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ORIGINAL RESEARCH ARTICLE

Effectiveness of Risk Minimization Measures for Fentanyl Buccal Tablet (FENTORA) in Canada: A Mixed-Methods Evaluation Using Surveys, Medical Chart Records and Web Surveillance

Sigal Kaplan[1] · Aurore Bergamasco[2] · Martin Sergerie[3] · Anne-Marie Castilloux[4] · Yola Moride[4,5,6]

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Abstract

Background Fentanyl buccal tablet (FBT), a potent opioid, was approved in Canada in 2013 for breakthrough pain in opioid-tolerant adult cancer patients. Additional risk minimization measures (aRMMs), consisting of communications to patients and healthcare providers (HCPs), were implemented from November 2014 through September 2015.

Objectives The aim of this study was to assess the effectiveness of FBT aRMMs as measured by prescriber knowledge, understanding, and behavior regarding key safety concerns (off-label use, use in non-opioid-tolerant patients, misuse/abuse/diversion, and drug–drug interaction) and to evaluate illicit FBT use.

Methods The study included three components: (1) a knowledge and understanding (KAU) survey of FBT prescribers conducted in two waves: November 2016–February 2017 and April–September 2018; (2) a retrospective prescription study of medical records of patients treated with FBT by a subgroup of prescribers from the KAU survey; and (3) Web surveillance of illicit FBT use in Canada using the search term FENTORA (May 2014–September 2018). The aRMMs were considered effective if the lower bound of the 95% confidence interval indicated that at least 65% of respondents met or partly met the knowledge objective for each key safety concern.

Results KAU survey: Of 46 eligible HCPs, 97.8% met or partly met the knowledge objective on use in breakthrough pain cancer patients, 97.8% on use in opioid-tolerant patients, 89.1% on dose and titration, 100% on abuse/addiction, and 58.7% on drug–drug interaction. Retrospective prescription study: Of 22 FBT-treated patients identified from 14 HCPs, 45.5% had cancer, 50.0% recorded a breakthrough pain indication, and 36.4% reported opioid tolerance; however, only 13.6% of patients were prescribed FBT according to the approved indication. Web surveillance: Of 932 FBT posts in Canada, only 40 (4.3%) mentioned illicit use.

Conclusions The aRMMs as measured by the prescriber KAU were effective for most key safety messages; however, not all key messages of the aRMMs were stringently followed in routine practice.

1 Introduction

In North America, clinicians commonly prescribe opioids for acute pain, palliative care (in particular, for patients with cancer) and chronic non-cancer pain when other treatments are ineffective [1]. In Canada, opioid consumption in morphine equivalence increased fivefold, from 150 to 750 mg per person, between 2000 and 2014, and the rate per capita is amongst the highest in the world [2, 3]. Furthermore, the dispensing rates of immediate-release opioid formulations in Canada gradually increased from 2008 to 2016 [4]. This increase in opioid use has been accompanied by an increase in opioid-related harm, such as overdose (including death), abuse, addiction and diversion [3, 5–12]. This public health emergency, referred to by Health Canada as the opioid

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✉ Sigal Kaplan
Sigalit.Kaplan@teva.co.il

1 Teva Pharmaceutical Industries Ltd, Netanya, Israel

2 YOLARX Consultants, Paris, France

3 Teva Canada Innovation, Montreal, QC, Canada

4 YOLARX Consultants, Montreal, QC, Canada

5 Faculty of Pharmacy, Université de Montréal, Montreal, QC, Canada

6 Rutgers, The State University of New Jersey, New Brunswick, NJ, USA

Key Points

Respondents to the knowledge and understanding survey showed a good understanding of fentanyl buccal tablet (FBT) indication (use in opioid-tolerant adult cancer patients for breakthrough pain) and three of the four key safety messages included in the additional risk minimization measures: use in non-opioid-tolerant patients; dose and titration; and risk of abuse/addiction.

The fourth key safety message, risk of drug–drug interaction with agents that affect cytochrome P450 (CYP) 3A4 activity, was not well understood, resulting in the potentially inappropriate prescribing of concomitant medications that affect CYP3A4 activity.

While knowledge of FBT indication was good, in practice the FBT label was not always stringently followed.

epidemic, has led to the implementation of policies and the need for appropriate interventions, including increased awareness, better harm prevention, improved opioid prescribing, development of opioid prescribing guidelines, as well as conduct of more studies to improve evidence-based treatment and harm reduction programs needed to inform public health action [1, 5, 6].

Due to this opioid public health safety concern, the approval of a potent analgesic opioid, fentanyl buccal tablet (FBT; FENTORA®, Teva Canada Innovation, Canada), in November 2013 in Canada, was subject to the implementation of a Canadian Risk Management Plan to ensure that the benefits of the drug outweigh the risks. This product was intended for buccal mucosal administration and was approved for the management of breakthrough pain in cancer patients 18 years of age and older who are already receiving and are tolerant to continuous opioid therapy for their persistent baseline cancer pain [13].

Breakthrough pain is a frequently encountered pain syndrome in cancer patients, with a prevalence ranging between 40 and 80% [14, 15]. It has been defined as a transient exacerbation of pain that occurs either spontaneously or in relation to a specific predictable or unpredictable trigger, despite relatively stable and adequately controlled background pain [16]. Guidelines for the management of breakthrough pain in patients with cancer recommend using opioids with rapid- or short-acting onset, such as FBT [17].

Similar to other opioid analgesic substances of its therapeutic class, FBT is associated with safety concerns that include, amongst others, abuse, misuse, diversion and overdose (including death). Thus, FBT is classified in Canada as a Schedule I controlled substance, which restricts its use. Aside from these concerns, FBT use is also associated with major adverse drug reactions, including respiratory and central nervous system depression [13].

To optimize the safe and effective use of FBT, as well as prevent and mitigate adverse events, the Canadian Risk Management Plan for FBT required additional risk minimization measures (aRMMs) beyond the routine measures of the product labeling. The design of the aRMMs was guided by a conceptual framework that consolidates factors that could influence the success of the aRMMs and would allow the evaluation of the design and results. Education for healthcare professionals was considered an important component in reducing or preventing opioid-related harms for indicated patient populations, and needed to include interactive teaching methods along with information on the key components of opioid use [18]. These aRMMs included (1) educational material for healthcare providers (HCPs) and patients, and (2) training programs for sales representatives. The aRMMs aimed to reinforce knowledge of the product labeling and to prevent occurrence of important identified risks, including off-label use (e.g. unapproved indications), misuse, abuse, diversion, and pharmacodependence. In addition, the aRMMs targeted safe use behaviors, including monitoring practices prior to prescribing and during opioid treatment. The educational materials were qualitatively reviewed by internal and external stakeholders (including a country medical advisory board and an opioid prescriber). The final content, the risk communication tool and the dissemination method (i.e. sponsor's sales representatives) were approved by Health Canada.

The implementation of these aRMMs started in November 2014 and targeted FBT prescribers, including oncologists, pain and palliative care specialists, as well as general practitioners, who practice in outpatient and/or inpatient settings. The company's sales representatives were trained to highlight the various safety issues when contacting the HCPs. They disseminated the educational materials to HCPs at the time of the office visit or by email. As of September 2015, these visits by sales representatives were discontinued as per regulatory requirements. Since then, other actions were undertaken to increase awareness in Canada for all opioids, including a class labeling update related to serious drug interactions in March 2018, as well as a warning sticker and patient information sheets distributed with each opioid dispensing since October 2018 [13, 19].

In order to assess the effectiveness of the aRMMs for FENTORA®, a three-tier study was conducted consisting of a knowledge and understanding (KAU) survey, a retrospective prescription study, and Web surveillance. The research question was: What proportion of FBT prescribers has adequate knowledge, understanding, and prescribing/monitoring behavior regarding each key safety concern in a real-world clinical practice setting?

The objectives of this study were to assess the effectiveness of the aRMMs for FBT as measured by prescriber

knowledge, understanding, and behavior regarding important identified key safety concerns (off-label use, use in non-opioid-tolerant patients, misuse/abuse/diversion, and drug–drug interaction) and to qualitatively evaluate the illicit use of FBT in Canada.

2 Methods

This study was conducted in Canada and included three components: (1) a cross-sectional KAU survey of FBT prescribers; (2) a retrospective prescription study of prescribing practices of FBT prescribers; and (3) Web surveillance of illicit FBT use in Canada. The study was approved by the Canadian SHIELD Ethics Review Board.

In order to take into account changes in the number of prescribers and prescribing settings over time, the survey was conducted in two waves: from November 2016 to February 2017 (Wave I), approximately 30 months after product launch; and from April to September 2018 (Wave II), approximately 47 months after product launch (Fig. 1). In addition, at the time of Wave II, a qualitative assessment of illicit FBT use in Canada was performed using Web surveillance.

2.1 Knowledge and Understanding Survey

The cross-sectional KAU survey conducted during Waves I and II aimed to assess prescriber knowledge, understanding, and behavior regarding off-label use, focusing on the FBT indication and the four key safety concerns associated with FBT: (1) use in non-opioid-tolerant patients; (2) incorrect/no dose titration; (3) misuse/abuse/diversion; and (4) potential drug interactions with agents that affect CYP3A4 activity.

Potential prescribers were identified through a national directory (Professional Targeted Marketing), as well as through the study sponsor's affiliates. The survey targeted all potential FBT prescribers, including oncologists, pain and palliative care specialists, and general practitioners, who practice in outpatient and/or inpatient settings. For Wave II, a more targeted list of all fentanyl prescribers in Canada ($n = 156$) was supplied by the sponsor's marketing division.

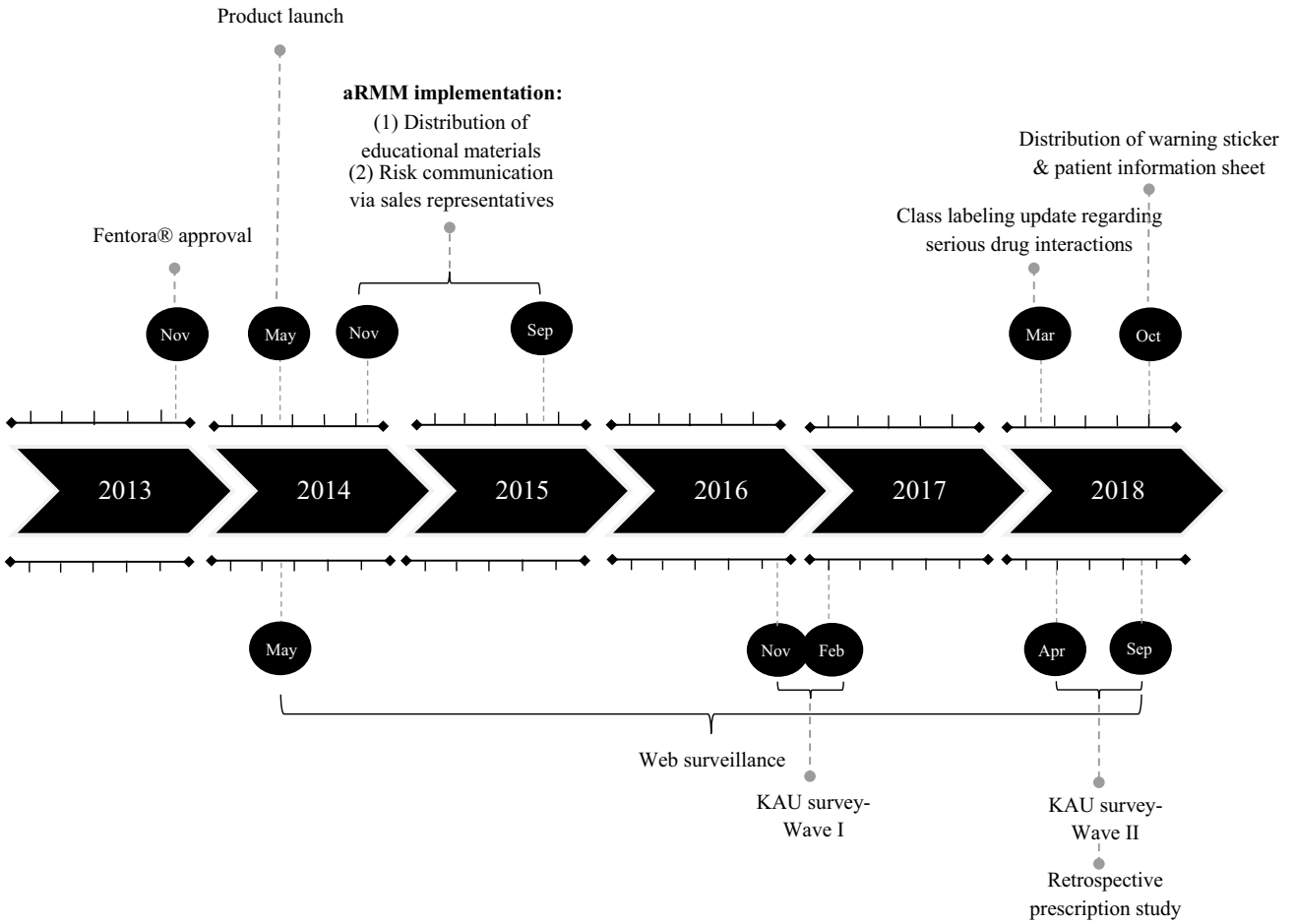

Fig. 1 Study time periods, Canada, *aRMMs* additional risk minimization measures, *KAU* knowledge and understanding

Due to the low use of this product in Canada, no sampling was used and invitations to participate in the survey were sent to all potential prescribers via email or phone. Respondents were offered financial compensation within the fair market value for completing the KAU survey.

Surveys were sent by email (accessible via a Web link) or fax to all prescribers, with up to three email reminders and telephone calls to non-respondents. All respondents were screened to determine eligibility for the survey. Physicians were considered eligible if they met the following inclusion criteria: (1) had prescribed FBT at least once; and (2) had consented to participate in study. There were no exclusion criteria for Wave I, but prescribers participating in Wave I were excluded from participating in Wave II.

The KAU questionnaire was self-administered and was available online or in paper form in both English and French (electronic supplementary Appendix 1). It comprised a total of 30 questions: 5 eligibility screening questions (mandatory); 18 knowledge, understanding, and behavior questions (mandatory); and 7 questions on prescriber or practice characteristics (optional). All KAU questions were close-ended, with multiple-choice answers allowing participants to indicate one correct answer or all answers that applied.

Prior to the study, the survey was pretested by a physician who had prescribed FBT at least once. The physician reviewed both the French and English versions of the questionnaire to validate the comprehension and acceptability of the survey design and wording, and face and content validity, and to estimate the time required to complete the survey.

To address the study objectives, the 18 knowledge, understanding, and behavior questions were mapped to the specific safety concerns associated with FBT (electronic supplementary Table 1). The answer was categorized into a dichotomous variable of 'met' or 'not met' the knowledge objective (yes/no) for each of the 18 questions. For each of the four safety concerns, the KAU was then evaluated as a composite outcome by combining answers to individual questions pertaining to this safety concern. The knowledge objective was considered 'met' when all questions pertaining to this safety concern were correctly answered (i.e. most stringent definition). Otherwise, the knowledge objective was considered 'partly met' (some of the questions were correctly answered) or 'not met' (either all questions or all questions except one were incorrectly answered). For the indication question (Sect. 1, Question 4), as respondents could select more than one answer, the knowledge objective of indication was considered 'met' when the only answer selected was 'Treatment of breakthrough pain in cancer patients'. When another answer was also selected, the knowledge objective was considered 'partly met'. When the selected answers did not include this indication, the knowledge objective was considered 'not met'. The aRMMs were considered effective if at least 65% (lower bound of the 95% confidence interval [CI] of the estimated rate) of respondents had met or partly met the knowledge objective of the FBT indication and each of the four key safety concerns associated with FBT.

The expected sample size of survey respondents was about 20 prescribers per wave. Given that there is no recognized threshold of KAU above which the risk minimization strategy would be considered to be effective, the sample size was derived from various assumptions of 'meeting' the knowledge objective. A sample of 20 physicians would provide the following 95% CIs for various percentage levels that meet the knowledge objective: 90.0% (95% CI 86.3–93.7%); 80.0% (95% CI 75.0–85.0%); and 70.0% (95% CI 64.3–75.7%).

The statistical analysis was descriptive in nature. Frequency distributions were used to describe categorical variables, i.e. prescriber characteristics and the level of understanding for each safety concern ('met', 'partly met', and 'not met'). For each KAU category, the proportion of respondents was estimated along with the corresponding 95% CI. Additional sensitivity analyses were performed to evaluate the KAU of prescribers using the most stringent definition of meeting the knowledge objective (i.e. correct answers to all questions) for the FBT indication and for each of the four key safety messages. All analyses were performed using SAS statistical software version 9.4 (SAS Institute, Cary, NC, USA).

2.2 Retrospective Prescription Study

The retrospective prescription study was conducted during Wave II to evaluate compliance of prescribers with the labeling recommendations, including indication, contraindications, and recommended monitoring practices prior to treatment initiation and during treatment with FBT.

Physicians who participated in the KAU survey were invited to participate in the retrospective prescription study and complete case report forms for up to three of their most recent patients treated with FBT in the previous 12 months. These forms were sent by email (accessible via a Web link) or fax to prescribers, with up to three email reminders and telephone calls to non-respondents. Respondents were offered financial compensation within the fair market value for each completed case report form. For this study component, only those who had prescribed FBT at least once in the past 12 months were eligible. The case report form was available online or in paper form in both English and French (electronic supplementary Appendix 2). Information on patient demographic characteristics, indication for FBT, type of pain (i.e. breakthrough pain or chronic), concomitant use of opioids, and concomitant use with CYP3A4 agents was abstracted from the patient medical records. Data collection also included prescriber characteristics and any physician prescribing practices to monitor misuse, abuse, overdose, or diversion with FBT treatment.

Compliance with the approved FBT indication was assessed using three outcome measures: (1) initiation of FBT for cancer breakthrough pain; (2) use in patients who are opioid-tolerant; and (3) use in patients aged 18 years or older at treatment initiation. Indications reported as free-text by physicians were classified using the International Classification of Diseases 10th revision dictionary. Patients were considered opioid-tolerant if they received around-the-clock opioid maintenance therapy of at least 60 mg of oral morphine daily or of an equianalgesic dose of another opioid for one week or longer prior to FBT initiation. The daily dose of each opioid used was converted into a morphine-equivalent dose using conversion factors (electronic supplementary Table 2). Appropriate monitoring for abuse was evaluated at treatment initiation and during treatment. In addition, information on concomitant use of FBT with medications that affect CYP3A4 activity (i.e. amiodarone, diltiazem, verapamil, triazole, imidazole antifungals, HIV protease inhibitors, macrolides, benzodiazepines, anticonvulsants, and anti-infectious agents) was collected in the case report form.

For this component of the study, the main evaluation criteria consisted of the proportions of patients treated with FBT according to the approved Canadian indication, monitored for misuse/abuse/overdose/diversion with FBT treatment, and having no concomitant use of medications that affect CYP3A4 activity.

The statistical analysis was descriptive in nature. Frequency distributions were used to describe categorical variables, i.e. prescriber characteristics and the main evaluation criteria, including treatment details, opioid tolerance, and concomitant medication use. All analyses were performed using SAS statistical software version 9.4 (SAS Institute).

2.3 Web Surveillance

Digital surveillance methods were used to evaluate illicit use of FBT among recreational drug users in Canada. All publications related to illicit FBT use in Canada since product launch in May 2014 were considered.

Potential illicit use of FBT in Canada was qualitatively evaluated on a monthly basis from 1 May 2014 to 24 September 2018 using various Web-based tools. Searches were conducted in English and French, focusing on the terms Fentora and Canada to evaluate illicit use of FENTORA specifically and not of fentanyl-containing products. Publications on FBT indexed in the Canadian section of Google News were identified. In addition, Google Trends was used to monitor the frequency with which the branded term (FENTORA®) appeared in a Google search engine in Canada compared with its appearance in other regions of the world where the search rate of the term was the highest (value of 100). Social media monitoring tools, such as Boardreader (a search engine designed to search discussion forums), Social Mention (a real-time search engine that tracks specific subjects by screening results of social media websites, including Facebook, Twitter, and LinkedIn), and Social Searcher (a search engine that monitors all public Social Mentions in social networks and the Web), were used to identify discussions or posts specifically related to illicit use of FBT. Furthermore, individual searches in Facebook, Twitter, and Instagram websites were conducted in order to uncover other relevant publications not identified previously. Finally, targeted discussion forums about drugs, such as Bluelight, Drugs-Forum, Healing Well, and Reddit, were also searched to identify discussions or posts about illicit use of FBT in Canada. Information on the illicit use of FBT was extracted into a standardized matrix of characteristics, including details on the source of the publication and the keywords or strategy used (electronic supplementary Appendix 3).

3 Results

3.1 Knowledge and Understanding Survey

3.1.1 Physician Characteristics

In Wave I, more than 2700 potential FBT prescribers were invited to participate in the survey. Of those, 32 physicians (1.2%) had prescribed FBT at least once and agreed to participate (Fig. 2). After the exclusion of six respondents who were deemed ineligible (not yet prescribed FBT), 26 physicians completed the KAU survey. In Wave II, a total of 156 physicians were invited to participate. Of those, 21 (13.5%) were eligible and agreed to participate (Fig. 2). After the exclusion of one respondent who was deemed ineligible (not yet prescribed FBT), 20 physicians completed the KAU survey. Ultimately, 46 physicians participated in the KAU survey across the two waves.

Half of the participants in the KAU survey were from Ontario (Table 1). A majority of respondents reported being palliative care physicians ($n = 31$, 67.4%) and practiced mainly in a hospital setting ($n = 29$, 63.0%). Most respondents reported practicing in urban areas ($n = 38$, 82.6%). Over half of the respondents ($n = 27$, 58.7%) reported 11 years or more of practice. Almost one-third of respondents ($n = 15$, 32.6%) reported seeing more than 30 cancer patients with breakthrough pain per month, and a similar proportion of respondents (34.8%) indicated seeing 11–30 such patients per month, suggesting that the survey respondents were familiar with the cancer patient population and its therapeutic management. At least half of the prescribers in the survey mentioned that professional/scientific journals or conferences, and/or product monographs (54.3% and 52.2%,

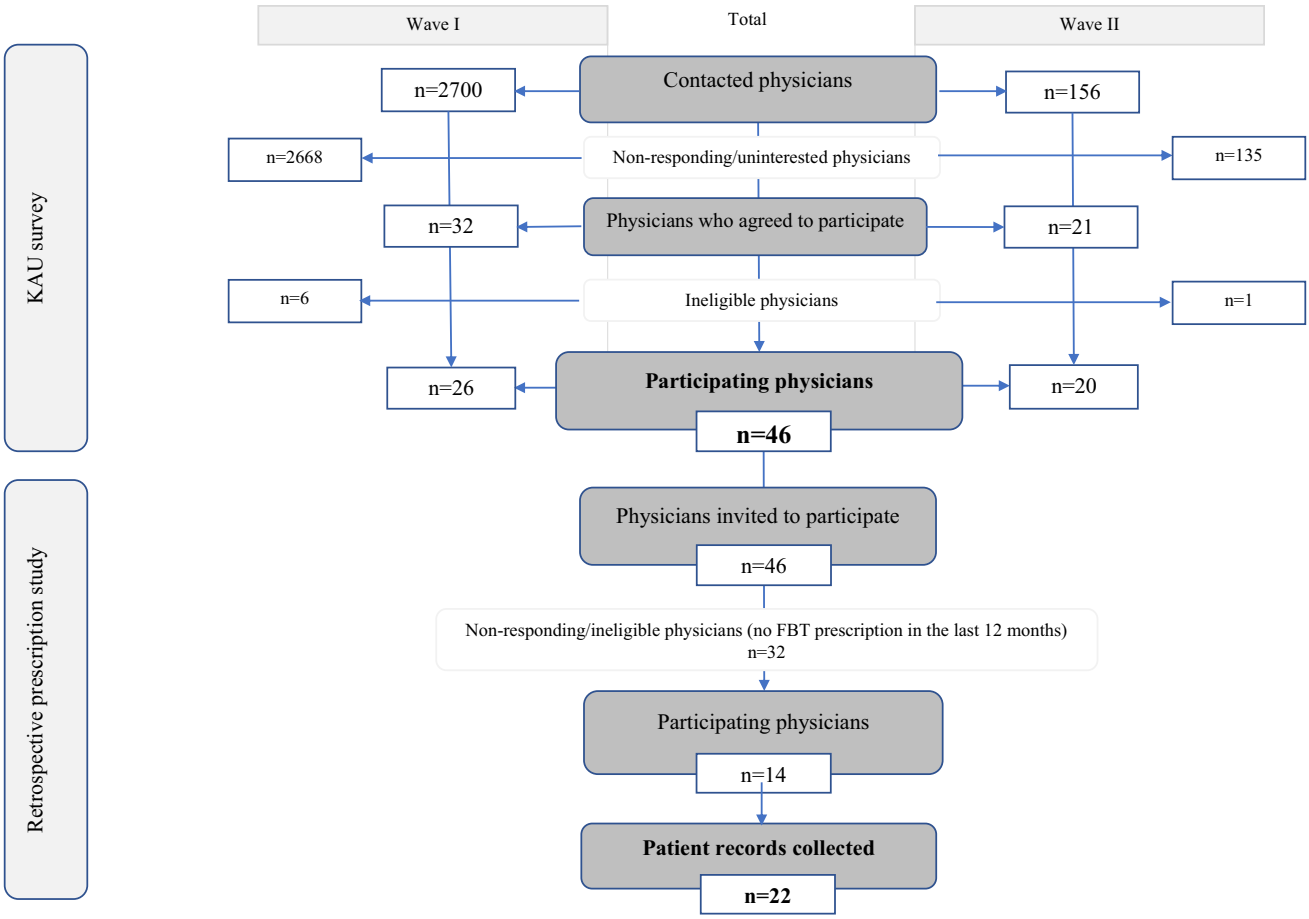

Fig. 2 Prescriber recruitment for the KAU survey and the retrospective prescription study for FBTs. *KAU* knowledge and understanding, *FBT* fentanyl buccal tablet

respectively) were their main source of information on FBT (data not shown). In addition, almost half of respondents (41.3%) recalled having received information on FBT through HCP information sheets or educational material sent by the sponsor.

3.1.2 Knowledge and Understanding of Fentanyl Buccal Tablet (FBT) Indication and Key Safety Messages

Results for the 18 individual mandatory KAU questions, as well as distribution of the number of correct answers per safety concern, are presented in the electronic supplementary material (electronic supplementary Appendix 4). The majority of the 46 respondents ($n = 45$; 97.8%, 95% CI 88.5–100.0) understood well (i.e. 'met' or 'partly met' the knowledge objective) that FBT is indicated for cancer breakthrough pain but also considered other indications as appropriate (Fig. 3). Of the 46 respondents, 32 (69.6%) selected only the correct indication of treatment of breakthrough pain in cancer patients ('met' the knowledge objective), and 13 (28.3%) selected incorrect indications in addition to cancer breakthrough pain ('partly met'), such as treatment of breakthrough pain in chronic non-cancer pain. Only one respondent (2.2%) selected the incorrect indication ('not met').

Most respondents 'met' or 'partly met' the knowledge objective for the first three key safety messages: use of FBT in opioid-tolerant patients ($n = 45$; 97.8%, 95% CI 88.5–100.0), dose and titration of FBT ($n = 41$; 89.1%, 95% CI 76.4–96.4), and abuse/addiction with FBT ($n = 46$; 100%, 95% CI 92.3–100.0). For these three messages, of the 46 respondents, 19 (41.3%), 23 (50.0%), and 30 (65.2%) correctly answered all questions ('met' the knowledge objective), and 26 (56.5%), 18 (39.1%), and 16 (34.8%) 'partly met' the knowledge objective, respectively. Only a small number of respondents (1 [2.2%], 5 [10.9%], and 0 [0%], respectively) did not select the correct answer ('not met') for these key messages.

Only approximately half of respondents 'met' or 'partly met' the knowledge objective for the fourth key safety message: drug–drug interaction ($n = 27$; 58.7%, 95% CI 43.2–73.0). Of the 46 respondents, 24 (52.2%) selected the correct response to these questions ('met' the knowledge objective) and 3 (6.5%) 'partly met' the knowledge

Table 1 Demographic and baseline characteristics of FBT prescribers, knowledge and understanding survey, Wave I (November 2016–February 2017) and Wave II (April 2018–September 2018)

Total physicians	Wave I [$n = 26$]		Wave II [$n = 20$]		Total [$N = 46$]	
Physician characteristics	*n*	%	*n*	%	*n*	%
Geographical distribution						
Ontario	11	42.3	12	60.0	23	50.0
Quebec	5	19.2	6	30.0	11	23.9
Central or western Canada	8	30.8	2	10.0	10	21.7
Atlantic provinces	2	7.7	0	0.0	2	4.3
Medical specialty						
Palliative care	21	80.8	10	50.0	31	67.4
Pain specialist	2	7.7	2	10.0	4	8.7
Family medicine	3	11.5	7	35.0	10	21.7
General practice	0	0.0	0	0.0	0	0.0
Oncology	0	0.0	0	0.0	0	0.0
Other	0	0.0	1	5.0	1	2.2
Practice setting						
Community hospital	12	46.2	8	40.0	20	43.5
University hospital	6	23.1	3	15.0	9	19.6
Private clinic	5	19.2	7	35.0	12	26.1
Other	3	11.5	2	10.0	5	10.9
Geographical location						
Urban	22	84.6	16	80.0	38	82.6
Rural	4	15.4	4	20.0	8	17.4
Medical experience, years						
< 2	1	3.8	1	5.0	2	4.3
2–4	3	11.5	1	5.0	4	8.7
5–10	4	15.4	8	40.0	12	26.1
11–20	8	30.8	4	20.0	12	26.1
> 20	9	34.6	6	30.0	15	32.6
Missing	1	3.8	0	0.0	1	2.2
Number of cancer patients with BTP seen per month						
1–10	5	19.2	10	50.0	15	32.6
11–30	10	38.5	6	30.0	16	34.8
> 30	11	42.3	4	20.0	15	32.6

FBT fentanyl buccal tablets, *BTP* breakthrough pain

objective. More than one-third of respondents ($n = 19$, 41.3%) answered all questions about the risk of drug–drug interaction incorrectly ('not met').

3.1.3 Monitoring Practices for Abuse/Addiction

Before initiating treatment with an opioid medication, a majority of physicians in the survey reported always assessing the patient's level of pain using a scale (73.9%) and the patient's level of function (87.0%). In addition, most survey respondents reported explaining the potential benefits and harms of long-term opioid therapy (65.2% and 63.0%, respectively) (Fig. 4). However, several other recommended screening practices were infrequently used by survey respondents, including risk assessment of addiction using a screening tool, conduct of a formal psychological screening, conduct of a urine drug screening, and distribution of written information about opioid therapy (Fig. 4).

During treatment with opioids, almost all study participants carefully monitored the treatment in order to limit risk of abuse/addiction (Fig. 5). These monitoring practices included keeping records of the quantity prescribed, the frequency of drug use, and the renewal requests, as well as re-evaluating therapy and monitoring the signs of abuse.

3.2 Retrospective Prescription Study

3.2.1 Physician Characteristics

A total of 22 case report forms were obtained from 14 physicians (30.4%) of the 46 respondents who participated in the KAU survey across the two waves (Fig. 2). Of these

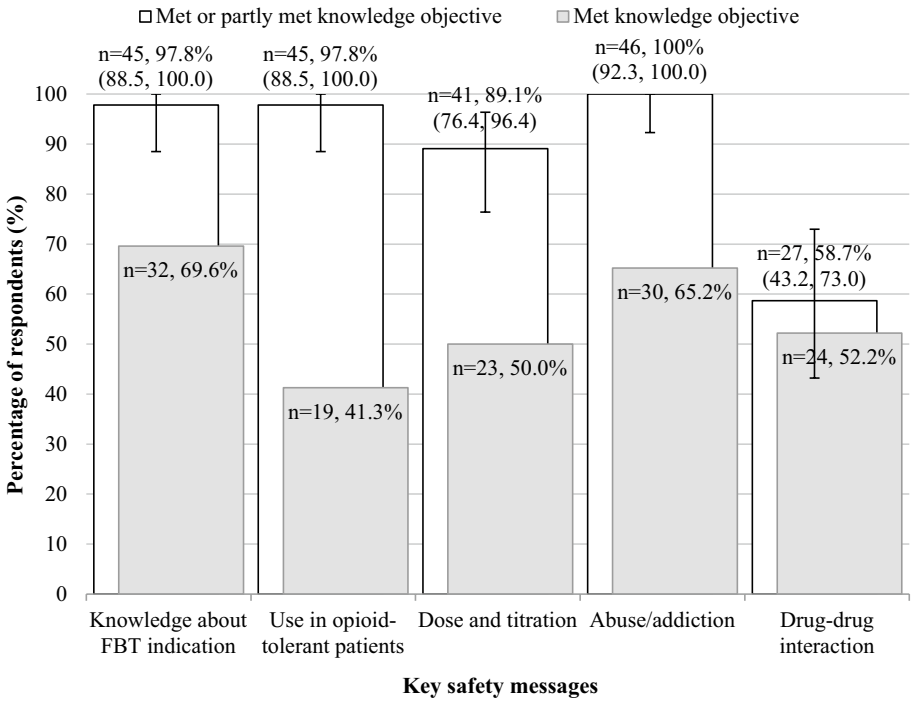

Fig. 3 Percentage of respondents (total $N = 46$) who 'met' or 'met or partly met' the knowledge objective of key safety messages (four bars on the right) in the knowledge and understanding survey (95% confidence interval given in parentheses for responses that 'met or partly met' the knowledge objective; n = number of respondents). *FBT* fentanyl buccal tablet

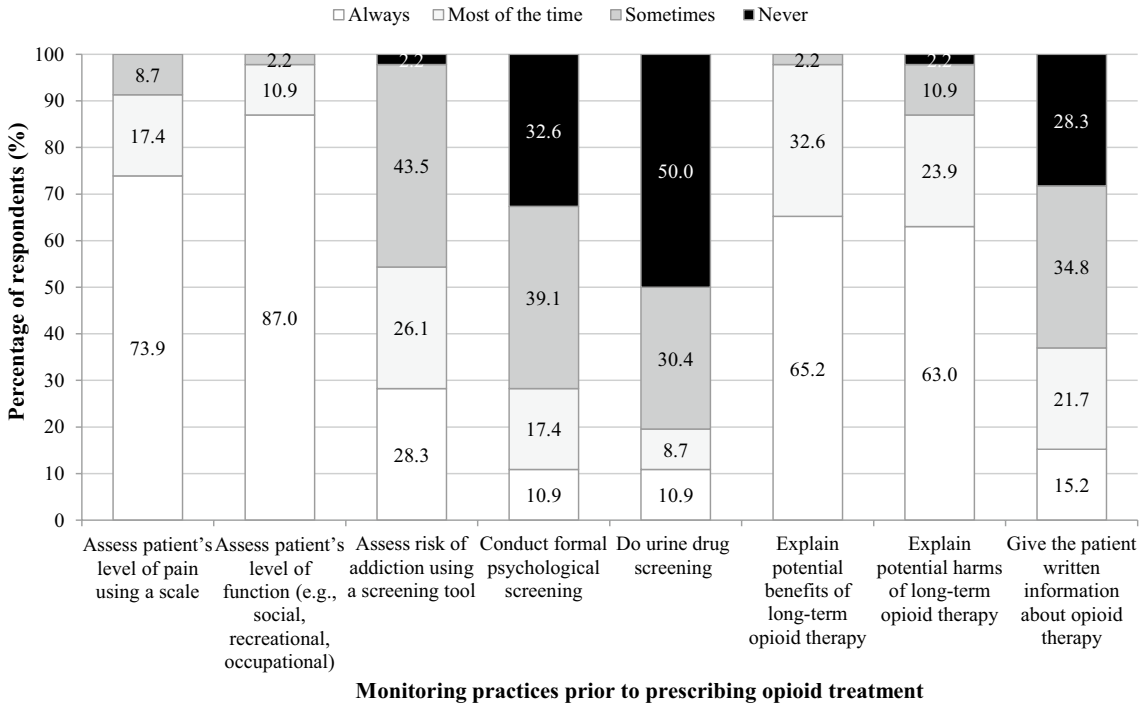

Fig. 4 Distribution of responses related to the monitoring practices used prior to prescribing opioid treatment among respondents (total $N = 46$) in the knowledge and understanding survey (Sect. 2, Question 8)

physicians, nine (64.3%) filled case report forms for only one patient. In this sample of patients, FBT was prescribed during 2018. The characteristics of the 14 physicians who agreed to participate in the retrospective prescription study were generally similar to those reported for the participants in the KAU survey (Tables 1 and 2, respectively). Comparing participants in the retrospective prescription study with those in the KAU survey, similar proportions reported

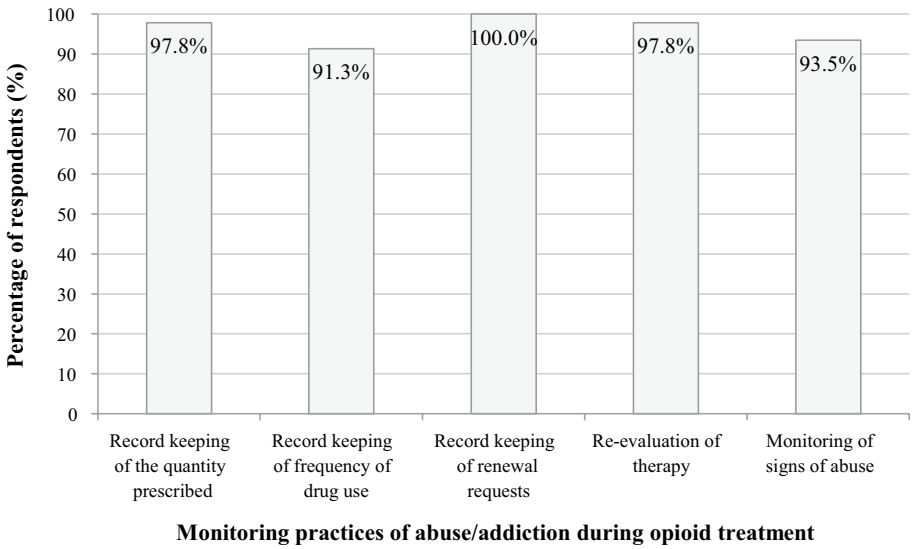

Fig. 5 Percentage of respondents who reported monitoring abuse/addiction during opioid treatment among respondents (total $N = 46$) in the knowledge and understanding survey (Sect. 2, Question 9)

being palliative care physicians ($n = 8$ [57.1%] vs. $n = 31$ [67.4%]), practiced in a hospital setting ($n = 7$ [50.0%] vs. $n = 29$ [63.0%]), practiced in urban areas ($n = 14$ [100%] vs. $n = 38$ [82.6%]), reported 11 years or more of practice ($n = 8$ [57.1%] vs. $n = 27$ [58.7%]), and reported seeing more than 30 cancer patients with breakthrough pain per month ($n = 5$ [35.7%] vs. $n = 15$ [32.6%]). The main difference was geographical distribution; the proportion of participants from Ontario was larger for the retrospective prescription study than for the KAU survey ($n = 10$ [71.4%] vs. $n = 23$ [50%]).

3.2.2 Demographic Characteristics and Prescribing Practices in Patients Prescribed FBT

The majority of the 22 patients receiving FBT for whom case report forms were completed were women ($n = 15$, 68.2%) (Table 3). The mean age was 54.7 years (standard deviation 13.2 years), ranging from 35 to 95 years, with the majority of patients (68.2%) aged 45–64 years. Only a few patients ($n = 3$, 13.6%) included in the retrospective prescription study received FBT according to the approved indication, i.e. adult patients (18 years of age and older) treated for cancer breakthrough pain who were opioid-tolerant at FBT treatment initiation.

The most common opioid identified in the medication history of patients treated with FBT was oral hydromorphone ($n = 13$, 59.1%), followed by methadone ($n = 11$, 50.0%) and fentanyl transdermal ($n = 9$, 40.9%) [data not shown]. In addition, almost half the patients who were prescribed FBT ($n = 10$, 45.5%) concomitantly received at least one medication with CYP3A4 activity, with the most common class being benzodiazepines ($n = 8$, 36.4%), and others being verapamil and anticonvulsants.

Table 2 Demographic and baseline characteristics of FBT prescribers, retrospective prescription study

Total physicians	$N = 14$	
Physician characteristics	*n*	%
Geographical distribution		
Ontario	10	71.4
Quebec	4	28.6
Medical specialty		
Palliative care	8	57.1
Pain specialist	2	14.3
Family medicine	3	21.4
Other	1	7.1
Practice setting		
Community hospital	6	42.9
University hospital	1	7.1
Private clinic	5	35.7
Other	2	14.3
Geographical location		
Urban	14	100
Rural	0	0.0
Medical experience, years		
< 2	1	7.1
2–4	1	7.1
5–10	4	28.6
11–20	3	21.4
> 20	5	35.7
Number of cancer patients with BTP seen per month		
1–10	5	35.7
11–30	4	28.6
> 30	5	35.7

FBT fentanyl buccal tablets, *BTP* breakthrough pain

Table 3 Demographic characteristics and prescribing practices in patients prescribed FBT, retrospective prescription study

Total patient CRFs	$N = 22$	
Patient characteristics *n* (%)	*n*	%
Age, years		
18–44	4	18.2
45–64	15	68.2
≥65	2	9.1
Missing	1	4.5
Sex		
Male	7	31.8
Female	15	68.2
Cancer patients		
Yes	10	45.5
No	11	50.0
Unknown	1	4.5
Breakthrough pain		
Yes	11	50.0
No	10	45.5
Unknown	1	4.5
Opioid-tolerant patients		
Yes	8	36.4
No	12	54.5
Unknown	2	9.1
Use of FBT according to the approved indication		
Yes	3	13.6
No	19	86.4
Concomitant medications with CYP3A4 activity		
Yes	10	45.5
No	12	54.5
Screening for abuse at FBT treatment initiation		
Assess patient's level of pain using a scale	19	86.4
Assess patient's level of function (e.g. social, recreational, occupational)	20	90.9
Assess risk of addiction using a screening tool	12	54.5
Conduct formal psychological screening	7	31.8
Do urine drug screening	3	13.6
Explain potential benefits of long-term opioid therapy	18	81.8
Explain potential harms of long-term opioid therapy	18	81.8
Give the patient written information about opioid therapy	3	13.6
Screening for abuse during FBT treatment		
Overwhelming focus on opioid drug-related issues		
Yes	7	31.8
No	15	68.2
Do not know	0	0.0
Drug use escalation (early refills/larger amounts) unexplained by change in clinical condition		
Yes	2	9.1
No	20	90.9
Do not know	0	0.0
Reports of lost, spilled. or stolen medications		
Yes	0	0.0
No	22	100
Do not know	0	0.0

Table 3 (continued)

Total patient CRFs	$N = 22$	
Patient characteristics *n* (%)	*n*	%
Unclear etiology and/or exaggeration of pain		
Yes	1	4.5
No	20	90.9
Do not know	1	4.5
Requests for treatment from multiple prescribers		
Yes	1	4.5
No	21	95.5
Do not know	0	0.0
Overdose or diversion		
Yes	0	0.0
No	21	95.5
Do not know	1	4.5

FBT fentanyl buccal tablets, *CRFs* case report forms, *CYP* cytochrome P450

In agreement with findings for physician monitoring practices (see Sect. 3.1.3), before initiating FBT treatment, a large majority of patients were screened for their level of pain (86.4%) and level of function (90.9%), and were explained the potential benefits and harms of long-term opioid therapy (81.8% each). However, several other recommended screening practices were not commonly used (Table 3). During FBT treatment, most of these patients did not present any behavior raising the suspicion of a potential risk for opioid abuse or diversion (such as overwhelming focus on opioid drug-related issues; drug use escalation; reports of lost, spilled or stolen medications; unclear etiology and/or exaggeration of pain; requests for treatment from multiple prescribers; overdose; or diversion), as reported by their physicians.

3.3 Web Surveillance

Over the period 1 May 2014–24 September 2018, Google Trends indicated that Google searches for the term FENTORA® were made half as often in Canada than in the region/country where this keyword's search rate was the highest (reference United States) (Fig. 6).

A total of 932 publications were identified through the digital surveillance of Web sources: 636 were retrieved from discussion forums (i.e. Bluelight, Drugs-Forum, Healing Well, Reddit), 235 from social media monitoring tools (i.e. Boardreader, Social Mention, Social Searcher), 48 from Google News, and 5 from Facebook. Of these, only 40 (4.3%) publications reported information related to the illicit use of FBT in Canada. The majority of these 40 publications ($n = 31$, 77.5%) provided data on the supply of FBT, including contact information of the seller and name of the website where the drug could be bought online; the remaining were publications on recreational use ($n = 8$, 20.0%) and adverse effects ($n = 1$, 2.5%).

4 Discussion

This study provides the first insight into physician prescribing and monitoring practices with FBT in Canada following the implementation of safety communications, including product labeling and educational materials for prescribers and patients. The objectives of this three-tier study were

Fig. 6 Trends of searches for the keyword FENTORA® in Canada* (Source: Google Trends), 1 May 2014–24 September 2018. Proportions depicted are relative to the usage rate for the region/country where the keyword's usage was highest (reference value = 100). E.g., a value of 50 denotes that the keyword was used half as often in Canada than in the reference region/country (US)

to assess the effectiveness of FBT aRMMs as measured by HCP knowledge, understanding, and behavior regarding important identified key safety concerns, and to qualitatively evaluate the illicit use of FBT in Canada. Findings from the KAU survey suggest that the aRMMs as measured by HCP knowledge, understanding, and behavior were effective regarding most, but not all, key safety concerns. FBT indication and three of the four key safety messages (i.e. use in opioid-tolerant patients, dose/titration procedures, and risk of abuse/addiction) were correctly understood by the survey respondents, with the lower bound of the 95% CI greatly exceeding the prespecified threshold of 65% that was set to determine aRMM effectiveness. Prescriber knowledge could be attributed to aRMM implementation, but could also result from the high publicity surrounding opioids. Compared with the three key messages listed above, knowledge about drug–drug interaction was suboptimal, with only half the respondents meeting or partly meeting the knowledge objective, even though the product monograph includes a list of drugs with CYP3A4 activity. Furthermore, prescribers seemed to be vigilant about the potential for abuse/addiction with opioids, and generally monitored for these concerns at treatment initiation and during treatment. However, a sensitivity analysis that required all answers to be correct ('met' knowledge objective) to be considered an acceptable KAU indicated suboptimal KAU among the respondents (41.3–69.6%) for the FBT indication and the four key safety messages. This suboptimal finding resulted mainly from selecting incorrect indications, such as treatment of breakthrough pain in chronic non-cancer pain and/or treatment of cancer with background pain.

While the results of the KAU survey suggest that prescribers are knowledgeable about the FBT indication, in practice, compliance with the recommended labeling and monitoring practices was not optimal. The retrospective prescription study suggests that not all prescribers heed the indication of FBT (i.e. adult cancer patients, use for breakthrough pain, and opioid tolerance). In addition, there was variability in compliance with the different key messages of the aRMMs, with not all messages in the labeling being followed to the same extent. These results are consistent with previous post-approval safety studies conducted in the UK and France that found that FBT is primarily prescribed as indicated, but off-label use has been reported [20, 21]. They also agree with the results of a previous survey conducted among Canadian pharmacists who reported opioid prescription-related incompliance, including lack of opioid maintenance, issues with drug–drug interaction, and use in patients with mild to moderate pain that could have been managed with a non-opioid analgesic [22].

The deviations from the labeling found in this study could stem from lack of knowledge or from accumulated data from evidence-based practice. Insufficient knowledge could be due to the opioid guidelines being excessively long and consequently being used only limitedly [23, 24]. It could also be because some physicians may not prescribe the product regularly, and thus may not have read the Canadian Product Monograph or been exposed to the educational material. Evidence-based practice leading to use in non-cancer patients could be based on previous randomized clinical trials that had examined the use of FBT in non-cancer patients with chronic pain and found that it was efficacious and generally well tolerated [25–31]. More importantly, the 2010 and 2017 Canadian guidelines for safe and effective use of opioids for chronic non-cancer pain indicate the important role of opioids, including fentanyl, in the management of chronic non-cancer pain, while recommending careful prescribing to minimize potential harms [1, 11]. Physicians may have followed these guidelines that do not differentiate between fentanyl and transmucosal immediate-release fentanyl formulations regarding the indicated population of cancer patients rather than following the labeling and educational material for FBT. Thus, physicians in the survey may have considered that prescribing fentanyl for chronic pain is acceptable in certain situations.

Our study results indicate that prescribers follow at least some of the recommended practices for screening for risk of abuse prior to prescribing an opioid therapy. Yet, these results should be interpreted with caution because the questions about screening practices did not explicitly mention FBT, but rather opioid treatment; therefore, respondents may have interpreted the questions as being applicable to their general practice in initiating opioid therapy for the treatment of cancer pain (either baseline pain or breakthrough pain). It should be noted that when assessing the abuse potential of either long- or short-acting opioids, all opioids have the potential to activate the brain reward system [32], and that there is no evidence that transmucosal formulations, such as FBT, are more addictive than other fentanyl formulations.

A major strength of this study was the use of a mixed-methods approach—a KAU survey, a retrospective prescription study, and Web surveillance. The KAU survey, designed to evaluate the KAU of physicians regarding the aRMMs, appeared to be useful. This tool is most frequently used to assess the effectiveness of aRMMs involving educational material [33]. The KAU survey results provide evidence for the implementation of the aRMMs and offer insight on the extent to which the aRMMs have been executed as planned. This survey serves as a proxy for behavior and outcome indicators in real-world clinical practice. The retrospective prescription study effectively evaluated the prescribing of FBT and the safe use behavior and compliance with recommended labeling and monitoring practices. The Web surveillance of internet sources was an additional tool to evaluate trends in illicit drug use in Canada.

Physician recruitment for the KAU survey, and consequently their recruitment for the prescription study, were challenging. This difficulty in recruitment and the low response rate to surveys have been described previously, indicating that surveys may represent a burden on clinical practice [34]. The low number of participants could be due to a lack of interest and time, the low compensation, and/or the perception that survey-based studies have limited scientific impact compared with clinical trials [34, 35]. Moreover, low recruitment could derive from a low prescribing of FBT in Canada, especially if the product is not reimbursed or is not in the formulary. As physicians had to prescribe FBT at least once to participate in the surveys, many may not have responded due to ineligibility. Anticipating this challenge in recruitment, no specific sampling strategy was applied, and all potential prescribers were contacted, irrespective of their medical specialty or practice setting, in order to achieve a minimal sample size. Eventually, a sample size of 46 prescribers was achieved in the KAU, exceeding the target sample size. The low response to the KAU survey and the retrospective prescription study may have affected the precision of the results and consequently their generalizability. In addition, the distributions of geographic region (one half from Ontario) and physician specialty (mainly palliative care physicians practicing in the hospital setting) were not well-balanced, and could have also affected the representativeness of the study. Due to the potential for selection bias as a result of the small sample size, a comparison was performed between responders and non-responders to the KAU survey (based on the sponsor's Fentora prescriber list). For geographic regions, half the responders were from Ontario and 23.9% were from Quebec in the KAU survey, while 40.0% of non-responders were from Ontario and 40.0% were from Quebec per the sponsor list. For physician specialty, the responders were mainly palliative care (67.4%), followed by family medicine (21.7%), while the non-responders were mainly family medicine and general practice (82.0%). Nonetheless, the sample in this study reflects the FBT prescriber distribution in real-world practice and the relatively low FBT use in Canada.

Several limitations of this study should be noted. First, selection bias due to the voluntary nature of the study as well as the low response rate is possible and could affect the survey results. Second, recall bias could have been introduced, specifically in the KAU survey, as completion of the questionnaire was likely based on the prescriber's recall of specific practices/events or expectations [35, 36]. Moreover, since the survey was conducted a considerable time after the educational material was distributed (30 and 47 months after product launch), recall bias in the evaluation of the aRMMs could also have occurred. Third, the reach and extent of the implementation of the aRMMs are not clear; the study did not examine whether physicians had received and read the educational material, and did not establish their source of knowledge for the FBT indication and the key messages (educational material versus other sources, including the labeling or guidelines). Fourth, the study lacked a comparison of the effectiveness measure before and after implementation of the aRMMs [37] because this design was not feasible since the FBT Canadian Product Monograph and communication materials were available immediately at market launch and were accessible to all prescribers and patients. Fifth, there may have been changes in knowledge and prescribing practices from Wave I to Wave II, especially since the labeling and other risk minimization measures had been strengthened, but the sample size in each wave was too small to assess such trends. Sixth, the threshold of 65% chosen to indicate that the knowledge objective was met was determined arbitrarily only for the KAU survey based on the estimated CIs for a sample size of 20 prescribers per wave. Yet, it provided a reference point given the absence of a recognized threshold of KAU above which the risk minimization strategy can be considered to be effective. Of note, recent FDA guidance on survey methodologies considers 80% or higher to be an acceptable knowledge performance threshold for each key message domain [38]. As evaluation of prescription practices through a retrospective review of medical charts was dependent on KAU and other factors, this analysis was only descriptive, and no prespecified thresholds were defined.

In the retrospective prescription study, selection bias may have been introduced due to the physicians who agreed to participate in the study, and due to the patient medical records that were selected for the study. However, this study's method minimized the additional challenges of patient recruitment by the prescriber, as well as the recall bias associated with patients reporting themselves [34]. Since this component involved patient medical records rather than the reports of patients, recall and information bias while documenting prescribing patterns was reduced. Lastly, since physicians could complete up to three case report forms, the collected observations could have been correlated. Due to the limited sample size, non-independence could only be assessed qualitatively, but as the majority of physicians filled case report forms for only one patient, this potential correlation was minimal.

In this study, the effectiveness of the aRMMs was evaluated by whether the intervention achieved the desired effect. An additional domain to determine the effectiveness of the aRMMs is assessment of the sustainability of this intervention effect [39]. However, the study did not specifically evaluate the sustainability of knowledge and behavior over time. Nonetheless, the conceptual framework that guided this study is useful in understanding the various domains for evaluation, enabling improvement in the design of risk minimization tools and guiding their implementation and evaluation in various settings.

5 Conclusions

This study used a mixed-methods approach of a KAU survey, a retrospective prescription study, and Web surveillance. The KAU survey and retrospective prescription study provide a comprehensive view and evidence of the effectiveness of FBT aRMMs in Canada. The aRMMs for FBT as measured by the prescriber KAU were well understood regarding the indication and three of the four key safety messages: use in opioid-tolerant patients, dose and titration, and risk of abuse/addiction. However, the retrospective prescription study indicated that not all key messages of the aRMMs were stringently followed in routine practice, and FBT was prescribed to non-cancer patients and concomitantly with medications that affect CYP3A4 activity. As physicians do not completely follow the labeling for FBT, Canadian guidelines for chronic non-cancer pain may require modification to guide physicians regarding the use of FBT and to differentiate between the fentanyl formulations.

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Compliance with Ethical Standards

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Conflict of interest Sigal Kaplan and Martin Sergerie are employees of Teva Pharmaceutical Industries Ltd and/or its affiliates. Aurore Bergamasco, Anne-Marie Castilloux and Yola Moride are employees of YOLARX Consultants, which received financial support from Teva Canada Innovation to conduct this research.

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