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A population-based study of transdermal fentanyl initiation in Australian clinical practice

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Abstract

Purpose—Although guidelines caution against initiation of transdermal (TD) fentanyl among those who are opioid naïve, there is concern that not all people receive adequate prior opioid exposure. This study examined the percentage of people who are opioid naïve at the time of TD fentanyl initiation in Australia; strengths initiated; and characteristics associated with being opioid naïve.

Methods—This is a national retrospective cohort study derived from a 10% sample of Pharmaceutical Benefits Scheme concessional beneficiaries initiating TD fentanyl between 29 September 2009–31 December 2013. Individuals were deemed opioid naïve if they had no opioid dispensings in the previous 90 days. Logistic regression was used to determine characteristics associated with being opioid naïve, including socio-demographics, likely comorbidities and previous analgesic use.

Results—A total of 13,166 people initiated TD fentanyl; 60.4% were female and 76.2% were aged ≥ 65 years. Three in ten (30.4%) were opioid naïve and 63.2% initiated the 12 mcg/h patch. Those who were opioid naïve were more likely to be female (adjusted odds ratio (aOR) 1.35; 95% CI 1.25–1.46), older (aOR 1.85; 95% CI 1.54–2.28 for those ≥ 85 years) and previously dispensed medicines for dementia (aOR 1.37; 95% CI 1.04–1.80). People previously dispensed medicines for cancer were less likely to be opioid naïve (aOR 0.57; 95% CI 0.48–0.67).

Conclusions—Three in ten Australians initiating TD fentanyl are opioid naïve. Our findings suggest that specific patient subpopulations already at increased risk of opioid-related adverse

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Author contributions NG conceived the idea, undertook the analysis and wrote the first draft of the manuscript. All other authors (SAP, LD, BL, SL, BB) were involved in the conceptualisation of the study from which this data was drawn, assisted in data interpretation and critically revised drafts of the manuscript. All authors approved the final manuscript prior to submission.

Compliance with ethical standards

Competing interests LD and BL have received untied educational grants from Reckitt Benckiser, Mundipharma and Seqirus to conduct post-marketing surveillance of new opioid medications in Australia. LD, BL and SL have also received untied educational grants from Indivior. No company had any knowledge or involvement in this study.

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events are not receiving prior opioid treatment before initiation, highlighting the need for greater adherence to current treatment guidelines.

Keywords

(MeSH): Analgesics; Drug utilization; Fentanyl; Opioids; Pain; Pharmacoepidemiology

Introduction

Fentanyl is a potent opioid widely used across many clinical settings to manage acute and chronic pain [1]. Transdermal (TD) patch preparations account for the majority of fentanyl consumption globally [2], and are used clinically for the treatment of severe chronic cancer or non-cancer pain [1]. However, safety concerns regarding TD fentanyl initiation have been raised in several countries due to increasing reports of preventable adverse events resulting from inappropriate prescribing and incorrect use by patients [3]. In the USA, the Food and Drug Administration issued safety warnings in 2005 and 2007 emphasising the appropriate use of fentanyl patches, including correct application instructions for patients and the need for opioid tolerance to be established prior to initiation [4]. Similar safety alerts have since been issued by various agencies in Europe [5] and Australia, including the New South Wales (NSW) Therapeutic Advisory Group [6].

National and international treatment guidelines recommend avoiding initiation of TD fentanyl in opioid-naïve patients (i.e. those without prior opioid exposure) unless in monitored clinical settings [7, 8]. This is due to the risk of excessive sedation and respiratory depression. However, substantial practice and knowledge gaps are evident with prescribing opioids for chronic non-cancer pain (CNCP), particularly in relation to the prescribing of TD fentanyl in opioid naïve patients [9]. Moreover, there appears to be a large variation in practices between countries. Earlier studies have shown that 40% of individuals in the Netherlands have not used other opioids prior to commencing TD fentanyl [10], while 85% of individuals commencing TD fentanyl in Germany had no evidence of prior exposure to high-potency opioids [5]. In Canada, almost 75% of TD fentanyl initiations were considered 'unsafe' on the basis of inadequate opioid tolerance and older adults were more frequently opioid naïve [11]. Meanwhile in the USA, 52% of long-stay nursing home residents were deemed to be opioid naïve at the time of fentanyl initiation [12].

Although guidelines specify the importance of establishing opioid tolerance prior to TD fentanyl initiation [7, 8], fentanyl patches are currently subsidised on Australia's national medicines subsidy program (the Pharmaceutical Benefits Scheme (PBS)), for chronic, severe disabling pain that has previously been unresponsive to non-opioid analgesics [13]. Findings from an Australian cohort study of people with chronic non-cancer pain (CNCP) in the community indicate that about 14.5% of people use fentanyl [14]. Overall, rates of fentanyl use are highest among older adults [15, 16], with almost half of all use between 2009 and 2014 accounted for by people aged 70 years and over [16]. With the exception of one study among residential aged care facilities in NSW [17], data on the safety of TD fentanyl use in the wider Australian population are limited. Hence, the overall aim of this study was to examine the nature of TD fentanyl initiation in Australian clinical practice. The specific

objectives were to: determine the percentage of people that are opioid naïve at the time of TD fentanyl initiation; examine the strengths initiated; and determine the characteristics associated with being opioid naïve.

Methods

Study design

This is a secondary analysis of data from a nationally representative cohort study of people who initiated a strong prescription opioid analgesic in Australia between 29 September 2009 and 31 December 2013 [18, 19].

Setting

The PBS is a national government-funded system that allows eligible Australian citizens and permanent residents to access prescription medicines. Under this scheme, the federal government subsidises the cost of a range of prescription medicines that are dispensed in approved community pharmacies, private hospitals and some public hospitals. During the study period, the PBS dataset captured all original and repeat dispensings for PBS-listed medicines attracting a government subsidy, which occurs when the price of a medicine is above the set PBS copayment threshold [20]. Each year the government sets two PBS co-payment thresholds: a general co-payment amount [e.g. 32.90 AUD (2009)-36.10 AUD (2013)] and a concessional (reduced) co-payment amount [e.g. 5.30 AUD (2009)-5.90 AUD (2013)]. Consequently, only concessional beneficiaries, who account for approximately 25% of Australians [21], had complete ascertainment of their PBS records as all PBS medicines cost more than their co-payment threshold. This concession is available to individuals who receive a low household income and are entitled to government benefits (e.g. senior citizens and those who are un-employed or unable to work due to chronic illness or disability).

Data source

The Department of Human Services extracted de-identified dispensing records for a randomly-selected 10% sample of individuals initiating a strong PBS-listed opioid between 29 September 2009 and 31 December 2013 in accordance with an approved data request ($n = 143,681$) [18]. All individuals were aged at least 18 years at the time of their initial strong opioid dispensing and had no previous strong opioid dispensing in the 90 days prior to their initial dispensing date. The 90-day opioid-free window was selected on the basis of findings from sensitivity analyses examining the optimal window to apply to the dataset provided [18]. Basic socio-demographic information for the cohort, as well as all dispensing records of subsidised opioid and non-opioid medicines, were provided.

Opioids were classified as either strong or weaker in accordance with the World Health Organization's pain management plan, i.e. strong opioids are those which are indicated for moderate-severe pain (e.g. [22]). Included opioids and corresponding Anatomical Therapeutic Classification (ATC) codes are listed in Appendix, Table A1.

Study cohort

Applying the 90-day opioid-free window to TD fentanyl preparations only, a subset of individuals from the larger population who initiated TD fentanyl was identified. To obtain complete capture of dispensing records, the cohort was restricted to individuals who were concessional beneficiaries for the 90 days up to and including the date of TD fentanyl initiation ($n = 13,288$).

Covariates

Socio-demographic characteristics—Data based on the 2007 Statistical Local Area (SLA) of each individual's last recorded address was used to determine the socio-demographic characteristics of each individual's area of residence and remoteness classification. SLAs were linked to the Australian Bureau of Statistics 2011 Remoteness Areas classification system. Areas are defined as *Major Cities*, *Inner Regional*, *Outer Regional*, *Remote* or *Very Remote* according to the distance required to travel to access different services [23]. Where SLAs covered multiple remoteness areas, remoteness was defined by the category which represented the majority of the SLA. SLA data were also linked to the 2006 Index of Relative Socio-economic Disadvantage which represents the economic and social resources of people and households within an SLA (e.g. low income, low education, high unemployment). Each SLA is ranked into deciles on the basis of their relative lack of disadvantage (i.e. lower deciles indicate greater disadvantage) [24], which were then collapsed into quintiles.

Opioid and non-opioid analgesic use prior to TD fentanyl initiation—To establish whether individuals were opioid naïve (i.e. had no evidence of previous opioid exposure) or were opioid exposed at the time of TD fentanyl initiation, use of any strong or weaker opioids in the 90 days up to and including the date of dispensing was evaluated. In light of current PBS restrictions for the subsidy of TD fentanyl [13], prior use of non-opioid analgesics (listed in Appendix, Table A1) was also examined over the same period.

Medical conditions and co-morbidities—As indications for use are not included in PBS records, an adaptation of the RxRisk-V classification tool was used to identify treatment for specific medical conditions in the 90 days up to and including TD fentanyl initiation. The RxRisk-V tool uses data from records of dispensed medicines to identify existing medical conditions from 43 ATC code groupings and has previously been validated in the Australian setting [25]. The tool was subsequently modified to include newly registered medicines (Appendix, Table A2).

Statistical analyses

All analyses were conducted using SAS Enterprise Guide 5.3 (SAS Institute Inc., Cary, NC, USA). Logistic regression was used to calculate unadjusted and adjusted odds ratios (aORs) and 95% confidence intervals (95% CI) to determine characteristics associated with being opioid naïve. Records were excluded for 122 individuals with missing data on socioeconomic status and/or residence level of remoteness. The multi-variable model was adjusted for sex, age, initiation on the 12 mcg/h patch, prior use of non-opioid analgesics, and medical conditions significant at the $p < 0.05$ level in the univariate analysis.

Ethical review

The protocol for this study was approved by the NSW Population and Health Services Research Ethics Committee (2013/10/481) and the Department of Human Services External Review Evaluation Committee (MI0166).

Results

Cohort demographics

A total of 13,166 people initiated TD fentanyl over the study period, with 30.4% ($n = 4006$) identified as being opioid naïve (Table 1). More than half of the cohort was female ($n = 7946$; 60.4%) and residing in a major city ($n = 7941$; 60.3%). Three quarters were aged 65 years with 52.8% ($n = 6945$) between 65 and 84 years and 23.5% ($n = 3087$) 85 years. Overall, 96.2% ($n = 12,678$) had evidence of at least one other medical condition besides pain, with 74.9% ($n = 9856$) dispensed a medicine for a circulatory system disease, 55.7% ($n = 7330$) a digestive system disease and 50.6% ($n = 6660$) a mental and behavioural disorder, primarily depression ($n = 4970$; 37.8%).

Fentanyl patch strengths initiated

The median patch strength initiated was 12 mcg/h (interquartile range 12–25), representing the lowest patch strength available in Australia over the study period. Overall, 63.2% ($n = 8319$) of individuals initiated on the 12 mcg/h strength, followed by 25.1% ($n = 3306$) on the 25 mcg/h and 6.9% ($n = 904$) on the 50 mcg/h strength (Table 2).

Opioid and non-opioid analgesic use prior to TD fentanyl initiation

The majority of the cohort ($n = 11,464$; 87.1%) had evidence of a dispensing for any analgesic in the 90-day period prior to TD fentanyl initiation; 60.9% ($n = 8017$) were dispensed a non-opioid analgesic and 69.5% ($n = 9160$) were dispensed an opioid (Table 2). Less than one-fifth of the cohort ($n = 2304$; 17.5%) were only dispensed non-opioid analgesics prior to TD fentanyl initiation. Overall, half of those who were opioid naïve at the time of TD fentanyl initiation had evidence of prior non-opioid analgesic use ($n = 2304$; 57.5%), mostly paracetamol ($n = 1186$; 47.1%). Weaker opioids were dispensed to 31.5% ($n = 4148$) of the cohort and strong opioids to 55.3% ($n = 7286$). The opioids most commonly dispensed were oxycodone preparations ($n = 4986$, 37.9%), paracetamol/codeine combinations ($n = 2708$; 20.6%) and buprenorphine ($n = 2535$; 19.3%).

Characteristics associated with being opioid naïve

In the adjusted analysis, females were 1.35 (95% CI 1.25–1.46) times more likely to be opioid naïve compared to males (Table 3). Compared to those aged 18–44 years, individuals aged 65–84 years were 1.65 (95% CI 1.37–1.99) times more likely to be opioid naïve, while those aged 85 years were 1.88 (95% CI 1.54–2.28) times more likely to be opioid naïve. Individuals dispensed the 12 mcg/h patch strength were 1.56 (95% CI 1.44–1.69) times more likely to be opioid naïve.

Individuals dispensed medicines to treat cancer were 0.57 (95% CI 0.48–0.66) times less likely to be opioid naïve and those dispensed medicines for digestive system diseases were

0.79 (95% CI 0.73–0.86) times less likely to be opioid naïve. Although most mental and behavioural disorders were associated with a lower likelihood of being opioid naïve, those dispensed medicines for dementia were 1.37 times more likely to be opioid naïve (95% CI 1.04–1.80).

Discussion

There is ongoing concern about the safety and appropriateness of fentanyl use both internationally and in the Australian community. The findings from this study therefore provide a timely insight into the manner in which TD fentanyl is initiated in Australian clinical practice. As recommended by treatment guidelines, [7], initiation on 12 mcg/h preparations (i.e. the lowest strength available) was most common. However, the finding that almost one-third of individuals initiating TD fentanyl appear to be opioid naïve highlights potential safety concerns. Similarly, a previous Australian study among residential aged care facilities in NSW deemed that 34% of residents initiating TD fentanyl were opioid naïve [17]. Encouragingly, the proportion of people who are opioid naïve at the time of TD fentanyl initiation in Australia is substantially lower than in treatment settings across Europe [5, 10], Canada [11] and the USA [12].

Among those who were opioid naïve prior to TD fentanyl initiation, 58% had evidence of previous non-opioid analgesic use. It is important to note that although treatment guidelines reinforce the need for opioid tolerance prior to TD fentanyl initiation [7], this is not reflected in PBS subsidy restrictions on the use of fentanyl patches. As with other strong opioids, TD fentanyl is currently listed on the PBS for use in chronic severe disabling pain that has previously been unresponsive to non-opioid analgesics [13]. As such, there is no explicit reference to the need for opioid tolerance to be established, which may contribute to clinicians prescribing TD fentanyl to patients without adequate previous opioid exposure. Updating the PBS listing for fentanyl patch preparations is therefore one potential strategy that can be implemented to improve the safety of TD fentanyl initiation.

Individuals without a history of cancer were more likely to be opioid-naïve at the time of TD fentanyl initiation. This is consistent with the high prevalence of CNCP in the Australian community [26], and an increasing tendency for CNCP to be managed with strong opioids [27]. TD fentanyl is generally considered a second-line agent in the management of CNCP [7,28], with Canadian guidelines further emphasising that of all opioids, codeine use alone is insufficient to establish opioid tolerance [28]. Opioid overdose risk is noted to be highest within the first week after opioid initiation [29], and although fentanyl-related mortality accounts for relatively fewer opioid-related deaths overall, the rising trend in fentanyl mortality rates in Australia over the last 12 years remains a concern [30].

Being female, of older age and having a history of dementia were all independently associated with being opioid naïve at the time of TD fentanyl initiation. These findings are consistent with data from Canada where females and older adults were also more likely to have inadequate opioid tolerance prior to initiation of TD fentanyl [11]. Similarly, in the USA, nursing home residents who were female, older and diagnosed with dementia were also more likely to be opioid naïve at the time of initiation of long-acting opioids [31].

Under-treatment of pain is common among people with dementia [32], and TD fentanyl offers a convenient and long-acting dose form for patients unable to tolerate oral formulations and who have difficulties managing medicines. However, older adults are also more susceptible to experiencing opioid-related adverse events due to a range of age-related changes in pharmacokinetics and pharmacodynamics [22, 33], including a decline in central nervous system function resulting in heightened central nervous system sensitivity. These risks are further heightened among those without adequate opioid tolerance. Therefore, where possible, clinicians are encouraged to ensure that adequate opioid tolerance is achieved prior to TD fentanyl initiation and to consider other treatment alternatives. TD buprenorphine for example, offers a better safety profile for older adults while maintaining the convenience of TD administration [22].

Strengths and limitations

The primary strength of this study was the use of data representing a 10% sample of concessional beneficiaries initiating TD fentanyl in Australia. Consequently, the findings provide nationally-representative data on the characteristics of individuals receiving subsidised medicines in the concessional population. More than 90% of fentanyl utilisation in Australia is PBS-subsidised [34]; however, given that the cohort was restricted to concessional beneficiaries to determine complete ascertainment of dispensed medicines, the findings may not be representative of the general Australian population. Nevertheless, given that older adults account for the majority of TD fentanyl use in Australia [16], and also represent the majority of the concessional population [21], it is highly probable that our data have captured a large percentage of TD fentanyl use in the Australian community. As records of medicines dispensed to hospital inpatients are not captured in PBS data, it is possible that some individuals may have been misclassified as opioid naïve if TD fentanyl was prescribed upon discharge after using other opioids in hospital. However, this is expected to only be relevant to a minority of individuals as TD fentanyl is not indicated for acute pain. Finally, as PBS dispensing records have limited capture of over-the-counter medicines, prior use of non-opioid analgesic preparations and low-dose codeine combinations may have been underestimated. However, given that use of low-dose codeine combinations is unlikely to be sufficient to establish opioid tolerance in most individuals [28], the impact on the findings of this study are expected to be minimal.

Conclusion

A considerable proportion of Australians are opioid naïve at the time of TD fentanyl initiation. Our findings suggest that specific patient sub-populations already at increased risk of opioid-related adverse events (i.e. older adults and those with dementia) are not receiving prior opioid treatment before TD fentanyl initiation, highlighting the need for additional strategies to promote greater adherence to current treatment guidelines.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1
Cohort demographics according to previous opioid exposure prior to TD fentanyl initiation

	Overall (n = 13,166) n (%)	Opioid exposed (n = 9160) n (%)	Opioid naïve (n = 4006) n (%)	Unadjusted odds ratio (95% CI)
Sex				
Male	5220 (39.7)	3824 (41.8)	1396 (34.9)	Reference
Female	7946 (60.4)	5336 (58.3)	2610 (65.2)	1.34 (1.24–1.45)
Age				
18–44	877 (6.7)	691 (7.5)	186 (4.6)	Reference
45–64	2257 (17.1)	1678 (18.3)	579 (14.5)	1.28 (1.06–1.55)
65–84	6945 (52.8)	4808 (52.5)	2137 (53.3)	1.65 (1.39–1.96)
85	3087 (23.5)	1983 (21.7)	1104 (27.6)	2.07 (1.73–2.47)
Residence level of remoteness ^a				
Major city	7941 (60.3)	5514 (60.2)	2427 (60.6)	Reference
Inner regional	3506 (26.6)	2450 (26.8)	1056 (26.3)	0.98 (0.90–1.07)
Outer regional	1532 (11.6)	1076 (11.8)	456 (11.4)	0.96 (0.85–1.09)
Remote/Very remote	187 (1.4)	120 (1.3)	67 (1.7)	1.27 (0.94–1.72)
Residence Index of relative socio-economic disadvantage ^b				
Most disadvantaged	2156 (16.4)	1458 (15.9)	698 (17.4)	Reference
Second quintile	3796 (28.8)	2630 (28.7)	1166 (29.1)	0.93 (0.83–1.04)
Third quintile	2852 (21.7)	2021 (22.1)	831 (20.7)	0.86 (0.76–0.97)
Fourth quintile	2377 (18.1)	1711 (18.7)	666 (16.6)	0.81 (0.72–0.92)
Least disadvantaged	1985 (15.1)	1340 (14.6)	645 (16.1)	1.01 (0.88–1.15)
Number of medical conditions other than pain ^c				
0	488 (3.7)	268 (2.9)	220 (5.5)	Reference
1–2	2628 (20.0)	1797 (19.6)	831 (20.7)	0.56 (0.46–0.69)
3–4	4195 (31.9)	2873 (31.4)	1322 (33.0)	0.56 (0.46–0.68)
5	5855 (44.5)	4222 (46.1)	1633 (40.8)	0.47 (0.39–0.57)
Dispensed medicines to treat: ^c				
Neoplasms (cancer)	1019 (7.7)	812 (8.9)	207 (5.2)	0.56 (0.48–0.66)

	Overall (<i>n</i> = 13,166) <i>n</i> (%)	Opioid exposed (<i>n</i> = 9160) <i>n</i> (%)	Opioid naïve (<i>n</i> = 4006) <i>n</i> (%)	Unadjusted odds ratio (95% CI)
Endocrine, nutritional, metabolic disorders	2641 (20.1)	1840 (20.1)	801 (20.0)	0.99 (0.91–1.10)
Mental and behavioural disorders	6660 (50.6)	4944 (54.0)	1716 (42.8)	0.64 (0.59–0.69)
Alcohol dependence	9 (0.1)	7 (0.1)	2 (0.1)	0.65 (0.14–3.15)
Anxiety	2243 (17.0)	1730 (18.9)	513 (12.8)	0.63 (0.57–0.70)
Bipolar disorder	28 (0.2)	23 (0.3)	5 (0.1)	0.50 (0.19–1.31)
Dementia	238 (1.8)	145 (1.6)	93 (2.3)	1.48 (1.14–1.92)
Depression	4970 (37.8)	3731 (40.7)	1239 (30.9)	0.65 (0.60–0.71)
Nicotine dependence	156 (1.2)	121 (1.3)	35 (0.9)	0.66 (0.45–0.96)
Psychosis	1310 (10.0)	944 (10.3)	366 (9.1)	0.88 (0.77–0.99)
Diseases of the nervous system	1502 (11.4)	1101 (12.0)	401 (10.0)	0.81 (0.72–0.92)
Diseases of the circulatory system	9856 (74.9)	6803 (74.3)	3053 (76.2)	1.11 (1.02–1.21)
Diseases of the respiratory system	2755 (20.9)	1952 (21.3)	803 (20.0)	0.93 (0.84–1.02)
Diseases of the digestive system	7330 (55.7)	5273 (57.6)	2057 (51.4)	0.78 (0.73–0.84)
Diseases of the musculoskeletal system and connective tissue	2335 (17.7)	1640 (17.9)	695 (17.4)	0.96 (0.87–1.06)
Diseases of the genitourinary system	574 (4.4)	403 (4.4)	171 (4.3)	0.97(0.81–1.16)
End stage renal disease	220 (1.7)	140 (1.5)	80 (2.0)	1.31 (1.00–1.73)

Values in bold indicate statistical significance at $p < 0.05$

^aClassified using 2011 Remoteness Area Indices. Based on postcode of last recorded address

^bClassified using Index of Relative Socio-economic Disadvantage 2006. Based on postcode of last recorded address

^cIdentified using the RxRisk-V classification system using each individual's previous 3-month dispensing history and mapped to International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) categories (Appendix, Table A2)

Patch strengths initiated and analgesic use in the 3 months prior to TD fentanyl initiation

Table 2

	Overall (<i>n</i> = 13,166) <i>n</i> (%)	Opioid exposed (<i>n</i> = 9160) <i>n</i> (%)	Opioid naïve (<i>n</i> = 4006) <i>n</i> (%)	Unadjusted odds ratio (95% CI)
Patch strength initiated				
12 mcg/h only	8319 (63.2)	5459 (59.6)	2860 (71.4)	1.69 (1.56–1.83)
25mcg/h only	3306 (25.1)	2520 (27.5)	786 (19.6)	0.64 (0.59–0.70)
50 mcg/h only	904 (6.9)	704 (7.7)	200 (5.0)	0.63 (0.54–0.74)
75 mcg/h only	267 (2.0)	198 (2.2)	69 (1.7)	0.79 (0.60–1.05)
100 mcg/h only	147 (1.1)	112 (1.2)	35 (0.9)	0.71 (0.49–1.04)
Multiple strengths	223 (1.7)	167 (1.8)	56 (1.4)	0.76 (0.56–1.04)
Previous analgesic use				
Any analgesic use	11,464 (87.1)	9160 (100)	2304 (57.5)	N/A
Non-opioid	8017 (60.9)	5713 (62.4)	2304 (57.5)	0.82 (0.76–0.88)
Paracetamol (single ingredient)	6440 (48.9)	4554 (49.7)	1886 (47.1)	0.90 (0.84–0.97)
Pregabalin	292 (2.2)	242 (2.6)	50 (1.3)	0.47 (0.34–0.63)
Non-steroidal antiinflammatories ^a	1242 (9.4)	957 (10.5)	285 (7.1)	0.66 (0.57–0.75)
Selective cox-2 inhibitors ^b	1993 (15.1)	1424 (15.6)	569 (14.2)	0.90 (0.81–1.00)
Weaker opioid	4148 (31.5)	4148 (45.3)	N/A	N/A
Codeine (single ingredient)	203 (1.5)	203 (2.2)	N/A	N/A
Codeine (combined with paracetamol)	2708 (20.6)	2708 (29.6)	N/A	N/A
Dextropropoxyphene	10 (0.1)	10 (0.1)	N/A	N/A
Tramadol	1743 (13.2)	1743 (19.0)	N/A	N/A
Strong opioid	7286 (55.3)	7286 (79.5)	N/A	N/A
Buprenorphine	2535 (19.3)	2535 (27.7)	N/A	N/A
Hydromorphone	235 (1.8)	235 (2.6)	N/A	N/A
Methadone	66 (0.5)	66 (0.7)	N/A	N/A
Morphine	1370 (10.4)	1370 (15.0)	N/A	N/A
Oxycodone (inc combinations)	4986 (37.9)	4986 (54.4)	N/A	N/A
Non-opioid only	2304 (17.5)	0 (0.0)	2304 (57.5)	N/A
Weaker opioid only	765 (5.8)	765 (8.4)	N/A	N/A

	Overall (<i>n</i> = 13,166) <i>n</i> (%)	Opioid exposed (<i>n</i> = 9160) <i>n</i> (%)	Opioid naïve (<i>n</i> = 4006) <i>n</i> (%)	Unadjusted odds ratio (95% CI)
Strong opioid only	1820 (13.8)	1820 (19.9)	N/A	N/A
Non-opioid and weaker opioid	1109 (8.4)	1109 (12.1)	N/A	N/A
Non-opioid and strong opioid	3192(24.2)	3192 (34.9)	N/A	N/A
Weaker opioid and strong opioid	862 (6.6)	862 (9.4)	N/A	N/A
Non-opioid and weaker opioid and strong opioid	1412 (10.7)	1412 (15.4)	N/A	N/A

CI confidence interval, *IQR* interquartile range, *N/A* not applicable

Values in bold indicate statistical significance at $p < 0.05$

^aIncludes: diclofenac, ibuprofen, indomethacin, ketoprofen, mefenamic acid, naproxen, piroxicam, sulindac

^bIncludes: celecoxib, meloxicam

Table 3

Adjusted odds ratios for the characteristics associated with being opioid naïve prior to TD fentanyl initiation

	Adjusted odds ratio (95% CI)
Female sex	1.35 (1.25–1.46)
Age	
18–44	Reference
45–64	1.36 (1.12–1.65)
65–84	1.65 (1.37–1.99)
85	1.88 (1.54–2.28)
Previous use of a non-opioid analgesic	0.75 (0.70–0.82)
Initiated on 12 mcg/h patch strength	1.56 (1.44–1.69)
Previously dispensed medicines for: ^a	
Neoplasms (cancer)	0.57 (0.48–0.67)
Anxiety	0.72 (0.64–0.80)
Dementia	1.37 (1.04–1.80)
Depression	0.69 (0.63–0.75)
Nicotine dependence	0.83 (0.57–1.30)
Psychosis	0.82 (0.70–0.97)
Diseases of the nervous system	0.89 (0.78–1.00)
Diseases of the circulatory system	1.01 (0.91–1.11)
Diseases of the digestive system	0.79 (0.73–0.86)

CI confidence interval, *OR* odds ratioValues in bold indicate statistical significance at $p < 0.05$ ^aClassified using the RxRisk-V tool