Immediate release fentanyl. Real world data on abuse and dependence in Spain

González-Bermejo D[1], Rodríguez-Pascual A[1], Rayón-Iglesias P[1], Montero-Corominas D1, Huerta-Álvarez C[2]
1. Pharmacoepidemiology and Pharmacovigilance Division. Medicines for Human Use Department. Spanish Agency for Medicines and Medical Devices (AEMPS). Madrid Spain.
2. Public Health Department. Complutense University of Madrid. Spain.

Fecha de recepción: 17/11/2023 - Fecha de aceptación: 18/12/2023

DOI: http://dx.doi.org/10.4321/S1699-714X2024000100003

ABSTRACT

Purpose: A substantial increase in the prescription of immediate release fentanyl (IRF) outside hospitals was observed in previous studies between 2012 and 2017, however it remains unknown the extent of immediate release fentanyl use disorders (IRFUD). This study aimed to estimate the incidence and risk factors of IRFUD, such us abuse and dependence, in Spain during this period.

Methods: Retrospective cohort study performed in a Spanish electronic primary care healthcare records database (BIFAP). The incidence rate of IRFUD was calculated by dividing the number of incident cases by the total patient-years (p-y) of exposure. Demographic data, lifestyle, cancer diagnosis, comorbidities and concomitant medication were described and analyzed overall and in patients developing IRFUD using Cox regression models. Effect of the type of treatment (continuous/discontinuous) and duration were also evaluated.

Results: The incidence of IRFUD in the 12,267 patients analyzed was 1.8 cases per 100 p-y of exposure. Baseline analysis showed higher frequencies of IRFUD for smokers, patients with a history of substance abuse, non-oncology indication and diagnosis of depression and anxiety, respect to non-IRFUD patients. Patients aged ≥ 80 were less likely to develop IRFUD abuse/dependence. Significant differences were for concomitant use of other treatments with potential for dependence and abuse, such as benzodiazepines. The risk of IRFUD increased with treatment duration, being the highest for treatments lasting 180 days and longer.

Conclusion: Incidence of IRFUD is difficult to contrast due to the lack of similar studies. It could be considered not too higher outside hospitals but possible in cancer and non-cancer patients. It is potentially associated to longer periods of use and not necessarily in continuous treatment, which might reflect the presence of frequent episodes of BTCP, uncontrolled background pain, concomitant psychological distress and misunderstanding about the usage of the product.

Keywords: **abuse, misuse, dependence, opioids, fentanyl, drug use disorders, incidence.**

Fentanilo de liberación inmediata. Datos de vida real de abuso y dependencia en España

RESUMEN

En estudios previos se ha observado un aumento considerable en la prescripción de fentanilo de liberación inmediata en el ámbito extrahospitalario entre 2012 y 2017. Sin embargo, aún se desconoce la magnitud de dependencia y abuso derivada de su uso. Este estudio tiene como objetivo estimar la incidencia y los factores de riesgo de los trastornos derivados del uso de fentanilo de liberación inmediata en España, tales como el abuso y la dependencia durante este período.

Métodos: Estudio de cohortes retrospectivo realizado en España en la base de datos de historias clínicas electrónicas de atención primaria (BIFAP). La tasa incidencia de trastornos por el uso de fentanilo, se calculó dividiendo el número de casos incidentes entre el total de personas-año de exposición. Se analizaron datos demográficos, estilo de vida, diagnóstico de cáncer, comorbilidades y medicación concomitante. Para el análisis se utilizaron modelos de regresión de Cox. También se evaluó el efecto del tipo de tratamiento (continuo/discontinuo) y la duración de tratamiento.

Resultados: La incidencia de trastornos por el uso de fentanilo en los 12,267 pacientes analizados fue de 1.8 casos por 100 personas-año de exposición. Se observó una frecuencia más elevada en aquellos pacientes que al inicio del tratamiento eran fumadores, pacientes con antecedentes de abuso de sustancias, con indicaciones no oncológicas y en pacientes con diagnóstico de depresión y ansiedad en comparación con los pacientes que no desarrollaron el evento. Los pacientes mayores de 80 años presentaron menos probabilidades de desarrollar estos trastornos. Se observaron diferencias significativas en el uso concomitante con otros tratamientos con potencial de desarrollar dependencia y abuso, como las benzodiacepinas. El riesgo aumentó con la duración del tratamiento, siendo más elevado para aquellos tratamientos que duraban 180 días o más.

Conclusiones: La incidencia de dtrastornos por el uso de fentanilo de liberación inmediata es difícil de contrastar debido a la falta de estudios similares publicados. En el ámbito extrahospitalario, puede considerarse no demasiado alta, pero con posibilidad de desarrollarse tanto en pacientes oncológicos, como no oncológicos. Estos trastornos están potencialmente asociados a períodos de uso más prolongados, pero no necesariamente a tratamientos continuos, lo que podría reflejar la presencia de episodios frecuentes de dolor irruptivo, dolor basal crónico mal controlado, trastornos psicológicos concomitantes y a una falta de conocimiento sobre el manejo del medicamento.

Keywords: **abuso, mal uso, dependencia, fentanilo, trastornos por consumo de fármacos, incidencia**

Diana González Bermejo · Pharmacoepidemiology and Pharmacovigilance Division, Medicines for Human Use Department. Spanish Agency for Medicines and Medical Devices (AEMPS). Calle Campezo 1, Edificio 8, E-28022 Madrid, Spain
dgonzalezb@aemps.es

INTRODUCTION

The increase in analgesic opioids prescription for the management of pain has been paralleled by increases in adverse outcomes associated with misuse and abuse, particularly in the United States (US)[1,2]. Opioid use has also increased over the last decade in the European Union (EU), including Spain, with fentanyl being the most frequently used substance in many countries[3-5]. In the EU, formulations of immediate release fentanyl (IRF) are exclusively approved for patients with breakthrough cancer pain (BTCP) already receiving opioid maintenance therapy for chronic cancer pain.

The Committee for Medicinal Products for Human Use of the European Medicines Agency considered that, although the use of IRF is accepted in cancer patients who have limited survival, further data were needed to support its safe use in adults with non-cancer-related pain, who have normal life expectancy and may need long-term treatment. The Committee noted that several cases of misuse or abuse of the medicine had been reported in the studies, and was concerned about the risk of addiction in non-cancer patients when using IRF in the long term[6].

IRF formulations include sublingual tablets, lozenge, buccal tablets and film and nasal sprays[7]. The rapid onset of pain (usually peaking at 3-5 min) and its spontaneous resolution (30 min) make conventional short-acting opioids, such as morphine and oxycodone, less appropriate to relieve this type of pain[8-10]. The use of rapid-onset opioids in this scenario might necessitate repeated administration or the co-administration of another opioid formulation, which might increase the risk of abuse and poisoning[11].

In Spain, prescriptions of IRF increased 53% from 2012 to 2017, being the patients without previous cancer diagnosis around 30% of incident users[12]. Few studies have investigated the extent of abuse and dependence in patients using IRF. The majority of data published in the EU are cases reports[13-21] and rarely provide data on the immediate release forms. Clinical trials do not usually consider the development of abuse in the context of opioid therapy as an outcome criterion and patients are well screened for addiction and abuse risks[22-25]. Several factors are involved in the assessment of abuse and dependence. Among them genetic predisposition, dose, personal history of alcohol or drug abuse, obesity, younger age, severe psychiatric conditions and social environment[26,27]. Although a standardized definition is lacking, we will use the definition of opioid use disorder referred to as "abuse or dependence" or "addiction"[28] being a problematic pattern of use that causes significant impairment or distress. We will apply the same definition to IRF use disorders (IRFUD hereinafter). A more comprehensive understanding of use disorders patterns may help on the treatment management.

This study evaluated the incidence of IRFUD in a cohort of IRF users, and the influence of several factors related to patient or treatment characteristics. Additionally, IRF prescribed for cancer and non-cancer patients diagnosed was also evaluated. Patients were selected from a multiregional primary care electronic healthcare record (EHR) database in Spain.

METHODS

Study design and source of data

A retrospective cohort study between 1st January 2012 to 31st December 2017 was conducted in BIFAP, an EHR database from primary care in Spain, validated through multiple studies[12] and successfully compared with other similar European databases. Over the study period, BIFAP included anonymized information from 9 million of patients from 9 regions, covering almost 20% of the Spanish population, with an average follow up of 7.2 years. Clinical events are recorded by using the International Classification of Primary Care (ICPC-2) and the International Classification of Disease (ICD-9)[29,30]. All prescriptions written by the primary care physician (PCP) are recorded including product name, quantity, dosing regimens, indication and date of prescription. Additionally, BIFAP includes results from laboratory, complementary tests and PCP´s free annotations. BIFAP has been described and reviewed in detail elsewhere[31].

Study population

Participants entered in the cohort when they met the criteria of being registered with the PCP for at least 1 year at any time in the study period, which was the entry date. Each patient was then followed from the entry date until the index date, which was considered as: a prescription of any medicine containing IRF, death, loss to follow up or end of the study period (31st December 2017). The analysis was restricted to new IRF users by excluding patients with a prescription of IRF any time before the entry date. Follow-up of each patient ended with the presence of IRFUD, end of the follow up of the patient in the database, death or end of the study period, whichever came first.

Exposure definition

Exposure to IRF was defined with the ATC code N02AB03 (see supporting information online, Table S1, pharmaceutical forms included in the study). For each patient periods of current IRF use during the follow-up were assessed. Prescription duration was calculated by using information on the prescribed number of tablets and the dosage. When information on the number of tablets and/or dosage was lacking, we imputed duration to the median of the prescription duration in BIFAP. Periods of current use were constructed according to the method of Gardarsdottir et al.[32] defining a treatment episode as a series of subsequent IRF prescriptions (independently of dose and pharmaceutical form change) considering a 30 days gap from the theoretical end date of a preceding prescription. A 30 days gap was selected based on the pharmaceutical form with the highest number of units per package and its potential off-label use for chronic pain[33]. If the gap was > 30 days, we assumed that the patient discontinued treatment until the occurrence of a new treatment episode or end of the follow up or the study period. Periods of use were further stratified according to the duration of each treatment episode (not cumulatively over follow-up) in the following cut-off points 1-30, 31-90, 91-180, >180 days.

All treatment episodes generated for each patient during the follow up were included in the analysis; additionally, in order to explore the effect of continuous use, only first treatment episode were considered.

Identification of IRFUD and validation

Like for opioid use disorders, IRFUD was defined as "abuse" or "dependence" or "addiction"[28]. Potential cases

were identified using ICPC-2 and ICD-9 recorded codes and searches in the free text comments from the clinical patient profile. Specific terms that could identify IRFUD, and therefore be used in the free text searches, were reviewed in: a) a random representative sample of 350 EHR from patients IRF prescribed; b) a published article on opioid use disorders[34] and 3) descriptors of the ICPC-2 and ICD-9 codes (PCP might include information in free text quite similar to descriptor of codes). With all this information, a third level hierarchical algorithm was considered: the first level included ICPC-2 and ICD-9 diagnosis codes (see Table S2 for ICPC-2 and ICD-9 diagnosis codes); the second level included a proximity search in which specific terms, potentially related to IRFUD ("abuse" or "dependence" or "intoxication"), had to be present in the free text but not more than three words apart from other terms such as "drugs", "opioids", "narcotics", "fentanyl" or "morphine"; the third level included remaining potential cases, in which specific terms of "abuse" or "dependence" or "intoxication" appeared in the free text but they did not meet the previous condition or additional terms were not present (see Table S2. Algorithm for IRFUD identification). The search was carried out throughout the entire period of patients follow up. Finally, all cases identified with the algorithm were manually reviewed to discriminate firstly if the cases corresponded to fentanyl or other opioids and secondly whether fentanyl was transdermal or immediate release form, as we were interested only in the last one

Statistical analysis

The baseline characteristics (demographics [sex, age]), lifestyle and comorbidities (chronic kidney disease, chronic hepatic impairment, pulmonary disease and mental disorders), were measured at any time before the index date (ICPC-2 and ICD-9 codes in Tables S3-S4 online). The incidence rate of IRFUD was calculated by dividing the total number of incident cases by the total patient-years (p-y) of exposure to IRF prescription, by adding the duration of all treatment episodes (and therefore excluding any time gaps between them for the calculation).

Cox proportional hazards models were estimated to identify factors associated to IRFUD, including the effect associated to the different categories of duration that were expressed as hazard ratios crude (HR) and adjusted (aHR) with 95% confidence intervals (CI). Since only periods of use were considered in this analysis, the first category of duration (1-30 days) was considered as the reference for the analysis of duration. Comorbidity variables were measured at baseline and as time dependent confounders and their status was updated at the start of each treatment episode. Opioid maintenance therapy and potential interacting drugs were considered as concomitant to IRF when they had at least one day of common use during the treatment episodes. Analysis was replicated until discontinuation of the first treatment episode or a record of an IRFUD whichever came first, in order to explore the effect of the continuous use on the IRFUD.

Patients were considered to have a diagnosis of cancer if a recorded code compatible with cancer was registered within a 3-month window after the index date or any time before (ICPC-2 and ICD-9 codes in Table S5 online). Cox proportional analysis were stratified according to the presence of a cancer diagnosis in the patient´s EHR.

Stata version 15 © Copyright 1996-2019 StataCorp LLC was used for all analysis.

RESULTS

Population

The study cohort consisted in 12,359 new users of IRF within the study period (Figure 1). Of them, an opioid use disorder according to the algorithm was identified in 975 cases. Out of 975 cases identified as opioid use disorder by the different levels of the algorithm, and after reviewing all the clinical record, 159 were confirmed as opioids use disorders of whom 67 were confirmed as cases of IRFUD, and 92 were excluded of the analysis as use disorders were due to opioids other than IRF. Remaining 12,200 patients did not have opioid use disorders. Of the total 12,267 patients analyzed, 84% presented only one treatment episode, 15% between two and four and 1% between five and sixteen. Median duration of treatment episodes was 30 days [Interquartil range (IQR): 10-84].

Risk factors for IRFUD. Baseline characteristics

Baseline analysis showed higher frequencies of IRFUD for smokers, patients with a history of substance abuse, non-oncology indications and patients with a diagnosis of depression or anxiety, respect to patients without IRFUD (Table 1). Significant differences were only observed for patients aged ≥ 80, being this subgroup less likely to develop IRFUD [HR 0.3 (0.1-0.9)] (Table 1).

Incidence

Overall incidence rate of IRFUD resulted in 1.8 per 100 p-y of exposure, being 1.6 per 100 p-y of exposure in patients on continuous use (Table 2).

Treatment characteristics of IRF and IRFUD. Indication

Results from table 2 suggested that the risk of IRFUD increased with duration of IRF treatment, being higher for treatments of 180 days and longer; age and sex adjustment resulted in a decrease and non-significant of risk estimates [aHR 1.9 (0.9-3.7)]. For continuous users, results do not show an increased risk with longer treatment duration [aHR 1.4 (0.6-3.1)]. Table 2 shows that patients who were on treatment with benzodiazepines, had a higher risk for IRFUD. Significant differences remained [aHR 1.9 (1.1-3.6)] when HR was adjusted according to sex and age. A higher risk for IRFUD was also observed for patients taking benzodiazepines, opioid maintenance therapy and gabapentin/pregabalin at the same time [aHR 1.9 (1.2-3.1)]. When IRFUD were analyzed only in periods of continuous use, results suggested similar results, although not statistically significant.

According to our definition, 73% of patients presented an indication compatible with cancer. Of the 67 IRFUD cases, 35 (52.2%) had a register of an oncology indication. The incidence rate of IRFUD in cancer patients was 1.6 per 100 p-y of exposure. Among non-oncology patients, incidence was 2.1 per 100 p-y of exposure (results obtained from Table 3 and Table 4).

Characteristics of those IRFUD diagnosed did not differ significantly when analysis were stratified by indication (Table 3 and Table 4).

DISCUSSION

Disorders such as abuse/dependence related to use of inmediate release fentanyl decreased in the elderly, and were associated to depression and anxiety at baseline, and the concomitant use of other treatments with potential for dependence and abuse such as benzodiazepines.

Incidence of IRFUD in new users was found to be 1.8 per 100 p-y which a priory is difficult to compare due to the lack of studies and a clear definition. Results suggested that the risk increases with longer treatment duration, being significantly increased with discontinuous use, which might reflect the presence of frequent episodes of BTCP, uncontrolled background pain, concomitant psychological distress or misunderstanding about the usage of the product.

The assessment of IRFUD raises a challenge. Definitions of addiction, dependence and related events are not clearly defined for opioid use disorders[35]. Definitions are made ad hoc for studies or in ways that overlap with other terms such as misuse or derive largely from experience with illicit drug uses[34]. In this sense we applied the same definition than for opioid use disorders as "abuse" or "dependence" or "addiction", representing a problematic pattern of use that causes significant impairment or distress[28].

Related to potential risk factors for IRFUD, opioids are known to have mood-altering properties that may prompt aberrant behaviors in depressed patients. Depressed patients may experience their pain as more severe, which may prompt misuse[36]. In our study depression and/or anxiety at baseline were observed in 71% of patients who developed IRFUD with respect to 46% in patients without use disorders (Table 2).

An increased risk of overdose in patients taking opioids and benzodiazepines at the same time has been described[37]; in our study concomitant use was observed in 80% of patients with IRFUD , being such concomitant use 52% in patients without IRFUD (6.344/12.200; data not shown, extracted from Table 2). Additionally, a higher proportion of patients developing IRFUD were prescribed other drug-induced abuse such as gabapentin/pregabalin when compared to patients with non-IRFUD.

Our results support an increased risk of IRFUD for substance abusers. There is evidence implicating opioids, alcohol and many substances in the endogenous processes of reward and reinforcement, leading to the acquisition of the drug seeking behavior[38]. These substance may also increase pain perception and lead to clinical symptoms producing signs that may be interpreted as increased pain levels (e.g. tachycardia and anxiety after alcohol and opioids withdrawal)[39].

Studies focusing on incidence of IRFUD are scarce and heterogeneous in study designs, method of assessment and clinical setting, which makes comparisons difficult. Furthermore, sometimes use disorders are underreported or improperly registered in the EHR and demographic and pain-related characteristics are usually missing.

Two studies of opioids prescription analyzed IRF separately. One of them reported 8% of frequency of aberrant behaviors (problematic prescription drug use which may derive in intentional misuse) during treatment with fentanyl buccal tablets in patients with chronic non-cancer pain[40]. An US study interviewed patients entering treatment for substance use disorders estimating a risk of IRF abuse of 0.0114 per 100,000 prescriptions (of note, it was higher than transdermal fentanyl, 0.0063)[20,41]. Reviews have estimated the frequency of opioid use disorders from <1% to 80%[42,43]. The majority of studies were performed in the US. Incidence estimated in our study for IRF is in the low end of the range.

As already mentioned, extensive literature has been published reporting opioid illicit use of this drug, but data in a clinical context are scarce. This study adds estimates in a clinical setting. Despite incidence cannot be considered higher; our study shows that it is possible even in a controlled setting.

Our data also show that the risk of IRFUD increased after 180 days of follow up and not necessarily associated to a continuous IRF use. To our knowledge, there are no additional studies on IRFUD providing data on the influence of treatment characteristics and duration. This information could help to better understand factors that may be involved in the development of use disorders.

Features of cancer pain management should also be addressed. BTCP has a time profile that is different from chronic persistent pain and thus should be managed differently[44] Notwithstanding IRF use in acute pain and off-label license should be avoided, we found that 48% (data extracted from table 4) of IRF users developing disorders did not present a cancer diagnosis registered in their complete clinical record. The development of opioid tolerance in patients with cancer is controversial in clinical practice, owing to the frequent inability to distinguish increasing opioid requirements because of disease progression from the pharmacological tolerance or opioid-associated hyperalgesia[45]. Other factors such as dosing adjustment of opioid maintenance therapy, IRF titration and opioid rotation should be addressed by specialized care centers, since patients may exhibit IRFUD because of inadequate pain relief[46-50].

One of the strengths of this study is the novelty of studying use disorders from prescribed IRF in clinical data and not under illicit use or chronic pain. In addition, this study includes information on treatment duration pattern and potential factors influencing use disorder appearance.

Specific limitations must be considered. Prescriptions in private centers, hospitals or specialist were not included, although the risk of bias is expected to be minimal given the large coverage of the NHS. Normally the specialist makes the first prescription and the patient is then followed by PCP and therefore captured in BIFAP. Prescribed medications might not be consumed, however, since indication is secondary pain, non adherence is expected to be low. Underreporting of cancer in EHRs like BIFAP cannot be ruled out, however considering the clinical implications of the diseases underreporting is not expected.

A broad searching including free text and a proactive search with a manually in-depth review of the clinical records were performed, which increases case validity. However, some underreporting cannot be ruled out and information from other data sources, such as specific registries in centers dealing with methadone programs or opioid dishabituation should be explored. Present results should therefore not be generalized beyond the population attended in primary care. The low numbers must be taken into account in interpreting the results making difficult further stratification analysis, and therefore results should be considered with caution.

Table 1. Characteristics of patients with IRFUD

	New IRF users n (%)	Patients with IRFUD n (%)	Patients without IRFUD n (%)	HR (95% CI) (with IRFUD vs without IRFUD)
Total	12267	67	12200	
Sex				
Female	5783 (47.1)	33 (49.2)	5750 (47.1)	ref.
Male	6484 (52.9)	34 (50.7)	6450 (52.9)	0.6 (0.3-1.2)
Age				
<40	427 (3.5)	11 (16.4)	416 (3.4)	ref.
40-49	950 (7.7)	11 (16.4)	929 (7.6)	0.4 (0.1-1.4)
50-59	2100 (17.1)	15 (22.4)	2085 (17.1)	0.4 (0.2-1.5)
60-69	2791 (22.8)	13 (19.4)	2778 (22.8)	0.5 (0.2-1.4)
70-79	2939 (24.0)	10 (14.9)	2929 (24.0)	0.3 (0.1-1.1)
≥80	3070 (25.0)	7 (10.4)	3063 (25.1)	0.3 (0.1-0.9)
Lifestyle BMI (kg/m2)				
Underweight (<18.5)	165 (1.4)	1 (1.5)	164 (1.3)	1.1 (0.1-8.9)
Normal weight (18.5-24.9)	2378 (19.4)	15(22.4)	2363 (19.4)	ref.
Overweight (25-29.9)	3508 (28.6)	16 (23.9)	3492 (28.6)	0.5 (0.2-1.4)
Obese (≥30)	2890 (23.6)	18 (26.9)	2872 (23.5)	1.1 (0.5-2.4)
Missing values	3326 (27.1)	17 (2.5)	3309 (27.1)	0.7 (0.3-1.6)
Non-smoker	3876 (31.6)	15 (22.4)	3861 (31.6)	ref.
Smoker	3008 (24.5)	31 (46.3)	2977 (24.4)	1.4 (0.8-2.6)
Missing values	5383 (43.9)	21 (31.3)	5362 (43.9)	0.8 (0.4-1.8)
Non-alcohol consumer	3800 (31.0)	32 (47.8)	3768 (30.9)	ref.
Alcohol consumer	6805 (55.5)	15(22.4)	6790 (55.7)	0.8 (0.4-1.7)
Missing values	4836 (39.4)	20 (29.8)	4816 (39.5)	0.5 (0.2-1.1)
Alcohol dependent	1353 (11.1)	4 (6.0)	1349 (11.0)	0.2 (0.1-1.6)
Substances abuse[a]	1430 (11.7)	15 (22.4)	1415 (11.6)	1.7 (0.8-3.7)
Indication for IRF use				
Oncology indication	8980 (73.2)	35 (52.2)	8945 (73.3)	0.7 (0.4-1.3)
Comorbidities				
Chronic kidney disease	1364 (11.1)	2 (3.0)	1362 (11.2)	0.4 (0.1-1.8)
Chronic Hepatic impairment	476 (3.9)	1 (1.5)	475 (3.9)	-
COPD, pulmonary hypertension, embolism	1985 (16.2)	10 (14.9)	1975 (16.2)	0.9 (0.4-2.2)
Mental disorders				
Psycosis[b]	249 (2.0)	2 (3.0)	247 (2.2)	-
Drug-induced psycosis	6 (0.0)	-	6 (0)	-
Alcohol-induced psycosis	22 (0.2)	-	22 (0.2)	-
Suicide[c]	47 (0.4)	1 (1.5)	47 (0.4)	-
Personality disorders	32 (0.3)	-	32 (0.3)	-
Eating behavior disorders	42 (0.3)	-	42 (0.3)	-
ADHD[d]	46 (0.4)	-	46 (0.4)	-
Depression and anxiety[e]	5657 (46.1)	48 (71.6)	5609 (46.0)	1.7 (0.9-3.3)
Stress	687 (5.6)	4 (6.0)	683 (5.6)	1.5 (0.5-4.3)
Alzheimer and Dementia	354 (2.9)	1 (1.5)	353 (2.9)	0.9 (0.1-6.7)
Sleep disorders	3228 (26.3)	16 (23.9)	3212 (26.3)	0.6 (0.3-1.4)
Patients with at least 1 mental disorder	7531 (61.4)	54 (80.6)	7477 (61.3)	1.9 (0.9-4.2)

Abbreviations: n: number of patients; %: percentage based on column total; IRF: immediate release fentanyl; IRFUD: immediate release fentanyl use disorder; HR: hazard ratio; CI: confidence interval; COPD: chronic pulmonary obstructive disease; ADHD: Attention deficit and hyperactivity disorder;

[a]Substances abuse: analgesic, benzodiazepines, opioids, nicotine, illicit drugs and other medicines and substances in general terms are included.

[b]Psycosis: schizophrenia, affective psychosis, childhood psychosis, bipolar disorder, puerperal psychosis, organic psychosis, other non-organic psychosis and delusional disorders are included.

[c]Suicide: suicide attempt and ideation are included.

[d]ADHD: patients diagnosed by codes or prescribed methylfenidate, atomoxetine, dexmetilphenidate are included.

[e]Depression and anxiety: patients diagnosed by codes or prescribed selective serotonin reuptake inhibitors and selective norepinephrine reuptake inhibitors drugs are included.

Table 2. Risk of IRFUD according to type of IRF treatment, duration and concomitant/interacting drugs

	All IRFUD (continuous and non-continuous treatment)				Continuous treatment			
	IRFUD cases N (%)	Total person-years	Crude HR (95% CI)	Adjusted[a] HR (95% CI)	IRFUD cases N (%)	Total person-years	Crude HR (95% CI)	Adjusted[a] HR (95% CI)
Total	67	3668.5			42	2648.1		
Treatment duration (days)								
<=30	11 (16.4)	923.2	ref.	ref.	9 (21.4)	722.2	ref.	ref.
31-90	11 (16.4)	920.1	1.0 (0.4-2.2)	0.9 (0.4-2.2)	8 (19.0)	689.9	0.9 (0.4-2.4)	0.9 (0.3-2.3)
91-180	10 (14.9)	619.1	1.3 (0.5-3.0)	1.2 (0.5-2.8)	8 (19.0)	437.6	1.4 (0.5-3.7)	1.4 (0.5-3.5)
>180	35 (52.2)	1206.2	**2.2 (1.1-4.3)**	1.9 (0.9-3.7)	17 (40.5)	799.3	1.4 (0.7-3.4)	1.4 (0.6-3.1)
Concomitant medication								
OMT[b]	58 (86.6)	3272.4	0.8 (0.4-1.6)	0.9 (0.1-6.8)	36 (85.7)	2374.0	0.7 (0.3-1.7)	0.7 (0.3-1.7)
Interacting drugs								
Benzodiazepines	54 (80.6)	2467.6	**2.0 (1.1-3.7)**	**1.9 (1.1-3.6)**	33 (78.6)	1733.4	1.9 (0.9-4.0)	1.8 (0.9-3.8)
SSRIs	11 (16.4)	697.1	0.8 (0.4-1.6)	0.8 (0.4-1.5)	8 (19.0)	492.0	1.0 (0.4-2.2)	0.9 (0.4-2.0)
SNRIs	37 (55.2)	1476.5	**1.8 (1.1-2.9)**	**1.7 (1.0-2.7)**	20 (47.6)	992.8	1.5 (0.8-2.8)	1.5 (0.8-2.7)
Gabapentin/Pregabalin	37 (55.2)	1612.2	1.5 (0.9-2.5)	1.4 (0.8-2.3)	21 (50)	1089.9	1.4 (0.8-2.6)	1.4 (0.7-2.5)
CYP3A4 inhibitors[d]	26 (38.8)	1273.8	1.2 (0.7-1.9)	1.2 (0.7-2.0)	18 (42.8)	903.6	1.5 (0.8-2.7)	1.5 (0.8-2.7)
Benzodiazepines and OMT[b] and Gabapentin/ Pregabalin at the same time	31 (46.2)	1077.7	**2.1 (1.3-3.4)**	**1.9 (1.2-3.1)**	17 (40.5)	2648.1	1.8 (0.9-3.4)	1.7 (0.9-3.1)
Contraindicated drugs								
MAOI	-	12.2	-	-	-	4.9	-	-

Table 3. Risk of IRFUD according to type of IRF treatment, duration and concomitant/interacting drugs in patients with an oncology indication

	All IRFUD (continuous and non-continuous treatment)				Continuous treatment			
	IRFUD cases N (%)	Total person-years	Crude HR (95% CI)	Adjusted[a] HR (95% CI)	IRFUD cases N (%)	Total person-years	Crude HR (95% CI)	Adjusted[a] HR (95% CI)
Total	35	2155.1			23	1658.7		
Treatment duration (days)								
<=30	7 (20.0)	647.8	ref.	ref.	6 (26.1)	533.4	ref.	ref.
31-90	8 (22.9)	632.3	1.1 (0.4-3.1)	1.1 (0.4-3.1)	5 (21.7)	504.3	0.9 (0.3-2.8)	0.9 (0.3-2.9)
91-180	6 (17.1)	381.1	1.3 (0.4-3.9)	1.3 (0.4-3.9)	6 (26.1)	288.2	1.7 (0.5-5.3)	1.7 (0.5-5.3)
>180	14 (40.0)	493.9	2.2 (0.9-5.6)	2.2 (0.9-5.5)	6 (26.1)	332.8	1.4 (0.4-4.3)	1.4 (0.4-4.3)
Concomitant medication								
OMT[b]	30 (85.7)	1985,6	0.5 (0.2-1.3)	0.5 (0.2-1.3)	20 (86.9)	1538.5	0.5 (0.2-1.8)	0.5 (0.1-1.7)
Interacting drugs								
Benzodiazepines	28 (80.0)	1410,5	2.1 (0.9-4.8)	2.1 (0.9-4.8)	19 (82.6)	1065.4	2.6 (0.9-7.7)	2.5 (0.8-7.4)
SSRIs	6 (17.1)	1410,5	1.0 (0.4-2.4)	1.0 (0.4-2.5)	4 (17.4)	263.5	1.1 (0.4-3.3)	1.1 (0.4-3.2)
SNRIs	15 (42.9)	711,0	1.5 (0.8-3.0)	1.6 (0.8-3.0)	10 (43.5)	525.8	1.1 (0.4-3.3)	1.7 (0.7-3.8)
Gabapentin/Pregabalin	17 (48.6)	817,7	1.5 (0.8-2.9)	1.4 (0.8-2.9)	11 (47.8)	584.5	1.7 (0.7-3.8)	1.7 (0.7-3.9)
CYP3A4 inhibitors[d]	11 (31.4)	667,9	1.0 (0.5-2.0)	0.9 (0.5-2.0)	6 (26.1)	502.9	0.8 (0.3-2.0)	0.8 (0.3-2.0)
Benzodiazepines and OMT[b] and Gabapentin/ Pregabalin at the same time	13 (37.1)	562,0	1.7 (0.9-3.3)	1.6 (0.8-3.2)	8 (34.8)	400.2	1.7 (0.7-4.0)	1.7 (0.7-4.0)
Contraindicated drugs								
MAOI	-	4.1	-	-	-	1.5	-	-

Table 4. Risk of IRFUD according to type of IRF treatment, duration and concomitant/interacting drugs in patients without oncology indication

	All IRFUD (continuous and non-continuous treatment)				Continuous treatment			
	IRFUD cases N (%)	Total person-years	Crude HR (95% CI)	Adjusted[a] HR (95% CI)	IRFUD cases N (%)	Total person-years	Crude HR (95% CI)	Adjusted[a] HR (95% CI)
Total	32	1513.5			19	989.4		
Treatment duration (days)								
<=30	4 (12.5)	275.4	ref.	ref.	3	188.8	ref.	ref.
31-90	3 (9.3)	287.8	0.7 (0.2-3.1)	0.7 (0.1-2.9)	3	184.7	0.9 (0.2-4.4)	0.8 (0.2-4.2)
91-180	4 (12.5)	238.0	1.1 (0.3-4.5)	1.0 (0.2-4.0)	2	149.4	0.8 (0.1-4.6)	0.7 (0.1-4.2)
>180	21 (65.7)	712.3	1.9 (0.6-5.6)	1.6 (0.5-4.7)	11	466.5	1.2 (0.3-4.3)	1.1 (0.3-4.0)
Concomitant medication								
OMT[b]	30 (85.7)	1985,6	0.5 (0.2-1.3)	0.5 (0.2-1.3)	16	835.6	0.9 (0.3-3.4)	1.0 (0.3-3.5)
Interacting drugs								
Benzodiazepines	28 (80.0)	1410,5	2.1 (0.9-4.8)	2.1 (0.9-4.8)	14	668.0	1.3 (0.5-3.6)	1.3 (0.5-3.6)
SSRIs	6 (17.1)	1410,5	1.0 (0.4-2.4)	1.0 (0.4-2.5)	4	228.6	0.8 (0.3-2.6)	0.8 (0.3-2.4)
SNRIs	15 (42.9)	711,0	1.5 (0.8-3.0)	1.6 (0.8-3.0)	10	467.0	1.2 (0.5-3.0)	1.1 (0.5-2.8)
Gabapentin/Pregabalin	17 (48.6)	817,7	1.5 (0.8-2.9)	1.4 (0.8-2.9)	10	505.4	1.1 (0.4-2.6)	2.7 (1.0-6.8)
CYP3A4 inhibitors[d]	11 (31.4)	667,9	1.0 (0.5-2.0)	0.9 (0.5-2.0)	12	400.8	2.4 (0.9-6.1)	0.9 (0.4-2.4)
Benzodiazepines and OMT[b] and Gabapentin/ Pregabalin at the same time	13 (37.1)	562,0	1.7 (0.9-3.3)	1.6 (0.8-3.2)	9	329.0	1.8 (0.7-4.4)	1.7 (0.7-4.1)
Contraindicated drugs								
MAOI	-	4.1	-	-	-	3.5	-	-

Abbreviations: n: number of patients; %: percentage based on total column; IRF: immediate release fentanyl; IRFUD: immediate release fentanyl use disorder; HR: hazard ratio; CI: confident intervals; OMT: opioids maintenance therapy; SSRIs: selective serotonin reuptake inhibitors SNRIs: serotonin norepinephrine reuptake inhibitors MAOI: monoamine oxidase inhibitors.

[a]Adjusted by sex and age

[b]Opioids maintenance therapy: morphine (oral), fentanyl (transdermal), oxycodone (oral), hydromorphone (oral), tapentadol are included.

[c]Patients might be prescribed more than one interacting drugs.

[d]CYP3A4 inhibitors: macrolide antibiotics, antifungals, verapamil, diltiazem, antituberculosis drugs, valproate, amiodarone, ticagrelor, metronidazole, and quinolones are included.

CONCLUSION

Our data yield incidence of IRF use diseases which is difficult to compare due to differences in studies methodologies and a lack of an uniform definition. Risk of IRF use disorders appear to increases with longer duration of use and not necessarily in continuous use, probably indicating the presence of frequent episodes of BTCP, uncontrolled background pain, concomitant psychological distress, misunderstanding about the usage of the product or irregular use. Concomitant drugs with potential for dependence and abuse such as benzodiazepines, are also associated to the development of such disorders. All these factors should be taken into account to potentially prevent use disorders in patients treated with IRF.

DECLARATIONS

Ethical approval

The scientific committee of BIFAP and the regional IRB from Madrid, granted a positive opinion to the study protocol (ref. 01/2019 and AEMFEN-2020-01 respectively).

Consent to participate

The investigators had access to only fully anonymized data. The information contained in BIFAP is anonymous due to a computer process of dissociation of the identity of the patient and the doctor (double dissociation).

Consent to publish

The content of the manuscript is original and that it has not been published or accepted for publication, either in whole or in part, other than on a preprint server, as a short abstract, communication or conference proceeding. No part of the manuscript is currently under consideration for publication elsewhere.

All authors have seen and approved the final version of the submitted paper.

Competing interest

The authors have no conflicts of interest to declare

Authors contribution

All authors:

1) Have made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data;

2) Been involved in drafting the manuscript or revising it critically for important intellectual content;

3) Given final approval of the version to be published. Each author has participated sufficiently in the work to take public responsibility for appropriate portions of the content; and

4) Agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Funding

Not applicable

Availability of data and materials:

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Disclaimer:

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