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ORIGINAL RESEARCH ARTICLE

Indicators of Drug-Seeking Aberrant Behaviours: The Feasibility of Use in Observational Post-Marketing Cohort Studies for Risk Management

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Abstract

Background Problematic prescription drug use is reflected by or associated with drug-seeking aberrant behaviours. Research gaps include lack of post-marketing evidence and instruments. As part of the pharmacovigilance requirements, a risk management plan was developed for fentanyl buccal tablets (FEBT) by the manufacturer, with an additional pharmacovigilance activity requested by the regulatory authority, to investigate the risks of misuse, abuse, criminal use, off-label use and accidental exposure to FEBT after the product became commercially available. A Modified Prescription-Event Monitoring (M-PEM), observational, post-authorisation safety surveillance (PASS) study was conducted, with an overall aim to examine the use of FEBT in relation to their safety as prescribed in primary care in England. One of the exploratory objectives included estimating the prevalence of aberrant behaviours during FEBT treatment.

Objective To determine the feasibility of estimating the prevalence of risk factors associated with dependence on starting treatment and aberrant behaviours in patients during treatment with a prototypical abuse liable substance (fentanyl), as based on the application of an existing index (the Chabal criteria).

Methods Data were collected as part of the M-PEM PASS study; exposure and outcome data (including risk factors for dependence and aberrant behaviours based on behavioural not clinical manifestations) were derived from questionnaires sent to primary care physicians in England during April 2008 to June 2011. For the exploratory objective of interest, descriptive statistics and simple (non-weighted) risk scores were constructed on aggregate counts (score $\geq$3 considered 'high-risk'). Supplementary analyses explored the relationship between the two indices and the characteristics of patients with aberrant behaviours and those without (crude odds ratios plus 95 % confidence interval (CI) were calculated).

Results In a cohort of 551 patients, the prevalence of at least one pre-existing risk factor for dependence was 26 % ($n = 145$), whilst the frequency of aberrant behaviours observed during treatment was 8 % ($n = 46$). Patients with aberrant behaviours had several different characteristics to

Key Points

The feasibility of estimating the prevalence of risk factors for dependence and aberrant behaviours in patients prescribed products with misuse potential was explored in a Modified Prescription-Event Monitoring, post-authorisation safety study for fentanyl buccal tablets

In this study, the prevalence of at least one pre-existing risk factor for dependence was 26 %, whilst the frequency of aberrant behaviours observed during treatment was 8 %

The systematic collection of physician reports of risk factors for dependence and aberrant behaviours is feasible and can support post-marketing risk management of products with misuse potential

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patients without. The two indices were associated (χ^2 df (20) = 58.72, $p < 0.001$), but a high-dependence risk-factor score provided a poor indication of high aberrant behaviour risk; the area under the receiver operating characteristic curve was 0.58 (95 % CI 0.41, 0.74).

Limitations Study limitations included subjectivity in relation to physicians identifying aberrant behaviours, and under-reporting thereof in PASS observational study designs. The presence of these criteria does not confirm misuse, but should be considered as a signal of problematic opioid misuse, which requires investigation. Further research is needed to develop a more robust analytical construct.

Conclusion In this PASS study, the prevalence of at least one pre-existing risk factor for dependence was 26 %, whilst the frequency of aberrant behaviours observed during treatment was 8 %. Patients with aberrant behaviours had several different characteristics to patients without. This study demonstrates the feasibility of the systematic collection of physician reports of risk factors for dependence and aberrant behaviours to facilitate the development of risk scores, using these reports to support the post-marketing risk management of products with misuse potential.

1 Introduction

Before a medicinal product is approved for marketing, regulatory authorities have to decide whether there are sufficient data to adequately demonstrate that the drug has a positive risk-benefit profile under the conditions of use proposed in the product information. Risk management of medicines is attracting immense interest in pharmacovigilance worldwide. In the European Union (EU), requirements for pharmacovigilance planning and risk management plans (RMPs) became a regulatory requirement in 2005 as set out in legislation, and have been further strengthened by the EU legislation on pharmacovigilance in 2010 [1]. When a medicinal product is licensed, defining its safety for the target population not only includes possible risks with the product's use but also considers how complete the information knowledge base is. This information can be used to better understand risks and or minimise such risks, as well as monitoring how well these activities work, and if they can be improved. Having a comprehensive RMP in place allows for timely implementation of risk minimisation strategies, as well as effective communication of any new information. The equivalent requirements for the USA is detailed in a set of guidelines published by the US Food and Drug Administration, which includes the guidance *Development and Use of Risk Minimisation Plans* (March 2005) [2].

The increasing prevalence of problematic prescription drug use is becoming a particularly important public health issue [3–5]. Problematic prescription drug use is reflected by or associated with drug-seeking aberrant behaviours. Such behaviours are suggestive of an elevated risk of likelihood of dependence presenting upon starting, or emerging during pain treatment, particularly with psychoactive agents (such as opioid analgesics, central nervous system (CNS) depressants such as benzodiazepines and CNS stimulants such as those used to treat attention-deficit hyperactivity disorder). Risk minimisation strategies are therefore necessary to prevent or minimise problematic prescription drug use and protect the public from the consequences of intentional misuse[1] of such substances, as well as unsanctioned diversion thereof to third parties, and clinically significant addiction and/or dependence.[2] The development of an abuse deterrent formulation is one example of a risk minimisation activity [9]. However, important research gaps include lack of post-marketing evidence to support the effectiveness of these risk minimisation activities in patients for whom long-term treatment is necessary for their disease [10]. This has become important since the definition of adverse drug reaction was extended in the EU in 2012 to include error, misuse, abuse and off-label use [11], accompanied by reporting requirements [12].

In September 2006, a novel buccal formulation of an opioid analgesic, fentanyl citrate buccal tablets (FEBT) [Effentora™; Cephalon] was approved in the USA for the management of breakthrough pain in patients with cancer who are already receiving and tolerant to opioid therapy for their underlying persistent cancer pain [13]. It was approved in the EU in April 2008 for the same indication

[1] Misuse and non-medical use can be considered synonyms of abuse. The definition of 'abuse' published in 1969 by the World Health Organisation Expert Committee on Drug Dependence was "persistent or sporadic excessive drug use inconsistent with or unrelated to acceptable medical practice" [3]. This definition is also included within the Good Pharmacovigilance guidelines [6]. More recent definitions make reference to intentionality for both misuse and abuse but make distinctions according to therapeutic and non-therapeutic use, respectively [7].

[2] Dependence refers to physiological adaptation that occurs when medications acting on the central nervous system are taken. It is a term often incorrectly used synonymously with the term 'addiction', which refers to uncontrolled drug-seeking behaviour. The *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition) (DSM-V) is the current official text on which diagnoses are based for substance dependence and other mental health problems in the general population [8]. Recent revisions aim to support the lack of boundaries between misuse (abuse) and dependence and include updates to disorder groupings and criteria of certain conditions particularly regarding addiction: 'Addictive Disorders' refers to behavioural markers associated with addictive illnesses, whilst 'Substance Use Disorder' now combines abuse and dependence into a single continuum to better match patient symptoms.

[14, 15]. Although the active ingredient has been available for many years, a risk minimisation action plan was developed for FEBT as part of the RMP by the manufacturer. This included a requirement for an additional pharmacovigilance activity, in response to a request by the regulatory authority to investigate the risks of misuse, abuse, criminal use, off-label use and accidental exposure to FEBT after the product became commercially available. A Modified Prescription-Event Monitoring (M-PEM) study was therefore conducted with an overall aim to examine the use of FEBT in relation to their safety as prescribed in primary care in England. One of the exploratory objectives of this post-marketing study was to examine the physician-reported frequency of risk factors associated with dependence at the start of FEBT treatment, and the prevalence of problematic prescription opioid misuse arising during exposure to FEBT in terms of aberrant behaviours, unsanctioned diversion and accidental exposure.

Evidence on the identification of drug-related aberrant behaviours is limited. Available instruments have not yet been adequately validated, each has methodological shortcomings and, to date, none have been universally incorporated into clinical practice. Therefore, there is no consensus regarding which criteria should be applied to the outcome definition [9, 10]. In terms of identification of specific criteria for problematic prescription opioid use and drug-seeking aberrant behaviours, there is a lack of standard definitions within the published literature [10]. Some studies have attempted to define instruments using knowledge derived from epidemiological and genetic studies as part of a structured approach to identify patients potentially at risk, as well as to support the recording of relevant outcomes in a standardised manner [16, 17]. The aim of such studies is to identify patients who may require special vigilance and monitoring. Further complexity arises from trying to differentiate between pseudo-addiction (abuse behaviours in legitimate patients secondary to common errors in opioid management such as inadequate treatment of pain) and misuse, whilst taking into account the numerous external and internal factors that can affect pain.

From examination of the various criteria and instruments previously identified, surrogate markers of indicators of aberrant behaviours suggestive of problematic prescription opioid misuse were proposed for this M-PEM study based on the Chabal criteria. This five-point checklist is used to evaluate opioid misuse in patients with chronic non-cancer pain (Table 1). Although the Chabal criteria were developed using a different vulnerable population with chronic non-cancer pain, the measures were considered broadly relevant to the exploratory objective of the M-PEM study because off-label prescribing (use in chronic non-cancer pain) was anticipated [18].

This paper describes the feasibility of estimating the prevalence of risk factors for dependence and aberrant behaviours in patients exposed to a prototypical abuse liable substance (fentanyl), as based on the application of an existing index (the Chabal criteria).

2 Methods

2.1 Study Design

The general methodology for M-PEM uses a retrospective, non-interventional, observational cohort design to provide active surveillance of targeted medicines on a national scale in England. Details of the study methodology have been provided elsewhere [19]. The sampling frame is hierarchical, comprising two levels: all general practitioners (GPs) in England who prescribe the study drug and their patients. This wide coverage aims to provide an evaluable cohort that is representative of the whole population of patients who are registered with a National Health Service (NHS) GP in England who take the study drug during the study period.

For this M-PEM study of FEBT, the eligible new user cohort was identified based on a single common exposure identifier (a prescription for the new medication under surveillance, Fig. 1). NHS primary care prescription data were provided to the Drug Safety Research Unit (DSRU) by the NHS Business Services Authority under a long-standing agreement. Prescription data collection began immediately after FEBT was launched (and covered the national population in England) and the observation period began on the date of the first prescription received for each individual patient. Confirmation of exposure status and outcome were ascertained retrospectively from M-PEM questionnaires sent at least 6 months after the beginning of observation to assemble the evaluable cohort (i.e., the cohort available for analysis).

As part of the overall M-PEM study of drug use and safety, data collected from the GP-completed questionnaires included patient demographics (age, sex), prescribing information and details of all significant events of interest (e.g., identified risks associated with use of fentanyl such as respiratory depression and respiratory failure) that had been recorded in the patient's medical records since starting FEBT treatment. GPs were offered a modest reimbursement to cover administrative costs, in recognition of the time spent completing the M-PEM data collection forms. Within the DSRU, each questionnaire was scanned into the system and the image reviewed by a scientific member of the DSRU staff to identify events (pregnancies, deaths and clinical reports of medical interest including serious adverse events [classified using the International

Table 1 Chabal criteria for problematic opioid use [18]. If a patient meets three or more of the following criteria, then they are considered a problematic opiate user

1. Overwhelming focus on opiate issues during clinic visits that occupy a significant proportion of the clinic visit and impedes progress with other issues regarding the patient's pain. This behaviour persisting beyond the third clinic session
2. Pattern of early refills (three or more) or escalating drug use in the absence of an acute change in his/her medical condition
3. Patient-generated multiple telephone calls of visits requesting more opiates, early refills or problems associated with opiate prescription. A patient may qualify with fewer visits if she/he creates a disturbance with office staff
4. Pattern of prescription problems for a variety of reasons that may include lost, spilled and/or stolen medications
5. Supplemental sources of opiates obtained from multiple providers, emergency rooms or illegal sources

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Conference on Harmonisation definitions] [20]) requiring expedited follow-up for purposes of an aggregate assessment of drug-relatedness, which puts each event into context regarding temporality co-morbidity, pre-existing disease and concomitant medications. For each patient, trained coding staff prepared a computerised, longitudinal, chronological record of demographic, exposure and outcome data associated with starting FEBT treatment. Selected attributes are linked to selected data, for example, if the event had a fatal outcome; or if the event was a reason for stopping. Data quality is routinely assured through a number of methods based on error prevention, data monitoring, data cleaning and documentation.

Specific to the exploratory objective, the M-PEM study collected information from the GPs on known risk factors strongly associated with substance dependence, thereby indicating elevated risk of likelihood of addictive behaviour at the start of therapy. Relevant data were collected via yes and no answers on well-known risk factors: prior history of psychiatric disorders, [21, 22] of substance misuse, alcohol misuse and smoking [23]. Information was also requested on the clinical diagnosis of opioid withdrawal syndrome because its manifestation early after starting a new pain treatment would suggest pre-existing dependence

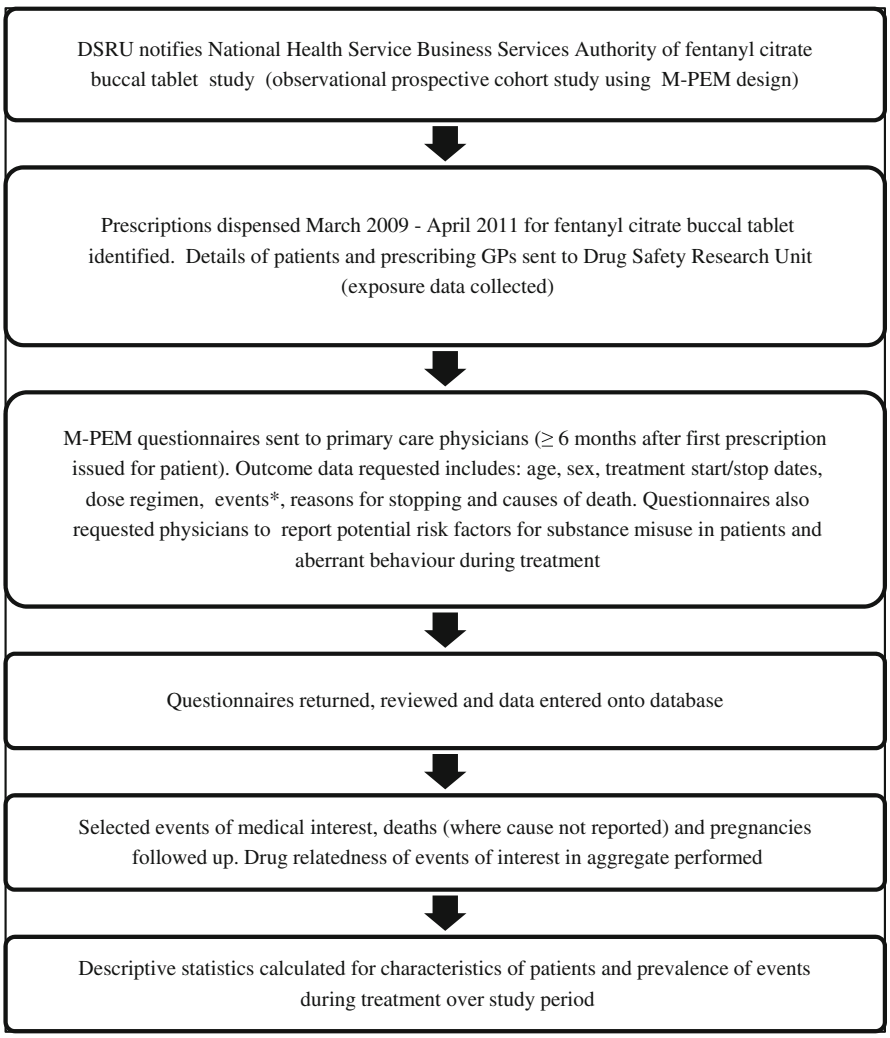

Fig. 1 Process of the Modified Prescription-Event Monitoring (M-PEM) study for fentanyl citrate buccal tablets *An 'event' in M-PEM, is defined as, "any new diagnosis, any reason for referral to a consultant or admission to hospital, any unexpected deterioration (or improvement) in a concurrent illness, any alteration of clinical importance in laboratory values, or any other complaint that was considered of sufficient importance to enter in the patient's notes"

Table 2 Summary of factors associated with dependence, indicators of aberrant behaviours and unsanctioned diversion or accidental exposure

Factors associated with dependence upon starting treatment	Risk score (range)
Alcohol misuse	
Smoker	
Substance misuse	0–5
Psychiatric disorder	
Opioid withdrawal syndrome during treatment	
Indicators of aberrant behaviours during treatment[a]	**Risk score (range)**
Overwhelming focus on opioid-related issues	
Escalating drug use (early refills/larger amounts for longer periods) unexplained by change in clinical condition	
Reports lost, spilled stolen medication	0–6
Unclear aetiology and/or exaggeration of pain	
Requests for treatment from multiple prescribers	
Accidental/unsanctioned diversion to third parties	

[a] General practitioners were asked to provide supplementary information (details of event such as date of first report, relevant medical history and other factors) as free text if a positive response was given

to the previous treatment [24]. Six questions were posed regarding the demonstration of aberrant behaviours at any time during the observation period after first exposure to FEBT treatment; the five outlined by Chabal et al. and an additional question that sought prescriber awareness of unsanctioned diversion to third parties or accidental exposure (Table 2).

This study was conducted in accordance with national and international guidelines [25–28]. In addition, under Section 251 of the NHS Act 2006, the DSRU have received support from the Ethics and Confidentiality Committee of the National Information Governance Board to gain access to and process patient identifiable information without consent for the purposes of medical research (October 2009).

2.2 Data Analysis

Per-protocol descriptive statistics summarised demographic data and drug use data with individual characterisation of risk factors strongly associated with substance dependence and the relevant aberrant behaviours. Simple (non-weighted) scores were separately constructed on aggregate counts of GP-reported indicators and behaviours. One point was assigned to each item so that an individual patient's score could be calculated and would be between zero (all responses negative) and the maximum score (all responses positive). None of the criteria in either index were ranked in order of importance because it was not feasible to fully define the clinical range (scale), content and quality of information at study start for the heterogeneous population under surveillance. Patients were classified as high risk of substance dependence based on three or more factors reported within the dependence index (similar to the DSM-VI substance dependence (addiction) diagnosis threshold of a minimum of three criteria current during the period the M-PEM study was conducted [29]) and/or classified as possibly engaged in aberrant behaviour based on three or more items within the aberrant behaviour index (in accordance with the aforementioned Chabal criteria).

Univariate analysis individually explored associations between potential risk factors for dependence and aberrant behaviour status. Differences between categorical variables were tested using Pearson χ^2 tests, and differences between continuous variables tested by using parametric two sample t tests, where appropriate. Crude odds ratios (ORs) plus 95 % confidence intervals (CIs) were calculated using simple logistic regression to explore relationships between baseline variables. Data were analysed using STATA version 12.0. Because this objective was exploratory, no sample size was calculated.

The investigation of possible relationships between the risk factor score and aberrant behaviour index was conducted as a supplementary ad hoc analysis. Data were further dichotomised to explore the relationships further. The aberrant behaviour index cut-off was defined according to three or more of the Chabal criteria; whilst the dependence risk factor score cut-off was variable (one or more, two or more or three or more). A simple logistic model was fitted for each comparison and a receiver operating characteristic (ROC) analysis used to examine model performance.

3 Results

3.1 Study Cohort

The final M-PEM cohort consisted of 551 evaluable patients (Fig. 2).

3.2 Risk Factors for Dependence

The most frequently reported, potential risk factor associated with dependence was smoking ($n = 119$, 21.6 % of cohort), followed by psychiatric disorders ($n = 42$, 7.6 % of cohort). Forty patients were specifically reported to have a prior psychiatric history, with two additional patients reported to have concurrent psychiatric disorder. Of the 42

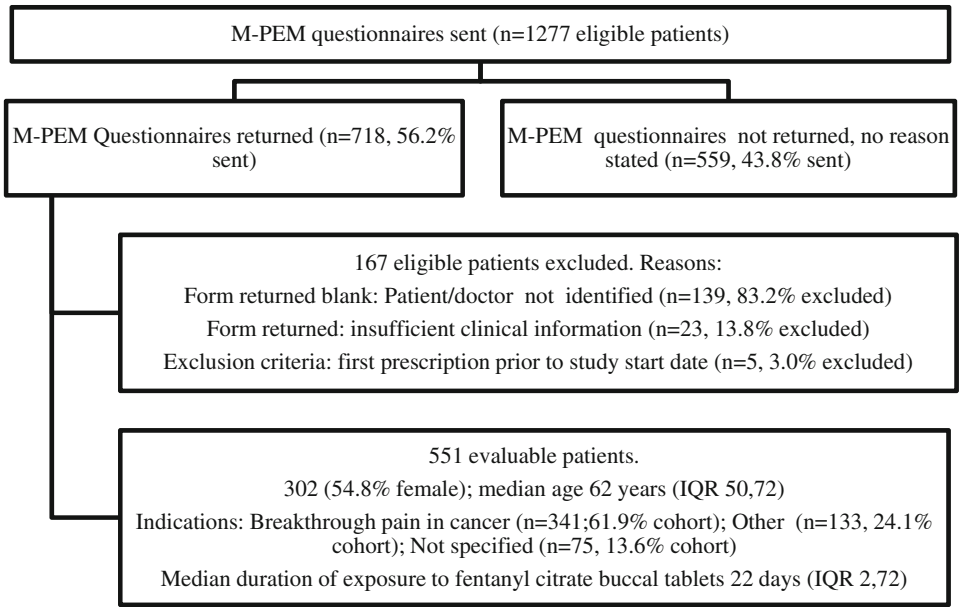

Fig. 2 Cohort accrual flow diagram. *M-PEM* Modified Prescription-Event Monitoring, *IQR* interquartile range

patients who were reported to have a prior psychiatric history, the most frequently reported psychiatric disorder was depression ($n = 21$, 46.7 % of 45 conditions specified), followed by personality disorder ($n = 3$, 6.7 % where condition specified) and anxiety ($n = 3$, 6.7 % where condition specified). There were also nine reports (1.6 % of cohort) of a previous history of substance misuse, of which three were specified as past misuse of heroin. There were two reports (0.4 % of cohort) of opioid withdrawal syndrome, but neither of these was specified as having occurred within 2 weeks of starting FEBT.

The majority of patients had no past medical history of factors associated with dependence ($n = 406$, 73.7 %, risk score = 0; Table 3); one or more risk factors were reported in 145 patients (26.3 %) of whom six patients were considered high risk including five patients who had a risk score of 3 and one patient who had a risk score of 4 (a history of alcohol misuse, smoking, substance misuse and psychiatric disorder)

3.3 Aberrant Behaviours

In total, 29 patients (5.3 % of cohort) were reported to have escalating drug use, which was the most frequently reported aberrant behaviour in the cohort. There were also 13 patients (2.4 % of cohort) who were reported to have an overwhelming focus on opioid-related drug issues (that occupies a significant proportion of consultation and impedes progress with other treatment-related issues) along with 22 patients (4.0 % of cohort) who were reported to have pain with unclear aetiology/exaggeration of pain. There were nine reports (1.6 %) of multiple requests for prescriptions from different prescribers. No reports of patients needing to restart FEBT without clinical need were recorded, but there was one report (0.2 % of cohort) of unsanctioned diversion to third parties or accidental exposure.

During the 6-month observation period, the majority of patients had no aberrant behaviours reported ($n = 506$, 91.8 %, risk score = 0; Table 3); one or more aberrant behaviours were reported in 46 patients (8.3 %) and nine patients were considered high risk of whom three had an aberrant behaviour risk score of 5. All of these patients were reported to have experienced an overwhelming focus on opioid-related issues, escalating drug use, reported lost medication, unclear origin of pain and multiple requests from different prescribers.

3.4 Characteristics of Patients with and without Aberrant Behaviours

Compared with those without aberrant behaviours (Table 4), patients with aberrant behaviours were: younger (median age (years) 48 vs. 63; $p < 0.001$); received higher test, effective and/or maintenance doses (all $p < 0.02$); had longer treatment duration (median (days) 87 vs. 21; $p < 0.001$); and were more likely to have indications other than breakthrough pain in cancer [OR 3.5 (1.1, 10.8)]. In terms of specific risk factors for dependence, patients with aberrant behaviours were more likely to have a history of alcohol/substance misuse [OR 4.2 (1.4, 12.5)] and psychiatric disorders [OR 4.1 (1.8, 9.7)]. Where specified ($n = 20$) in 11 patients, aberrant behaviours were pre-existing. For the remaining nine patients with incident aberrant behaviour events, the median time to onset of these events was 265 days (interquartile range 140–329).

Table 3 Risk score distribution of indicators of dependence and aberrant behaviours

Risk score distribution	*N*	% of Cohort
Score of indicators of dependence		
0	406	73.7
1	112	20.3
2	27	4.9
3	5	0.9
4	1	0.2
Score of aberrant behaviours		
0	505	91.8
1	27	4.7
2	10	1.8
3	5	0.9
4	1	0.2
5	3	0.5

3.5 Relationship Between Risk Factors for Dependence and Aberrant Behaviours

There was evidence of a crude association between risk factors for dependence at baseline and aberrant behaviours after exposure to FEBT treatment (χ^2 degrees of freedom (20) = 58.72; $p < 0.001$). The sensitivity of the dependency risk factor score using a cut-off of 1 or more as an indicator of aberrant behaviour was 55.6 % (5/9) and the specificity was 73.8 % (400/542); the corresponding values for a cut-off of 3 or more was 11.1 % (1/9) and 99.1 % (537/542). The positive predictive values were 3.4 and 16.7 %, respectively. Similarly, the likelihood ratio of positive and negative result for each was 3.44 vs. 0.97 and 11.35 vs. 0.85, respectively. The ROC analysis suggested that the high-dependence risk-factor score did not provide a very good indication of high risk of aberrant behaviour; the area under the ROC curve (AUROC) was 0.58 (95 % CI 0.41, 0.74), which includes the null AUROC value of 0.5.

4 Discussion

This study demonstrates the feasibility of systematic collection of physician-reported risk factors for dependence and indicators of aberrant behaviours within an M-PEM post-authorisation safety surveillance (PASS) study, along with the development of risk scores using these reports to support the post-marketing risk management of products with misuse potential in primary care practice in the UK. In this study of FEBT treatment conducted during April 2009 to June 2011, the crude period prevalence of at least one pre-existing risk factor for dependence was 26 %, whilst the frequency of aberrant behaviours observed during treatment was 8 %.

4.1 Quantifying Risk Factors Associated with Dependence

In this M-PEM study, the most frequent risk factor was smoking, followed by psychiatric disorders. Alcohol misuse, substance misuse and psychiatric disorders all tended to be reported more frequently for patients with aberrant behaviours. Epidemiological studies indicate prior psychiatric disorders are moderately strong predictors of opioid abuse and dependence [21, 22]. Patients with chronic pain commonly present with psychiatric co-morbidities, such as depression or anxiety, but the temporal relationship is unclear [24]. Most addiction specialists agree that those with current or past alcoholism, a past history of opioid abuse, other substance abuse (including smoking cigarettes) or other drug-addicted individuals should be viewed as being at risk of addiction to substances other than their drug of choice [23, 30]. However, evidence suggests that such high-risk patients do not necessarily present with an increased risk during pain treatment [31]. One explanation being that circumstances associated with misuse are avoided by careful monitoring.

This study only attempted to quantify the most common risk factors associated with dependence as found in the pain literature. It is acknowledged that other indicators exist such as family history or psychotropic drug use; however, the M-PEM questionnaire was designed to achieve a balance between maximising response and minimising workload burden of GP responders, therefore not all relevant factors could be collected as part of the survey.

4.2 Defining Aberrant Behaviours

This M-PEM study defined aberrant behaviours according to the Chabal criteria, which is usually applied to the study of vulnerable high-risk patients with chronic non-cancer pain. There is no standard normal definition within the published literature [10]. Furthermore, such behaviours are likely to exist in a continuum, with patterns being unique between individuals [32]. Thus, whilst primary care physicians are skilled in managing multiple morbidities in their patients, they face a dilemma when it comes to managing chronic non-cancer pain [33]. Physicians must rely on professional experiences and knowledge to interpret observations of behavioural patterns indicating problematic use. Such decision making may be only partially supported by diagnostic criteria, which have been constructed for high-risk populations (illicit drug users) [29, 34]. To help address such an issue, consensus definitions have been created by an expert committee for aberrant behaviours suggestive of dependence in patients with non-cancer chronic pain [35].

Table 4 Characteristics of patients with and without aberrant behaviours

Characteristics	Aberrant behaviours ($n = 46$)	No aberrant behaviours ($n = 505$)		
Age			Wilcoxon rank-sum test *P* value	
Median age (IQR)	48 (35, 63)	63 (52, 73)	<0.001	
Gender			Chi^2	*P* value
Male (%)	24 (52.2)	224 (44.4)	1.1	0.574
Female (%)	22 (47.8)	280 (55.5)		
Indication			Odds ratio	95% CI
Breakthrough pain in cancer (%)	20 (43.5)	321 (63.6)	1.1	0.4, 3.3
Breakthrough pain in cancer plus other (%)	0 (0.0)	2 (0.4)	–	–
Other (%)	22[a] (47.8)	111 (22.0)	3.5	1.1, 10.8
Not specified (%)	4 (8.7)	71 (14.1)	–	–
Dose			Wilcoxon rank-sum test *P* value	
Median test dose mcg/day (IQR)	200 (100,400)	100 (100, 200)	0.019	
Median effective dose mcg/day (IQR)	400 (200,700)	200 (100, 400)	0.009	
Median maintenance dose mcg/day (IQR)	400 (200,800)	200 (100, 400)	<0.001	
Regular maintenance opioid on starting FEBT therapy			Odds ratio	95% CI
Yes (%)	37 (80.4)	346 (68.5)	1.2	0.4, 3.6
No (%)	4 (8.7)	46 (9.1)		
Unknown (%)	5 (10.9)	113 (22.4)		
Duration of treatment			Wilcoxon rank-sum test *P* value	
Median duration (IQR)	87 (14, 276)	21 (1, 64)	<0.001	
Risk factors for dependence			Odds ratio	95 % CI
Alcohol misuse (%)	5 (10.9)	13 (2.6)	4.2	1.4, 12.5
Smoker (%)	10 (21.7)	109 (21.6)	0.9	0.4, 1.9
Substance misuse (%)	3 (6.5)	5 (1.0)	7.5	1.7, 33.2
Psychiatric disorders (%)	9 (19.6)	31 (6.1)	4.1	1.8, 9.7

CI confidence interval, *IQR* interquartile range, *FEBT* fentanyl buccal tablets, – indicates parameter value not calculated (ie. no OR and no CI)

[a] In total, 37 other indications for prescribing were reported in 22 patients with aberrant behaviours. The most frequently reported other indication for prescribing FEBT in patients with aberrant behaviours reported was breakthrough pain ($n = 4$, 17.2% of other indications). In all four cases, the breakthrough pain did not occur in cancer

Physicians are further hampered in their decision making by lack of relevant, general practice epidemiological evidence. Although a human abuse liability trial (an integral part of marketing authorisation applications in the USA but not to the same extent in the EU) is most appropriate to predict the likelihood of abuse by recreational users and the extent of diversion when a drug becomes available in the drug abuse community, the findings are not generalisable to the target patient populations in general practice [36]. Even within routine clinical trials, subjective effects are generally not collected systematically. Furthermore, confidence in the reliability of such studies is hindered by choice of design (randomisation method) and small sample sizes [37]. Thus, post-marketing surveillance is essential to provide insight into the abuse liability of psychoactive substances in a real-world setting [38]. The application of the Chabal criteria in this M-PEM study was successful as patients exhibiting these behaviours were identified. However, because this was only a small observational study, further research is needed to determine if these or other criteria can be used as a tool to support pharmacovigilance activities on a larger scale.

4.3 At-Risk Populations: Patients with Aberrant Behaviours

Patients with aberrant behaviours had several different characteristics to patients without aberrant behaviours. In particular, patients reported to have aberrant behaviours were three times more likely to have been prescribed FEBT for indications other than breakthrough pain in cancer. Such indications include chronic non-cancer pain, which is defined as pain that persists beyond normal tissue healing time, which is about 3 months (with a prevalence estimate in primary care setting in the UK between 5 and 33 %)

[33]. Guidelines for the treatment of patients with chronic non-cancer pain now include chronic opioid analgesic therapy [39–41]; however, the use of fentanyl with rapid duration of action is not recommended (or off label). The observation that patients with aberrant behaviours were younger is also expected given that a higher proportion of patients without aberrant behaviours had indications for breakthrough pain in cancer, which tends to be associated with older age. Patients with aberrant behaviours also tended to be prescribed higher test, effective and maintenance doses and have a longer duration of treatment. One explanation could be the development of tolerance, either as a result of prior exposure to opioid treatment or during treatment, whereby patients require higher doses to achieve adequate pharmacological treatment of symptoms. This is also supported by the observation that the most frequently reported aberrant behaviour was escalating dose. Another explanation is related to the indication for treatment in which patients without aberrant behaviours had a shorter duration of treatment because of their cancer. Alternatively, it could be that treatment was prolonged as a consequence of the aberrant behaviours themselves. Where date was specified, aberrant behaviours were pre-existing in 43.5 % of patients and for those for whom aberrant behaviours were only reported after starting treatment, such events generally occurred after long-term use. It is noted that the range of such behaviours is a continuum, which may develop insidiously over time. It is beyond the scope of this study because of the small sample size to explore the contribution of factors such as addiction, dependence and tolerance on long-term use.

In the M-PEM study, there was a specific need to try and quantify the incidence of unsanctioned diversions separate to identifying the prevalence of aberrant behaviours, in accordance with regulatory requirements of the RMP for FEBT. During the study observation period, there was one patient for whom unsanctioned diversion to a third party was reported. Unlike other drug-seeking behaviours, the identification of diversion (unsanctioned use of the medicine other than by its intended legitimate recipient [42]) is more elusive and thus under-detection is likely. Indeed, the prevalence of diversion is unknown [43]. The potential for unsanctioned diversion exists even if risk has been clinically assessed in a patient prior to initiating pain treatment [43].

4.4 Relationship Between Risk Factors for Dependence and Aberrant Behaviours

In the exploratory analysis of the relationship between the risk scores for dependence and aberrant behaviours, a cut-off of three or more risk factors for dependence was most discriminatory for identifying patients at high risk of engaging in aberrant behaviours. However, the ROC analysis suggested that in its current simple form, the dependence indicator is not useful as a means of identifying such patients. One explanation could be related to loss of information associated with simple dichotomisation of each individual factor, plus subsequent use of thresholds defining high risk. We acknowledge that further research is needed to develop a more robust construct that can be included within an observational non-interventional cohort study, if this is to be used as a tool within pharmacovigilance activity. Indeed, multi-dimensional constructs that take into account the breadth of range and severity of psychosocial factors, drug-related factors and genetic factors have been proposed elsewhere for use in clinical practice [4]. One example is the current opioid misuse measure, a patient self-report assessment validated in patients requiring speciality pain management in the USA [44].

4.5 Strengths and Limitations

M-PEM is an observational cohort technique used for the post-marketing surveillance of newly marketed drugs. One of the major strengths of M-PEM is that it uses data from day-to-day clinical practice. Additionally, the methodology of M-PEM is non-interventional and does not influence the prescribing practices of GPs. Thus, for this M-PEM study, data on the prevalence of risk factors for dependence and outcomes in terms of aberrant behaviours were captured retrospectively and systematically for all eligible patients prescribed and dispensed FEBT. There were no exclusion criteria applied to the identification of the eligible cohort, i.e., all patients prescribed and dispensed the study drug were eligible for inclusion. In M-PEM, exposure is based on dispensed prescription data. These data are more accurate than exposure data based solely on written prescriptions. However, as with many observational studies, the degree of patient compliance in using the prescribed medication cannot be ascertained, particularly when a product may be used intermittently. While it is not possible to be sure the patient used the medication, it is almost certain in M-PEM that the patient received it. Repeat prescriptions would indicate the patient continued to obtain the medication, although long-term adherence was not examined in this study.

Like all observational studies, a limitation is the potential for selection bias associated with missing data arising from non-response. It is unknown whether data are missing because the GPs who returned the questionnaire are different to those GPs who did not return the questionnaire, as is the potential selection bias in terms of representativeness of patients included in this cohort, of all patients receiving FEBT treatment. However, the response

rate in this study (56.2 %) is comparable to response rates reported elsewhere for GP postal surveys [45] and higher than the reporting rates of suspected adverse drug reactions in the Yellow Card scheme [46, 47]. For M-PEM studies in general, we have no reason to believe that the patient characteristics and occurrence of events reported for patients under surveillance whose GP responded differ to those patients whose GPs did not respond. However, as off-label use is acknowledged as a risk factor for dependence and aberrant behaviours, a potential non-response bias exists because GPs who were prescribing off label, or when contraindications and warnings exist, may have been less likely to complete the M-PEM questionnaire. Therefore, the prevalence estimates may be diluted by the high proportion of patients treated for breakthrough pain in cancer for which aberrant 'drug-seeking' behaviour is known to be less likely.

The surrogate markers of indicators of aberrant behaviours proposed for this M-PEM study reflected most closely the criteria proposed by Chabal et al. based on behavioural not clinical manifestations. In the M-PEM study, because physicians were requested to provide information if they had become *aware* of this issue for a patient after first exposure to FEBT treatment, it is acknowledged that these were likely to be subjective opinions, subject to recall bias and under-reporting. The M-PEM cohort was not opioid naïve and information on the prior history of aberrant behaviours was not specifically requested for the whole cohort, therefore this study was not able to inform on the development of de novo (iatrogenic) aberrant behaviours specific to FEBT. Furthermore, because the identification of a date or dose associated with the first report of such events could not be reliably captured (because such behaviours are insidious), estimates of time of onset are imprecise and exploration of dose relationships not feasible.

5 Conclusions

In this M-PEM PASS study, the prevalence of at least one pre-existing risk factor for dependence was 26 % whilst the frequency of aberrant behaviours observed during treatment was 8 %. Patients with aberrant behaviours had several different characteristics to patients without. This study demonstrates the feasibility of systematic collection of physician reports of risk factors for dependence and aberrant behaviours, to facilitate the development of risk scores using these reports to support the post-marketing risk management of products with misuse potential. The reporting of these behaviours does not confirm problematic opioid misuse, but should be considered as signals for further evaluation. Further research is needed to develop a more robust construct that can be used as a tool within pharmacovigilance activity and can be developed as part of evidence-based methodologies for surveillance of products liable to misuse and diversion within RMPs.

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