inconsistent location of application
- Translucent appearance of patches
- Administration of partial fentanyl patch doses
- Patient education not provided
- Lack of awareness of the duration of action
- Medication administration record (MAR) incorrect or unclear
- “Every 3 day” dosing difficult to keep track of
- Poor adhesion of fentanyl patch to patient’s body
- Patch came off patient’s body during shower
- Adhesive backing not completely removed
- Various transdermal fentanyl order misinterpretations
- Lack of awareness of the indications for use of fentanyl patches
- Transdermal fentanyl prescribed to patients with reduced functional status
- Transdermal fentanyl prescribed for non-compliant patients
- Improper disposal of fentanyl patches

b) Medication system-oriented analysis

The four themes identified from the patient-focused analysis described above presented the possible medication administration scenarios from the point of view of the patient. However, they are of limited value in suggesting potential improvements to medication systems. To address this perspective, a second classification scheme was developed. Under this classification scheme, the 21 potential contributing factors were categorized into six areas:

1. **Critical information** (e.g., inadequate knowledge on the part of healthcare practitioners on the potency and/or how to safely use fentanyl transdermal systems)
2. **Patient education**
3. **Complexity of administration**
4. **Communication pertaining to the prescribing and transcription** of orders for transdermal fentanyl
5. **Product design**
6. **Interfaces of care** (e.g, transdermal fentanyl not identified or recognized at interfaces of care)

Table 6 summarizes the potential contributing factors according six areas of medication system improvements. Case examples drawn from incident report narratives as well as from the literature were presented to illustrate each of the potential contributing factors.

Table 6: The six identified areas for medication system improvements

Areas	Potential Contributing Factors	Case Examples
Critical information – Health care practitioners' awareness of critical information about transdermal fentanyl	<ul style="list-style-type: none"> • Lack of awareness of critical information regarding transdermal fentanyl (e.g. potency, indication, duration and proper dosage titration) 	<ul style="list-style-type: none"> • <i>“Patient was receiving oxycodone 60mg SR bid plus prn oxycodone. Therapy was converted to fentanyl patches 75mcg/hr. The patient has their last dose of OxyContin 60mg at 0800 on [date]. Fentanyl patch was applied at 1200 [same day]. At 11:30 on [one day later] the patient had to be given a stat dose of...naloxone for opiate overdose.” (Starting dose too high)</i> • <i>“...patient was unable to take oral morphine which he was taking previously. While awaiting a</i>

Areas	Potential Contributing Factors	Case Examples
		<p>syringe driver being set-up I prescribed a fentanyl [100mcg/hr] patch. I failed to appreciate the strength of these patches until it was pointed out to me by the hospice doctor that this was equivalent to 315-404mg of morphine in 24 hours...a potentially fatal dose (the patient was previously taking [morphine sustained release] tablets 10mg bid)...no harm resulted from this incident as the patch was removed and replaced by a syringe driver...but I am concerned that it is not obvious how strong these patches are, particularly to doctors who are not accustomed to prescribing them.” (lack of awareness of the potency of transdermal fentanyl)</p> <ul style="list-style-type: none"> • “Patient started on fentanyl ‘25’ patch...advised by prescriber to apply one patch and then a second if the first was insufficient. She put another patch on after 12 hours of wearing one...patient was complaining of drowsiness and was unable to drive...” (lack of understanding of the proper usage of transdermal fentanyl: advising the patient to apply an extra fentanyl patch on a prn basis) • “...decision made to start fentanyl patches. Prescription written for 25 to 100mcg. Not stopped by pharmacy; no consultations with any of the pain teams...” (lack of understanding of the proper usage of transdermal fentanyl: order with dosing ranges) • “81 year old female patient admitted to [emergency] ... headache, [nausea and vomiting], light-headed. Recently started on Duragesic 50 patch by GP...[symptoms determined to be] related to side effects of fentanyl patch. Patient stopped. Spoke with patient – had previously been using panadol (paracetamol) alone for pain. Said not sufficient, therefore went to GP and got patch.” (Lack of awareness of the indications of transdermal fentanyl: prescribed for opioid naïve patient). • “A 14 year old boy was prescribed duragesic 25 for throat pain due to infectious mononucleosis. He was found in a respiratory arrest 14 hours after the first and only patch was applied.

Areas	Potential Contributing Factors	Case Examples
Patient education	<ul style="list-style-type: none"> Inconsistent provision of patient education regarding the potency, proper usage and disposal of fentanyl patches 	<p><i>Resuscitative efforts were unsuccessful.”(Lack of awareness of the indications of transdermal fentanyl: prescribed for acute pain)</i> ³</p> <ul style="list-style-type: none"> “A physician gave a 78 year old patient with chronic pain a prescription for fentanyl patch, with directions to apply on 25mcg patch. The patient was confused and put the patches “wherever it hurt.” She applied 6 patches in all...” (Transdermal fentanyl patches prescribed to a patient with reduced functional status) ¹⁴ “Patient demanding diclofenac extra to prescription. Has own [medications] in his bag and admits to having fentanyl patches but refuses to allow nurse to secure them. Appears from discussion to take whatever medication he wants when he wants it...” (Transdermal fentanyl prescribed to a patient not willing to follow instructions) “...a patient’s caregiver placed the fentanyl patch on the patient’s buttock, which was the site of her pain. When the patient went to bed, she also used a heating pad at the same place. The patient was discovered dead two days later...neither the prescribing physician nor the pharmacist had counselled her on how to use the patch properly, and they hadn’t told her to avoid applying heat over the patch.” (patient education not provided) ¹⁵ “.. when the child [a 6-year-old girl] complained of neck pain late one evening, her foster mother gave her an appropriate dose of ibuprofen but also paced a leftover fentanyl patch on the child’s neck to help treat the pain. The next day, the child as found unconscious in bed and was pronounced dead by the time she arrived in the emergency department... This tragedy may have been avoided had the foster mother received adequate education when the fentanyl patches were prescribed and dispensed.” ¹⁶ (patient education not adequate)

Areas	Potential Contributing Factors	Case Examples
Complexity of transdermal fentanyl administration	<ul style="list-style-type: none"> <li data-bbox="464 268 784 331">• Patient on more than 1 patch medication <li data-bbox="464 541 784 604">• Multiple patches needed for a dose <li data-bbox="464 877 784 940">• Inconsistent location of application <li data-bbox="464 1087 784 1150">• Administration of partial doses <li data-bbox="464 1717 784 1780">• “Every 3 day” dosing difficult to keep track 	<ul style="list-style-type: none"> <li data-bbox="821 268 1513 499">• <i>“I discovered that the patient had her fentanyl patch removed...instead of her nitroglycerin patch. This meant that she did not received the 6 hours break in nitroglycerin administration as prescribed and been under- administered pain relief.” (mix-ups between transdermal fentanyl and nitroglycerin patches)</i> <li data-bbox="821 541 1513 835">• <i>...a patient was found to have a 100mcg patch insitu (his current dose) as well as a 50mcg patch (an old patch). This patient’s fentanyl patch dosage was recently changed from 75mcg (25mcg + 50mcg patches) to 100mcg. When changing the dose, the 25mcg patch was removed and replaced by 100mcg, while the 50mcg patch was not removed. (Fentanyl dose requiring multiple patches)</i> <li data-bbox="821 877 1513 1045">• <i>“Resident had 4 patches in his body, removed the 2 old patches...note from previous staff member indicated that they were unable to find the patches.” (Difficulty in identifying patches on the patient’s body)</i> <li data-bbox="821 1087 1513 1381">• <i>“Patient is seen by GP...unwell and confused – query opiate overdose, on fentanyl patch 25mcg/hr plus morphine. Oral morphine discontinued but fentanyl patch cut in half by GP and reapplied....patient pale...pulse irregular...admitted directly to [emergency] by ambulance. Fentanyl patch empty of all gel...” (Partial doses: patches cut and transdermal fentanyl reservoir leaked out)</i> <li data-bbox="821 1423 1513 1654">• <i>“Fentanyl patch order was 6.25mcg/hr (cover ¾ of a 25mcg/hr patch with tegaderm). Patch was covered with tegaderm on the top, not between skin and patch therefore patient received full 25mcg/hr.” (Partial doses: Tegaderm placed on top of patch instead of between skin and patch).</i> <li data-bbox="821 1717 1513 1845">• <i>...caregiver thought it was “April 11th”, but it was only April 10th, therefore it [fentanyl patch] was changed one day early” (Every 3 day dosing difficult to keep track of)</i>

Areas	Potential Contributing Factors	Case Examples
Communication pertaining to the prescribing and transcription of orders for transdermal fentanyl	<ul style="list-style-type: none"> Decimal point missed 	<ul style="list-style-type: none"> <i>“Patient was reported to be unwell and drowsy. When attended by doctor it was discovered that patient had been given 125mcg of fentanyl patch instead of 12.5mcg...when I spoke to one of them they stated that they had not noticed the “.” dot between the 12.5mcg...”</i> (decimal point missed)
	<ul style="list-style-type: none"> Inconsistent dosage unit / expressions used when ordering transdermal fentanyl 	<ul style="list-style-type: none"> <i>...a prescriber ordered fentanyl 12.5 patches (intended to be 12.5mcg/hr patches). However, since the dose units were not specified, this was misinterpreted as fentanyl 12.5mg per patch. Since a fentanyl 25mcg/hr patch contained 2.5mg of fentanyl per patch and a fentanyl 100mcg/hr patch contained 10mg of fentanyl per patch, fentanyl 125mcg/hr (fentanyl 2.5mg per patch + 10mg per patch = fentanyl 12.5mg per patch) was dispensed, resulted in a 10 fold overdose. (Dose unit mix-up [mcg/hr vs. mg per patch])</i> <i>...a physician “gave a handwritten prescribed to a patient for fentanyl 10cm² patches. Outpatient hospital pharmacy dispensed fentanyl 100mcg/hr patches, but a pharmacist later learned that the physician had intended to prescribe fentanyl 25mcg/hr patches.” (According to the packing insert the size of the 25mcg/hr patch was 10cm².) (Dose unit mix-up (mcg/hr vs. patch area)¹⁷</i>
	<ul style="list-style-type: none"> Medication administration record (MAR) incorrect or unclear 	<ul style="list-style-type: none"> <i>“Fentanyl patch not changed. Two previous doses had been entered on the wrong date column and so dose omitted on the third day.” (MAR incorrect)</i> <i>“Pt fentanyl patch found not to have been changed the previous day as prescribed. There was a lot of crossing out and re-writing on the drug kardex.” (MAR unclear)</i>
	<ul style="list-style-type: none"> Other misinterpretation of orders 	<ul style="list-style-type: none"> <i>“75mcg fentanyl patch applied incorrectly, appeared to read 75mcg on chart but actually 25mcg (noted further checking in notes)...” (mix-ups between “25” and “75”)</i>

Areas	Potential Contributing Factors	Case Examples
Product design	<ul style="list-style-type: none"> • Translucent appearance of patches 	<ul style="list-style-type: none"> • “Resident had 4 patches in his body, removed the 2 old patches...note from previous staff member indicated that they were unable to find the patches.” (Difficulty in identifying patches on the patient’s body)
	<ul style="list-style-type: none"> • Poor adhesion of fentanyl patch to patient’s body 	<ul style="list-style-type: none"> • “...on night shift, enrolled nurse noticed that the patient was moaning and in obvious pain. Checked over and noted that her prescribed fentanyl patch (50mcg) was not on her shoulder. Enrolled nurse then checked the patient at [time] with staff nurse, and no patch found. Replace patch put on...” (patch fell off patient’s body, resulting in loss of pain control) • “Lady was prescribed and supplied with [a particular brand of] fentanyl 75mcg patches. After a few days she returned and complained that they were not adhering to the skin properly...” (poor patch adhesion)
	<ul style="list-style-type: none"> • Patch came off patient’s body during shower 	<ul style="list-style-type: none"> • “Patient had a shower and her fentanyl patch 50mcg came off...” (patch came off during shower)
	<ul style="list-style-type: none"> • Adhesive backing not easily removed 	<ul style="list-style-type: none"> • “Patient unable to use [a particular brand of fentanyl patches] as he could not separate the backing off of the patch...it was difficult to work out which was patch and which was backing. GP, community pharmacist or practice nurse could not work out how to use them either. Instructions completely inadequate...patient was in considerable pain.” (design of fentanyl patches)
	<ul style="list-style-type: none"> • Look-alike packaging and labelling 	<ul style="list-style-type: none"> • “The medication was properly transcribed from the prescription , but 75mcg patches were dispensed instead of 25mcg. Procedures were put in place at this particular pharmacy to ensure such an incident never occurs again. Staff are now more familiar with this new generic product, but believe another safeguard could have easily been put in place by the manufacturer, by making the packaging...with more difference in appearance between strengths.” (look – alike packaging between fentanyl patches of different strengths)

Areas	Potential Contributing Factors	Case Examples
Interfaces of care Patch not recognized on admission	<ul style="list-style-type: none"> Lack of a medication reconciliation process (or the uncoordinated processes of patient medication history taking) 	<ul style="list-style-type: none"> <i>"...patient sent to hospital from [nursing home], patient information stated patient was on a fentanyl 125mcg patch, upon checking it was noted the patient should be on a 25mcg patch. Doctor informed and decided to stop fentanyl due to patient being drowsy."</i> (Patient's initial medication history incorrect / incomplete)

Discussion

This study analyzed more than 3000 transdermal fentanyl incidents received from four countries. A sequential mixed method approach was adopted in which a quantitative analysis was conducted followed by a qualitative analysis. The quantitative analysis generated a “snapshot” of the data, while the qualitative analysis identified 21 potential contributing factors which were presented under two classification schemes to illustrate different perspectives (“patient-focused analysis and clinical impact to the patient” and “opportunities for medication system improvements”).

Quantitative analysis

8.3% of the voluntarily reported incidents received were associated with harm or death (8.0% and 0.3% respectively). Caution must be exercised when comparing data between different voluntary report systems. However, the higher harm ratio of transdermal fentanyl incidents compared to the overall harm ratio for all medications in other reporting systems (which have previously reported overall harm ratios of less than 2%¹⁸), seems to suggest that incidents involving transdermal fentanyl are more likely to be associated with patient harm.

There were 8 reports with an outcome of patient death. It is likely that this represents an underestimation due to the voluntary nature of medication incident reporting. In fact, a number of case reports of transdermal fentanyl-related deaths were found in the medical literature. These cases were not included in the quantitative analysis, but were used as examples in the qualitative analysis.

The most common types of error identified through the quantitative analysis were “wrong dose, strength or quantity” and “dose omission”. These accounted for almost 70% of incidents where an outcome of harm or death was reported. The most common medication system stage involved was “administration and supply of a drug from a clinical area,” constituting 66% of all incidents with an outcome of harm or death.

The quantitative analysis provided a “snapshot” of the data and suggested potential areas of focus (wrong dose and dose omission). However, taken alone, it is of limited practical value since it does not provide details of the specific contributing factors. The qualitative analysis bridges this gap as it does assess potential contributing factors.

Qualitative analysis

More than 20 potential contributing factors were identified through the qualitative analysis. As described above, these were presented under two classification schemes, addressing patient- and medication system-focused factors.

a. Patient-focused factors and clinical impact:

1. “Too much, too soon”:

According to the product monograph, transdermal fentanyl overdoses can lead to symptoms such as sedation, dizziness and confusion; in severe cases, respiratory depression and even death can result.¹ The frequent occurrence of this type of incident through the quantitative analysis (“wrong dose” errors, such as “too much” were the most commonly identified type of error) further highlights the significance of this category of incidents.

2. “Too little, too late”:

Although there were no incidents resulting in death in this category, in the context of pain control this category was associated with significant morbidity. This is particularly true for cases occurring in palliative care, where achieving patient comfort is the primary objective. Chronic pain (for which transdermal fentanyl is indicated) often may “cause more suffering and disability than the injury or illness that caused it in the first place.”¹⁹ This is confirmed by incident reports (see examples below), where on many occasions patients were described as experiencing pain at various levels from “discomfort” to “agony”. Unfortunately, reports suggest that some caregivers are not sensitive to the patient’s pain control requirements. In addition, abrupt decreases in fentanyl concentrations (from dose omissions) may result in opioid withdrawal and extreme patient distress.

“patient extremely agitated, restless and jerking – unable to settle – described feeling as if nerves jangling. Opioid withdrawal. On checking fentanyl 50mcg/hr patch, not secured properly. Therefore not receiving adequate dose for unknown amount of time.” (Of note, this incident was classified as no harm by the reporter.)

...the patient was discharged with the wrong dose fentanyl patch that “required readmission for breakthrough vomiting and pain”

“patient admitted for analgesia. Prescribed fentanyl patch to be applied at 12:00...Patient was not on ward for most of the afternoon, but present at 12:00. Patch not given at 12:00. Despite of patient complaining of pain to nurses, patch not given in late after /evening. [physician] on call was not contacted. Patient specifically asked for patch to be changed but staff made no attempt to contact doctor to enable patch to be given.”

3. “Don’t need (shouldn’t get)”:

Although these incidents occur at lower frequencies compared to the above two categories, they are a highly significant group of incidents because of the often devastating consequences to patients. This is evident from the case reports found in the literature¹³ where transdermal fentanyl was prescribed to opioid-naïve patients, resulting in patient death.

b. System-focused factors: Areas for medication system improvements

With this classification system, potential contributing factors were classified under six categories, reflecting areas where health system improvements could support and promote the safer utilization of transdermal fentanyl. Although these categories may appear to be quite general in nature, they illustrate the unique features of transdermal fentanyl systems and point to specific areas for medication system improvements:

- **Lack of awareness of critical information regarding transdermal fentanyl utilization:**

Because of the high potency, narrow therapeutic range and the serious potential side effects related to transdermal fentanyl, a good grasp of the critical information concerning this medication is essential. Lack of awareness of this information by healthcare practitioners has led to a variety of errors, some of which have led to severe patient harm. These errors include the prescription of transdermal fentanyl patches for opioid-naïve patients (lack of understanding of the indications for use) and starting dose too high (lack of awareness of the potency of transdermal fentanyl).

- **Patient education:**

Patient education is necessary to ensure transdermal fentanyl is used correctly. If patients are not fully aware of how to correctly use this medication or its potency, they may “see patches as benign devices akin to a bandage”.²⁰ Unfortunately, the incidents reviewed in this analysis, as well as case reports in the literature, suggest that patient education is not consistently provided. Lack of education can lead to serious adverse events, including death.

- **Complexity of transdermal fentanyl patch administration:**

The use of transdermal fentanyl differs in many aspects when compared to oral medications. Examples include the relatively complex process for applying partial doses or when a dose requires multiple patches. This complexity may be challenging for health care providers and/or patients. It is essential to realize these unique aspects of transdermal fentanyl use and provide appropriate support for healthcare providers and patients.

- **Communication pertaining to the prescribing and transcription of orders for transdermal fentanyl:**

Several unique aspects of transdermal fentanyl necessitate safeguards to minimize communication problems when they are being prescribed or orders are being transcribed. Transdermal fentanyl orders can span a wide dosage range (e.g., both 12.5 mcg per hour and 125 mcg per hour may be correct dosages, depending on the patient’s opioid tolerance). This differs from most other medications, in which a 10-fold overdose is more likely to be noticed. Moreover, although transdermal fentanyl is ordered by rate (mcg per hour), on some occasions practitioners have ordered transdermal fentanyl using different dosage expressions (such as dose per patch). The use of different dosage expressions greatly increases the risk of order misinterpretation.

- **Product design:**

Several issues were identified related to the design and packaging of transdermal fentanyl. . Issues include:

- the translucent appearance of most fentanyl patches can make it difficult to identify patches on patient’s body;
- poor adhesion of some patches can result in patches falling off (especially after showers);
- difficulty in removing adhesive backing of certain brands of transdermal fentanyl patches can result in under-dosing; and

- labelling and packaging issues such as the presence of different transdermal fentanyl dosing expressions (mcg per hour and total dose per patch) on the outer packaging.

- **Interfaces of care:**

As transdermal dosage forms are less common in comparison to oral dosage forms, there is a possibility that they may be overlooked when patients move between interfaces of care (e.g., hospital admission or transfer between units). This may either result in a loss of pain control or the inadvertent ordering of overlapping opioid analgesics.

Other existing transdermal fentanyl patch aggregate analyses

The findings of this study are generally consistent with other transdermal fentanyl aggregate analyses and alert bulletins.^{8,13,22} This is not surprising because of the common sources of incident data. Due to the larger number of transdermal fentanyl incidents included in this analysis and the incorporation of lessons learned from published alert bulletins and case reports, this study encompasses a wider scope and is more comprehensive than previous analyses.

Limitations

Due to the voluntary nature of medication incident reporting, it is impossible to infer or project the absolute occurrence rate of specific types of incidents. At the same time, it should be noted that there is no reason to expect differential reporting rates of transdermal fentanyl incidents by different types of error. As a result, it is reasonable to assume that the relative frequencies of the types of error presented reflect the true distribution of the types of transdermal fentanyl incidents.

Most of the incidents in this analysis were provided from hospital settings; therefore caution must be exercised when extrapolating the results to community settings. On the other hand, the six areas of medication system improvements (i.e., interfaces of care, communication of orders, lack of awareness of critical information on the part of health care practitioners and patients, complexity of patch administration, product design and patient education) are equally relevant for community settings.

It should be noted that the potential contributing factors identified in the qualitative analysis were derived solely from the event description fields in the received medication incidents. No follow-

ups were conducted with reporters. This limits the depth of information available for each incident. Nonetheless, the large number of incidents included in this analysis provides solid support for the identification of potential contributing factors.

Recommendations

Numerous recommendations have been published in the literature as well as in various medication safety alerts, newsletters and bulletins. These are listed in Appendix II for reference. Table 7 lists some key recommendations (some of which may be specific to a particular country) selected from Appendix II according to the hierarchy of effectiveness of error prevention strategies²¹; arranged by the six areas for medication system improvement.

Table 7: Key recommendations from existing literature

Medication system improvement category:	Recommendations
Critical information: Health care practitioners' lack of awareness of critical information regarding transdermal fentanyl	<ul style="list-style-type: none"> • Include a checklist or algorithm for initiation and titration of transdermal fentanyl in the product monograph.¹¹ • Conduct ongoing education and annual staff competencies on the safe administration of fentanyl transdermal patches.²⁸ • Create specific prescribing and dispensing guidelines for fentanyl transdermal patches that are aligned with the product labelling and referenced during computer entry of the medication.²⁶
Patient education	<ul style="list-style-type: none"> • Mandate patient, family member and/or caregiver education. It is imperative that patients who are using a transdermal fentanyl patch (as well as their caregivers) are educated on the safe use of this product and their level of understanding assessed.²² • Patients and caregivers who place the patches on the skin should be aware of the signs of fentanyl overdoses, including: respiratory distress; shallow breathing; tiredness, extreme sleepiness, or sedation; inability to think, talk, or walk normally; and feeling faint, dizzy, or confused. If these signs occur, patients (or their caregivers) should seek medical attention immediately (e.g., sighing, fluid retention, etc.)²⁸ • Teach patients to avoid exposure to direct heat sources (e.g., heating pads, saunas, hot tubs, heated water beds) while using the patches, because contact may increase fentanyl absorption. Patients with higher body temperatures are also more susceptible to toxicity.²⁸ Patients should be instructed to notify their doctors immediately if they develop a temperature above 102 degrees Fahrenheit or 39

Medication system improvement category:	Recommendations
Complexity of transdermal fentanyl administration	<p>degrees Celsius.²³</p> <ul style="list-style-type: none"> • Provide a dosing calendar so patients can keep track of the location and time of patch application at home.²⁸ • Improved methods of documentation can help guard against applying multiple patches to patients. In the hospital, the drug entry on the medication administration record should be accompanied by a second entry where nurses can document the location and time of application and removal of the patches. • Do not divide or cut patches as this may lead to uncontrolled release of fentanyl.
Communication: Prescribing and entering/ transcribing transdermal fentanyl orders	<ul style="list-style-type: none"> • Practitioners also need to be aware that, to prevent confusion with 125mcg per hour doses, the manufacturer has given the 12.5mcg patch trademark a suffix of “12” even though 12.5mcg of fentanyl per hour is released. Only “Duragesic-12” should be used in prescribing that strength.²⁴ • Healthcare providers should remain cautious about orders for the 125 mcg/hour strength because the decimal point has been overlooked at times with orders for 12.5 mcg/hour patches.⁸
Product design	<ul style="list-style-type: none"> • Drug manufacturers should consider designing a more distinguishable fentanyl patch (e.g. coloured patch) to enhance its visibility on the patient’s body. • Drug manufacturers should consider enhancements in the packaging and labelling of transdermal fentanyl patches to ensure better differentiation between different strengths of transdermal fentanyl.
Interfaces of care: Transdermal fentanyl patches not identified / recognized at interfaces of care	<ul style="list-style-type: none"> • For patients who are admitted to the hospital and using transdermal fentanyl patches at home, the dose should be verified during medication reconciliation, and the verified drug list should be sent to the pharmacy.⁸ • In the Emergency Department assess patient’s skin to check if patient is wearing any patches, as well as upon admission, during routine assessments, and at any change in the level of care.²⁸

Of the recommendations summarized in Table 7, two key areas for action were highlighted and deemed applicable for global implementation as soon as possible:

1. Lack of knowledge of appropriate use of fentanyl transdermal patch is evident from the analysis findings. Greater efforts must be focused on safe guards to ensure healthcare practitioners including physicians, pharmacists and nurses have adequate knowledge and training in the proper use of transdermal fentanyl patches.
2. Effective strategies should be put in place to ensure patients, care takers and their family are well informed and educated about the use of transdermal fentanyl patch. Emphasis should be made on their clear understanding of the complexity of the dosing regimen, proper disposal of patches as well as monitoring any side effects from the potent analgesic.

In order to achieve success in these areas, five specific recommendations are proposed:

- Require mandatory education on transdermal fentanyl as part of regulated entry to practice and continuing education programs for physicians and pharmacists (e.g., including labelled indications and appropriate dosing as well as the potential for harm);
- Require pharmacists to counsel patients at the time of dispensing of transdermal fentanyl and specifically discuss:
 - iv. the appropriateness of the dose ordered (i.e., confirm opioid tolerance and indication for use);
 - v. signs and symptoms of toxicity; and
 - vi. when to seek immediate medical attention.
- Request that software vendors build automated alerts requiring acknowledgement of opioid tolerance for all new transdermal fentanyl orders.
- Request all manufacturers of transdermal fentanyl to provide clear, legible and easy to understand warnings in patient education materials, using pictograms as applicable. (A sample patient information brochure, developed by the Institute for Safe Medication Practices (United States) illustrating these principles is provided in Appendix III.
- Request all manufacturers of transdermal fentanyl to make coloured patches, to increase visibility on the body and to reduce the likelihood of duplicate application or failure to remove.

Continued efforts will be necessary for the further development of effective systems-based solutions targeting the various areas of medication system improvements identified in this analysis.

Appendix I: Methodological details

Medication Incident Data Collection

This analysis was conducted by ISMP Canada. Transdermal fentanyl incident reports were received from patient / medication safety centres in the UK, US, Ireland and Canada.

Specifications of Medication Incident Submission

The following data field specifications had been developed for the purpose of this analysis:

- All available medication incidents involving transdermal fentanyl received by each of the patient / medication safety centre incident databases
- The following **de-identified** data fields were requested, if available:
 - Medication involved
 - Severity level
 - Error type
 - Event description, as well as other available narrative data fields
- **Comprehensive medication incidents:** Medication incidents submitted as per above specifications were classified as a *comprehensive medication incident* if they included both quantitative and qualitative data for analysis.
- **Uni-modal medication incidents:** Medication incidents submitted by medication or patient safety centres were classified as “uni-modal” if they included either qualitative or quantitative data, but not both.
- **Medication incidents in the literature:** A literature search was performed to identify case reports / articles containing transdermal fentanyl medication incident information. The information was used both in the qualitative analysis and for solution development. The following sources were searched (search terms included [“fentanyl”] & [“fentanyl”(MESH) AND “medication error”(MESH)]):
 - Medline
 - Embase
 - FDA website
 - NPSA website
 - ISMP US medication safety bulletin archives
 - ISMP Canada medication safety bulletin archives
 - Manual reference search from articles identified
 - Google

Data Cleaning/Preparation and Analysis

Table 8: Quantitative and qualitative data cleaning, preparation and analysis

Activity	Quantitative Data & Analysis	Qualitative Data & Analysis
Data cleaning/ preparation for analysis	Reports from patient/medication safety centres containing the relevant quantitative data fields were imported to individual Microsoft Excel spreadsheets. The medication incidents were classified according to the predefined criteria (see 'objectives' section). This resulted in five frequency tables for each set of data received.	The received incidents from patient/medication safety centres containing the relevant narrative data fields were imported into a combined Microsoft Access database for subsequent analysis.
Data analysis	<p>Mapping of data fields: Due to the lack of a global standardized data set for medication incident reporting, a mapping process was necessary to enable meaningful combination of fentanyl incident data from different patient/medication safety centres. Mapping schemes were developed for each of the relevant data fields: severity/outcome, type of error and stage of medication system involved (see mapping schemes, below).</p> <p>Combination of data: The corresponding frequency tables from each set of data were combined according to the mapping scheme, resulting in the final combined frequency tables.</p>	<p>Reports were reviewed by two independent analysts to identify the main themes. Four patient-focused themes emerged as reports were reviewed. Each incident was classified under each theme. Within each theme, incidents were further classified under sub-categories until clusters of incidents were achieved that were relatively homogenous in nature. Incidents within each subgroup were studied to identify potential contributing factors.</p> <p>Identification of contributing factors: The incidents of each of the subgroups were examined to detail the main category, subcategories and contributing factors. This made possible data sorting and organization.</p> <p>Presentation of contributing factors: The contributing factors were presented under two classification schemas:</p> <ul style="list-style-type: none"> • four patient-focused themes • six areas of medication system improvements.

Data Field Mapping Schemes for Quantitative Data

Table 9: Mapping scheme for severity / outcome

Data received from Canada	Data received from the United States	Data received from the United Kingdom	Data field name in report
No error	A	No corresponding field	No error
No harm	B-D	No harm	No harm
Harm	E-H	Low harm, moderate, severe	Harm
Death	I	Manual mapping of individual cases (i.e. The event description of all reports with "severe" is used to determine whether it should be classified as "Harm" or "Death").	Death

Table 10: Mapping scheme for type of incident

Data received from Canada	Data received from the United States	Data received from the United Kingdom	Data field name in report
"Incorrect dose", "Extra dose" & "Incorrect strength / concentration"	"Wrong / unclear dose or strength" & "Wrong quantity"	"Improper dose/quantity" & "Extra dose"	Wrong dose, strength or quantity
Dose omission	Omitted medicine / ingredient	Omission error	Dose omission
Incorrect time	NO CORRESPONDING FIELD	Wrong time	Incorrect time
NO CORRESPONDING FIELD	NO CORRESPONDING FIELD	Prescribing error	Prescribing error
Incorrect drug	Wrong drug / medicine	Unauthorized/wrong drug	Incorrect drug
Other	Other	NO CORRESPONDING FIELD	Other / unknown
NO CORRESPONDING FIELD	Wrong frequency	NO CORRESPONDING FIELD	Wrong frequency
Incorrect patient	Mismatching between patient and medicine	Wrong patient	Incorrect patient
Incorrect medication administration technique	NO CORRESPONDING FIELD	Wrong administration technique	Incorrect administration technique
NO CORRESPONDING FIELD	Wrong storage	NO CORRESPONDING FIELD	Wrong storage
Incorrect dosage form	Wrong formulation	Wrong dosage form	Incorrect dosage form
"Deteriorated drug" & "Deteriorated drug: Outdated drug"	Wrong / omitted / passed expiry date	"Expired product" & "Deteriorated product"	Expired or deteriorated drug
NO CORRESPONDING FIELD	Wrong method of preparation / supply	Drug prepared incorrectly	Drug prepared incorrectly
NO CORRESPONDING FIELD	Wrong / transposed / omitted medicine label	Mislabeled	Wrong / transposed / omitted medicine label
Incorrect duration	NO CORRESPONDING FIELD	NO CORRESPONDING FIELD	Incorrect duration
NO CORRESPONDING FIELD	Contra-indication to the use of the medicine in relation to drugs or conditions	NO CORRESPONDING FIELD	Contraindication
NO CORRESPONDING FIELD	Wrong route	Wrong route	Incorrect route of administration
Incorrect rate	NO CORRESPONDING	NO CORRESPONDING	Incorrect rate

Data received from Canada	Data received from the United States	Data received from the United Kingdom	Data field name in report
	FIELD	FIELD	
NO CORRESPONDING FIELD	Patient allergic to treatment	NO CORRESPONDING FIELD	Patient allergic to treatment
NO CORRESPONDING FIELD	Wrong / omitted verbal patient directions	NO CORRESPONDING FIELD	Wrong / omitted verbal patient directions
NO CORRESPONDING FIELD	Adverse drug reaction (when used as intended)	NO CORRESPONDING FIELD	Adverse drug reaction
NO CORRESPONDING FIELD	Wrong / omitted patient information leaflet	NO CORRESPONDING FIELD	Wrong / omitted patient information leaflet
NO CORRESPONDING FIELD	Unknown	A type not determined	Unknown
Drug therapy monitoring problem: Drug-drug interaction	NO CORRESPONDING FIELD	NO CORRESPONDING FIELD	Drug therapy monitoring problem: Drug-drug interaction
Drug therapy monitoring problem: Clinical	NO CORRESPONDING FIELD	NO CORRESPONDING FIELD	Drug therapy monitoring problem: Clinical

Table 11: Mapping scheme for stages involved

Data received from Canada	Data received from the United States	Data received from the United Kingdom	Data field name in report
Physician ordering	Prescribing	Prescribing	Physician ordering
Order entry & transcription	Transcription / Documenting	NO CORRESPONDING FIELD	Order entry & transcription
Dispensing & delivery	Dispensing	Preparation of Medicines in all locations / dispensing in a pharmacy	Preparation, dispensing and delivery of drugs
Administration	Administrating	Administration / supply of a medicine from a clinical area	Administration and supply of a drug from a clinical area
Monitoring	Monitoring	Monitoring / follow-up of medicine use	Monitoring / follow-up of drug use
N/A	Does not apply	N/A	N/A
Data fields not listed above	Data fields not listed above (i.e. "procurement")	Data fields not listed above (i.e. "other", "advice" and "supply or use of OTC medications")	Other

Appendix II: Recommendations from the literature

A literature search was performed to identify existing recommendations for the safe use of transdermal fentanyl. A comprehensive list of recommendations can be found below:

Critical information: Health care practitioners' lack of awareness of critical information regarding transdermal fentanyl

- Include a checklist or algorithm for initiation and titration of transdermal fentanyl in the product monograph.¹¹
- The following considerations for product monographs for the fentanyl transdermal fentanyl are recommended: Include information that will assist practitioners to assess opioid tolerance. Such information is currently lacking in the product monographs for all brands of transdermal fentanyl.¹¹
- Ensure that the complete medical history and full medication history are available to verify that all criteria for initiating and continuing transdermal fentanyl therapy are met.²⁵ ISMPC v716
- Patients should be receiving the equivalent of at least 60 mg oral morphine per day, and have been taking the opioid around-the-clock for an extended period of time. Refer to the product monograph for additional information.¹¹
- Prescribe transdermal fentanyl only for patients who are opioid-tolerant, and who have chronic pain that is not well-controlled with shorter-acting analgesics. This product should not be used for postoperative pain, or for pain that's short-term or intermittent. Pharmacists should ensure that the patient is opioid-tolerant and suffering from chronic pain before dispensing the drug, and should question the prescriber if this is not the case.²⁷
- Patches should not be used for acute or post-operative pain because the medication will not reach a steady state for 12-18 hours and will not reach peak until 24-72 hours. Therefore, transdermal fentanyl will not offer immediate pain relief, so "now" and "stat" orders are generally inappropriate.²⁸
- Dose increases should not exceed one 25 microgram/hour increment.
- Patient selection criteria for transdermal fentanyl use must include an assessment of the patient's ability to understand information about proper dosing, administration, and disposal.¹⁴

Critical information: Health care practitioners' lack of awareness of critical information regarding transdermal fentanyl

- Create guidelines. Specific prescribing and dispensing guidelines for transdermal fentanyl patches that are congruent with the product labelling should be developed and referenced during order entry of the medication in inpatient and outpatient settings. Equianalgesic conversion tables should also be included in guidelines to help prescribers convert patients to an appropriate fentanyl transdermal dose based on pre-existing opioid doses the patient has been taking.⁸
- Create specific prescribing and dispensing guidelines for transdermal fentanyl that are aligned with the product labelling and referenced during computer order entry.²⁶
- Set dosing limits. For example, pharmacy computer systems could be set to flash an alert if more than 25 mcg per hour has been prescribed as a first-time dose. Also, in evaluating whether the dose is appropriate, take into account other opioids or analgesics that may have been prescribed.²⁷
- Pharmacists should be involved in the review of all orders for transdermal fentanyl prior to dispensing and administration. In situations when a pharmacist is not available to review the order prior to administration (e.g. in an emergency department), there should be a double check by another licensed healthcare provider, who is knowledgeable about the appropriate prescribing of transdermal fentanyl.²⁶
- If a new prescription is received for an opioid-naïve patient or the drug is intended to treat short-term pain, intermittent pain, or post-operative pain, the prescriber should be called to question the order. Verification of the indication and any conversations with the prescriber regarding the patient and the prescribed medication should be documented in a consistent place (e.g., pharmacy computer system, progress notes, order form, outpatient prescription).
- Conduct ongoing education and annual staff competencies on the safe administration of fentanyl transdermal patches.²⁸
- Restrict prescribing privileges for transdermal fentanyl to providers who are knowledgeable in the continuous administration of potent opioids, in the management of patients receiving potent opioids for treatment of pain, and in the detection and management of hypoventilation including the use of opioid antagonists.²⁶
- The elimination half-life of the patch is 17 hours. Therefore, patients who have experienced serious adverse events, including overdose, will require monitoring for at least 24 hours after

Critical information: Health care practitioners' lack of awareness of critical information regarding transdermal fentanyl

the patch is removed since serum fentanyl concentrations decline gradually and reach an approximate 50% reduction 17 hours after system removal.²⁶

Patient education

- Mandate patient, family member and/or caregiver education. It is imperative that patients who are using transdermal fentanyl (as well as their caregivers) are educated and assessed for their understanding of the safe use of this product.²⁶
- As an additional measure, ISMP will continue pursuing a collaborative effort with community pharmacy chains and independent pharmacies to further develop the mandatory education (counseling) process for patients, including scripted topics that detail the information that should be provided and documented.⁸
- Fentanyl prescribing information contains a list of 22 points for practitioners to address with patients. Some of this is covered in patient information handed to patients along with their prescription but, all too often, this important information is overlooked or deemed too difficult to read. After reviewing this list (found in the "Precautions" section under "Information for Patients"), practitioners can determine how to best convey the information to patients or their caregivers.²⁸
- Patients and caregivers who place the patches on the skin should be aware of the signs of fentanyl overdoses, including: respiratory distress; shallow breathing; tiredness, extreme sleepiness, or sedation; inability to think, talk, or walk normally; and feeling faint, dizzy, or confused. If signs such as these occur, patients (or their caregivers) should seek medical attention immediately.²⁸
- Ensure that the patient and family members know to remove the patch and seek immediate medical attention should signs of overdose occur. (The Duragesic® monograph identifies a number of key issues to be reviewed with patients and provides a consumer information sheet.)¹¹
- Teach patients to avoid exposure to direct heat sources (e.g., heating pads, saunas, hot tubs, heated water beds) while using the patches, because contact may increase fentanyl absorption. Patients with higher body temperatures are also more susceptible to toxicity.²⁸ Patients should be instructed to notify their doctors immediately if they develop a temperature

Patient education

above 102 degrees Fahrenheit / 39 degrees Celsius.²⁷

- Patients (and caregivers) should also know that they may have a sudden and possibly dangerous rise in their blood level of fentanyl or have a stronger effect from fentanyl if they use other drugs that affect brain function; drink alcohol; or use other medications that affect how fentanyl is broken down in the body (e.g., ritonavir, ketoconazole).¹⁰
 - Educate patients to store patches and all other medications in a safe place out of the reach of children.²⁸
 - Fold used patches in half with sticky sides together and flush down the toilet.²⁷
 - When possible, ask family members who are with the patient at various times of the day and night if the patient is unknowingly experiencing any dangerous side effects.²⁹
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Complexity of transdermal fentanyl administration

- Provide a dosing calendar so patients can keep track of the location and time of patch application at home.²⁸
 - Develop a mechanism or process to “flag” or mark where patches are placed on a patient (e.g., use a human body pictogram) to alert practitioners and caregivers where to look when removing old patches (possibly multiple patches) which could be applied separately at several body surface area locations. Give the patient a copy of the diagram.²⁶
 - Improved methods of documentation can help guard against applying multiple patches to patients. In the hospital, the drug entry on the medication administration record should be accompanied by a second entry where nurses can document the location and time of application and removal of the patches.
 - An auxiliary label can also be applied to the patch to prompt documentation of application date and time; visibility may be poor if written directly on the patch and a pen may puncture the patch.³⁰
 - In facilities with computerized MARs, program administration information for transdermal fentanyl into the pharmacy computer system so that these entries automatically appear on the MAR.²⁸
 - Apply to dry, intact, non-hairy skin on torso or upper arm, removing every 72 hours and replace with a different patch applied to a different area.
 - Standardize placement and rotation of transdermal fentanyl patches so staff members
-

Complexity of transdermal fentanyl administration

anticipate where to look for the last patch/es. Document placement precisely.

- When increasing dosage, remove old patches and apply new ones rather than adding patches that require a different schedule. Multiple schedules become confusing and may result in an overdose.
 - Do not divide or cut patches as this leads to uncontrolled release of fentanyl.
 - Require a pharmacist review when the route or technique of medication is changed.²⁸
-

Communication pertaining to the prescribing and transcription of orders for transdermal fentanyl

- Healthcare providers should remain cautious about orders for the 125 mcg/hour strength because the decimal point has been overlooked at times with orders for 12.5 mcg/hour patches.⁸
 - Practitioners also need to be aware that, to prevent confusion with 125 mcg per hour doses, the manufacturer has given the 12.5 mcg patch trademark a suffix of “12” even though 12.5 mcg of fentanyl per hour is released. Only “Duragesic-12” should be used in prescribing that strength.³¹
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Product design

- Drug manufacturers should consider designing a more distinguishable transdermal fentanyl patch (e.g. coloured patch) to enhance its visibility on the patient's body.
 - Drug manufacturers should consider enhancements in the packaging and labelling of transdermal fentanyl to ensure better differentiation between different strengths of fentanyl patches.
 - A child-protective storage container provides a safe place to temporarily store partially used Actiq® (fentanyl) lozenges until they can be properly disposed. This type of risk management program could improve safety with transdermal fentanyl and also protect against theft of discarded patches.³⁰
 - Explore safety features applied to other products. For example, the Consumer Product Safety Commission requires child-protective packaging for LIDODERM (lidocaine patch 5%) requiring the use of scissors. In contrast, transdermal fentanyl packages are typically notched and easily torn open by hand.³⁰
 - One manufacturer provides TEGADERM-like dressings to patients who contact them about
-

Product design

their fentanyl patches falling off.³⁰

Interfaces of Care: Transdermal fentanyl not identified / recognized at interfaces of care

- In the Emergency Department assess patient's skin to check if patient is wearing any patch(es), as well as upon admission, during routine assessments, and at any change in the level of care.²⁸
 - For patients who are admitted to the hospital and using transdermal fentanyl at home, the dose should be verified during medication reconciliation, and the verified drug list should be sent to the pharmacy.⁸
 - Before discharge, fully assess effectiveness of transdermal fentanyl patch dose.
-

Other recommendations

- Observe caution when patches are discontinued. Other pain medication must be titrated to allow for fentanyl's duration of action.²⁸
 - Elderly, cachectic, debilitated patients, and those with renal or hepatic impairment, are particularly prone to adverse effects. They should be monitored and lower doses and slower titration may be required.²⁹
 - Assess the concomitant use of opioids. When the clinical appropriateness of the patient's dose is evaluated, prescribers must take into consideration all other opioids prescribed for the patient with the goal of preventing an overdose.²⁶
 - Consider the value of adjunctive treatment (e.g., a nonsteroidal anti-inflammatory agent) to decrease the opioid dose requirement.¹¹
 - Phase out previous analgesic therapy gradually during the first 24 hours of treatment with transdermal fentanyl.
 - Be alert for signs of possible drug-seeking behaviours.²⁸
 - A risk management program could require disposal of patches in biohazard containers that cannot be opened.
 - Patients scheduled for surgery should be reviewed at least 24 hours (preferably 3 days) pre-theatre by an anaesthetist to assess analgesic requirements and instructions on when to remove the patch.²⁹
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Appendix III: Sample Patient Information Brochure, Developed by the Institute For Safe Medication Practices (United States)

(draft version August 2009)



Read this important information before taking:

Fentanyl

Brought to you by the Institute for Safe Medication Practices

[Extra care is needed because fentanyl is considered a high-alert medicine.]

Just a handful of medicines are considered **high-alert medicines**. These medicines are necessary to keep people healthy. They have been proven to be safe and effective when taken properly. But these medicines can cause serious *injury* if a mistake happens while taking them. This means that it is vitally important for you to know about this medicine and take it exactly as intend.



Top 10 List of Safety Tips for Fentanyl

-  **Before you use the patches**
 - 1 Use for chronic pain only.** Fentanyl patches should **ONLY** be used to treat chronic pain by people who have previously taken high doses of prescription pain medicine for 7 or more days without relief. Otherwise, the medicine can cause you to stop breathing. _____
 - 2 Use Intact patches.** Never cut the patches or use damaged patches. _____
 - 3 Avoid broken skin.** Apply patches only on skin without cuts or sores. _____
-  **When picking up prescription**
 - 4 Ask for education.** Talk to a pharmacist when picking up your prescription. Tell your pharmacist the type of pain you are experiencing and any other pain medicines you have been taking and for how long. _____
-  **While wearing a fentanyl patch**
 - 5 Follow directions.** Use the patches exactly as directed to prevent serious side effects. Do not use more patches than prescribed. Take off the old patch before applying a new patch.
 - 6 Do not warm your patches.** While wearing a fentanyl patch do not expose the site to heat from a heating pad, electric blanket, sauna, hot tub, heated waterbed, or excessive sun exposure. Also avoid tight coverings over the patch and strenuous exercise, which can heat the body. _____
 - 7 Don't wear during MRI.** Remove your patch before an MRI to avoid burns from hidden metal in the patch.
 - 8 Report signs of an overdose.** Signs of fentanyl overdose include trouble breathing or shallow breathing; tiredness, extreme sleepiness; inability to think, talk, or walk normally; and feeling faint, dizzy, or confused.
-  **Storing and discarding the patches**
 - 9 Store patches safely.** Keep new patches far away from the reach or discovery of children. Do not let children see you apply patches or call them stickers, tattoos, or Band-Aids. This could attract children and encourage them to mimic your actions. _____
 - 10 Dispose of patches safely.** Safely dispose of used or unneeded patches by folding the sticky sides together and flushing it down the toilet. A fair amount of drug remains in the patch even after use. As a precaution, fentanyl patches should not be thrown in the trash since they contain a potentially dangerous narcotic that could harm others. _____

STOP **Do not use fentanyl patches to treat short-term pain after surgery!**

Fentanyl patches should **ONLY** be used by people with chronic pain who have been taking high doses of prescription pain medicine for 7 or more days without relief. Otherwise, the medicine can cause you to breathe too slowly or stop breathing.

Other Resources

Medication guide for fentanyl patches
www.fda.gov/cder/Offices/ODS/medication_guides.htm

FDA Public Health Advisory
<http://www.fda.gov/cder/drug/advisory/fentanyl.htm>

Proper Use of Fentanyl Pain Patches
http://www.fda.gov/fdac/features/2006/206_fentanyl.html

For more information to help keep you safe, visit: www.consumermedsafety.org.

Fentanyl

▼ New and used patches can be dangerous to children!



Off with the old, on with the new



New medicine patches contain lots of medicine. But did you know that used patches still contain a fair amount of medicine after you take them off? This is why it is important to always take off the old patch before placing a new one on your skin. If you don't, you could receive an overdose of the medicine.

Both new and used patches can also be dangerous to children or pets. In a tragic

story, a 4-year-old child died after placing a fentanyl patch on his body. His mother had been using these patches for pain from Crohn's disease, a digestive tract disorder. After she found her son dead, she also found a torn wrapper in an overturned bedroom trashcan. It was not clear whether the boy stuck a used patch on his body or opened a new one and applied it.

Children have also been exposed to medi-

cine patches that fell off a family member. In one case, the child sat on the fallen patch and it stuck to her thigh. Another child removed a patch while his grandmother was sleeping and applied it to himself. In these cases, the patches were noticed right away and the children were not injured.

See the **Top 10 List of Safety Tips of Fentanyl Patches** for safe ways to store and dispose of fentanyl patches.

Topics	Fast Facts
Generic name	■ fentanyl transdermal system patches (pronounced FEN ta nil)
Common brand names	■ Duragesic
Generic available	■ Yes
Common uses	■ Management of persistent, moderate-to-severe, long-term (chronic) pain when around-the-clock pain control is needed for an extended period of time
Safe dose limits	<ul style="list-style-type: none"> ■ Doses vary widely, from 12.5 mcg/hour to 100 mcg/hour ■ The initial safe dose is determined by the amount of pain medicine that has been previously required in a typical 24-hour period ■ The dose should not be increased more often than every 3 days after the initial dose or every 6 days thereafter
What to do if you miss a dose	<ul style="list-style-type: none"> ■ Apply the patch as soon as remembered after removing the old patch ■ Do not use more than the prescribed dose (typically just one patch at a time)
Special instructions and precautions	<ul style="list-style-type: none"> ■ Prior to application, clean the skin with clear water, allow it to dry completely, and clip hair if necessary (do not shave the area) ■ Apply the patch to unbroken skin on the chest, back, flank, or upper arm; do not apply to areas of radiation therapy ■ Firmly press the patch in place and hold for 30 seconds ■ Change the patch every 72 hours (or 48 hours if directed by your doctor) ■ Remove the old patch and clean the site; apply a new patch to a different site ■ Do not use damaged or cut patches (could result in an overdose) ■ If gel leaks from the patch, serious effects are possible; thoroughly wash the affected skin with lots of water (not soap or alcohol, just water) ■ Avoid heat on the site of the patch (e.g., heating pad, electric blanket, hot tub, sun) ■ Have a family member watch you closely during the first 24 hours after application of the first patch or if your doctor increases your dose
Safety during pregnancy/ breastfeeding	<ul style="list-style-type: none"> ■ Do not use during pregnancy; may result in newborn withdrawal symptoms ■ Enters breast milk; not recommended while breast-feeding
Tell your doctor if you have:	<ul style="list-style-type: none"> ■ Lung diseases such as asthma, sleep apnea, drug or alcohol use, liver or kidney disease, fever above 102 degrees (F)
Storage and disposal	<ul style="list-style-type: none"> ■ Do not store in temperatures above 77 degrees (F) ■ Dispose patch by folding the sticky side together and flushing it down the toilet
Side effects	<ul style="list-style-type: none"> ■ Confusion, dizziness, drowsiness, poor coordination, headache, blurred vision, sweating, nausea, vomiting, constipation, slowed or stopped breathing
Side effects to report to your doctor immediately	<ul style="list-style-type: none"> ■ Significant dizziness, chest pain, slow or rapid heartbeat, bad headache, confusion, swelling of extremities or unusual weight gain, temperature of 102° F or higher, shortness of breath, shallow or very slow breathing, vision changes
Over-the-counter medicines/herbals/vitamins that should not be taken when using fentanyl	<ul style="list-style-type: none"> ■ Alcohol, St. John's wort, kava kava, gotu kola, sleep aids, antihistamines, other pain medicines unless directed by your doctor
Prescription medicines that should not be taken when using fentanyl patches	<ul style="list-style-type: none"> ■ ritonavir, indinavir, nelfinavir, erythromycin, clarithromycin, fluconazole, ketoconazole, itraconazole, nefazodone, verapamil, aprepitant, quercetin, alvimopan, antipsychotic agents, beta blockers, dasatinib, many antidepressants

This information does not replace the need to read the drug information leaflet provided with your prescription and follow your doctor's instructions.

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