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THE EPIDEMIOLOGY OF PRESCRIPTION FENTANYL MISUSE IN THE UNITED STATES

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Abstract

Background: US opioid overdose deaths continue to climb, with a 12.0% increase from 2016 to 2017. Fentanyl, a synthetic opioid, has been a major contributor to opioid-related overdose deaths. While fentanyl-related overdose is driven by illicit fentanyl, little is known about individuals who misuse prescription fentanyl, which is also linked to elevated overdose and mortality risk. This work aimed to fill that gap through analyses of prescription fentanyl misuse correlates.

Methods: Data were from the 2015–16 National Survey on Drug Use and Health (N= 114,043), a nationally representative survey of the non-institutionalized US population. Respondents were (all past-year): those misusing prescription fentanyl (PF); those misusing other (non-fentanyl) prescription opioids (NFPO); and population controls. Respondent groups were compared using multinomial regression on sociodemographics, physical health, mental health and substance use. The PF and NFPO misuse groups were compared on opioid misuse characteristics, using logistic regression.

Results: An estimated 4.4% misused NFPO, and 0.1% misused PF (past-year). Past-year heroin use was more common in those who misused PF (44.3%) than those who misused other NFPO (4.4%; relative risk ratio [RRR]= 7.1, 95% confidence interval [CI]= 3.7–13.9) or population

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controls (0.1%; RRR= 35.1, 95%CI= 17.3–71.1). Non-alcohol SUD was similarly elevated in those who misused PF (78.7%) versus the other NFPO group (27.5%, RRR= 3.8, 95%CI= 1.8–8.2) or population controls (1.6%; RRR= 20.6, 95%CI= 9.4–45.5).

Conclusions: Respondents who misused prescription fentanyl are both more drug-involved generally and opioid-involved specifically, and they likely need a combination of significant interventions and monitoring for their polysubstance use.

Keywords

Prescription fentanyl; opioid; misuse; epidemiology

1. INTRODUCTION

The US has an opioid epidemic (Kanouse & Compton, 2015), with overdoses increasing by 12.0% from 2016 to 2017 (Scholl, Seth, Kariisa, Wilson, & Baldwin, 2018). In 2017, an estimated 47,600 US residents died from an opioid overdose, comprising nearly three-quarters of drug overdose deaths (Scholl et al., 2018). A major culprit in recent overdose increases are synthetic opioids (Jones, Einstein, & Compton, 2018; Seth, Scholl, Rudd, & Bacon, 2018). From 2016 to 2017, US synthetic opioid overdoses increased by 45.2%, with significant increases in both sexes, and across racial/ethnic groups, age groups and county urbanization levels (Scholl et al., 2018). The primary driver of increasing synthetic opioid-related overdose appears to be fentanyl and related analogs (e.g. carfentanil) (Jones et al., 2018; Phalen, Ray, Watson, Huynh, & Greene, 2018).

To the best of our knowledge, no nationally representative US data have been published on the characteristics of those who misuse *prescription* fentanyl (PF). While illicit, and not prescription, fentanyl misuse is the key driver of increased US overdose rates, reasons remain for concern about PF misuse. First, any fentanyl exposure in opioid-naïve individuals or those with limited opioid tolerance is associated with significant adverse effects (Friesen, Woelk, & Bugden, 2016). In particular, any PF misuse is associated with higher rates of respiratory depression and fatal overdose than with other opioid medications (Fox, Hoffman, Vlahov, & Manini, 2018; Haukka, Kriikku, Mariottini, Partonen, & Ojanpera, 2018). Furthermore, PF use (as with other long-acting opioids) is associated with higher mortality rates than with use of shorter-acting opioid medications (Ray, Chung, Murray, Hall, & Stein, 2016). Finally, young adults engaged in misuse of diverted PF had higher odds of fentanyl-contaminated heroin exposure than young adults engaged in non-fentanyl prescription opioid (NFPO) misuse (Macmadu, Carroll, Hadland, Green, & Marshall, 2017). Identifying the characteristics of those who misuse PF (i.e., use without prescription or in ways not intended by the prescriber) could inform public health efforts by highlighting those at-risk for misuse, substance use disorder (SUD) and overdose, allowing for targeted prevention and potential harm reduction interventions (e.g., naloxone distribution).

Given this gap in the literature, this study used the aggregated 2015–16 NSUDH data to examine the sociodemographic, physical health, mental health, other substance use (including heroin use) and prescription opioid misuse characteristics of those who misused PF in the past year, taking advantage of the newly available data.

2. METHODS

The NSDUH is an annual US survey of those 12 years of age and older. Sampling uses an independent, multistage area probability design, allowing for nationally representative estimates. The NSUDH assesses all sensitive questions (e.g., prescription fentanyl misuse) via audio computer-assisted self-interviewing (ACASI) to maximize honest reporting, with skip-outs and consistency checks to promote full responding and data consistency. More information on the NSDUH, including on psychometrics, is available elsewhere (Center for Behavioral Health Statistics and Quality, 2017b; 2010). The NSUDH was approved by the IRB of Research Triangle International (Center for Behavioral Health Statistics and Quality, 2017a), and the Texas State University IRB exempted this work from further oversight.

2.1 Participants

For 2015–16, 114,043 respondents were in the NSDUH public use files. The sociodemographic characteristics of respondents by age group are in online-only Supplemental Table A.

2.2 Measures

Initially, the NSDUH assessed past-year opioid exposure (i.e., any medical use or misuse) by asking about any use of a large number of generic and trade named pain relievers; this included a query on use of “Duragesic®, Fentora® or fentanyl”, with “Actiq®” included in 2015 but dropped for 2016 because of very low endorsement of misuse. In those with past-year exposure, past-year misuse is assessed. This instruction introduces the misuse assessment: “The next question asks about using [specific drug] in any way a doctor did not direct you to use them. [P]lease think only about your use of the drug in any way a doctor did not direct you to use it, including: Using it without a prescription of your own; Using it in greater amounts, more often, or longer than you were told to take it; Using it in any other way a doctor did not direct you to use it.”

Using respondent data on fentanyl and other opioid misuse, participants were classified as having: *past-year prescription fentanyl (PF) misuse*, *past-year other (non-fentanyl) prescription opioid (NFPO) misuse* and *past-year population controls* (i.e., no opioid misuse).

Sociodemographic correlates included: *sex*, *race/ethnicity*, *age group* (12–17, 18–25, 26–34, 35–49, 50–64 and 65 years and older), *income*, *educational attainment*, *sexual orientation* (dichotomized as heterosexual versus lesbian/gay/bisexual; adolescent sexual orientation was not assessed, so those 12 to 17 years of age were coded as “adolescents”), *employment status* and *population density* (residence in a US Census-defined Core-based statistical area [CBSA] of 1 million residents, residence in a CBSA less than 1 million residents, non-CBSA status). Physical health correlates included: *self-reported health* (poor versus fair/good/very good/excellent), *past-year emergency department utilization* (yes/no), and *past-year hospitalization* (yes/no). Dichotomous mental health correlates included: *past-year DSM-IV major depression*, *past-year suicidal ideation* (adult only), and *past-year serious psychological distress* (adult only) (Kessler et al., 2003).

Dichotomous substance use correlates included: *past-month binge drinking*, *past-year marijuana use*, *past-year cocaine use*, *past-year heroin use*, *past-year stimulant misuse*, *past-year benzodiazepine misuse*, *past-year alcohol use disorder (AUD)*, and *past-year non-alcohol DSM-IV substance use disorder (SUD)*. Count-based substance use correlates included: *number of DSM-IV SUD diagnoses*, *number of opioid SUD symptoms*, and *number of opioid types (e.g., oxycodone, hydrocodone, meperidine) misused*. Per the DSM-5, the number of opioid SUD symptoms can signal severity (American Psychiatric Association, 2013); here, the nine DSM-IV symptoms included in the DSM-5 (of 11) were retained. Also, opioid craving was not included, as it was not assessed in the NSUDH.

Prescription opioid misuse outcomes (assessed only in the past-year PF and NFPO groups) included: *past-year prescription opioid misuse initiation*, *30-day prescription opioid misuse frequency*, *past-year prescription opioid misuse type* (defined below), *non-pain relief motives* (at the respondent's most recent misuse episode), *past-year (non-heroin) opioid SUD*, *past-year heroin (only) SUD*. Opioid misuse type is one of nonmedical use (i.e., use of another's medication only), medical misuse (i.e., use of one's own medication in ways not intended by the prescribing clinician), or mixed misuse (i.e., both nonmedical use and medical misuse in the past year).

2.3 Data Analyses

Analyses utilized STATA 15.1 (College Station, TX) and incorporated the complex survey design; adjusted person-level weights (weight/two) created unbiased population-based estimates. The Taylor series approximation, with adjusted degrees of freedom, created robust variance estimates. Weighted cross-tabulations estimated prevalence and 95% confidence intervals (95% CI) of past-year PF misuse, NFPO misuse and population controls. Design-based multivariable multinomial regression models evaluated the sociodemographic correlates of PF/NFPO misuse status, followed by multivariable multinomial regressions evaluating the physical health, mental health and substance use correlates of PF/NFPO misuse status (controlling for sociodemographics). Also, design-based multivariable logistic regression analyses evaluated differences in opioid misuse characteristics between past-year PF misuse and NFPO misuse (controlling for sociodemographics). Finally, negative binomial regression analyses compared count-based outcomes (i.e., number of SUD diagnoses, number of opioid SUD symptoms, and types of opioid misused) between respondent groups. *A priori* significance was $p = 0.005$ (Ioannidis, 2018).

3. RESULTS

Only 0.1% engaged in past-year PF misuse (95% CI= 0.07–0.12), with 4.4% (95% CI= 4.2–4.6) engaged in past-year NFPO misuse. Educational status was the only sociodemographic characteristic that differentiated those who misused PF from the two other groups ($p < 0.001$), resulting from the relatively few college graduates who misused PF (see online-only Supplemental Table B). Male sex ($p = 0.003$) and age group ($p < 0.001$) differentiated the PF group from population controls. Those 18 to 45 years (87.0%) were particularly likely to engage in PF misuse, with no cases in those 65 years and older.

The unadjusted prevalence of all physical health, mental health and substance use correlates was highest in those engaged in past-year PF misuse, except past-month binge drinking (Table 1). In other words, those with past-year PF misuse had the highest prevalence rates of all poor physical health outcomes (e.g., past-year hospitalization), poor mental health outcomes (e.g., past-year major depression) and substance use outcomes (e.g., past-year nonalcohol SUD), save past-month binge drinking. In multivariable multinomial regression models, past-year benzodiazepine misuse, heroin use and DSM-IV non-alcohol substance use disorder (SUD) differentiated those who misused PF (past-year) from those engaged in NFPO misuse or population controls ($p < 0.001$; also Table 1). Also, past-year stimulant medication misuse differentiated the PF misuse group from population controls ($p = 0.001$). Sensitivity analyses including adolescents (excluding sexual orientation, past-year suicidal ideation and past-year SPD, which were not assessed in adolescents) produced the same pattern of significant correlates.

Finally, *post hoc* negative binomial regressions (not shown in Table 1) indicated that those engaged in past-year PF misuse had significantly more total SUDs (Mean = 1.82, 95% CI = 1.53–2.12) than those engaged in NFPO misuse (Mean = 0.64, 95% CI = 0.61–0.68; $B = 0.98$, $SE = 0.10$, $t = 9.45$, $p < 0.001$) or population controls (Mean = 0.07, 95% CI = 0.06–0.07; $B = 3.01$, $SE = 0.11$, $t = 26.93$, $p < 0.001$).

As depicted in Table 2, past-year prescription opioid-related SUD was more likely in those with past-year PF misuse (53.7%) than those with NFPO misuse (15.6%; adjusted odds ratio [AOR] = 2.85; $p = 0.002$). Heroin SUD prevalence was similarly significantly elevated in those with PF misuse (38.2%) versus those with NFPO misuse (3.1%; AOR = 8.59; $p < 0.001$). *Post hoc* negative binomial regressions (not shown in Table 2) indicated that PF group members had a mean of 3.80 (95% CI = 3.03–4.57) opioid SUD symptoms, while those in the other NFPO misuse group had 0.96 (95% CI = 0.89–1.03; $B = 2.74$, $SE = 0.38$, $t = 7.27$, $p < 0.001$).

PF group members misused an average of 4.92 (95% CI = 4.23–5.62) different types of opioid (e.g., oxycodone, methadone) in the past year, while the NFPO misuse group's mean was 1.21 (95% CI = 0.89–1.03; $B = 1.35$, $SE = 0.07$, $t = 20.49$, $p < 0.001$). Also, 12.6% of those who used heroin in the past year had misused PF, while 44.3% of those who misused PF also used heroin. These results are not shown in Table 2.

4. DISCUSSION

Overall, this study found that PF misuse was rare in a household survey sample, at 0.1%, with roughly 2% of those engaged in opioid misuse also engaged in PF misuse. US individuals engaged in past-year PF misuse were significantly more likely to have misused benzodiazepines, heroin, and have a non-alcohol SUD in the past year versus those engaged in NFPO misuse or population controls. They also had higher non-heroin opioid SUD (53.7%) or heroin SUD (38.2%) rates than the other NFPO misuse group (15.6% and 3.1%, respectively), with 44.3% of those who misused PF also using heroin in the past year, as opposed to 4.4% of those with NFPO misuse. Finally, they had a greater number of SUD diagnoses than other groups, and they had a larger number of opioid SUD symptoms and

opioid medications misused than those who misuse other prescription opioids, with both likely signifying greater opioid misuse severity.

Thus, those who misused PF are both more drug-involved generally and opioid-involved specifically than those engaged in other NFPO misuse, highlighting them as a particularly high-risk group of those engaged in prescription opioid misuse. The elevated prevalence of benzodiazepine misuse in those who misused PF is notable, given the high rates of suicidal ideation in those with misuse of both opioid and benzodiazepine medication (Schepis, Simoni-Wastila, & McCabe, 2019). Also, and consistent with past work (Carroll, Marshall, Rich, & Green, 2017; Nechuta, Tyndall, Mukhopadhyay, & McPheeters, 2018), males were overrepresented in the PF group, with lower educational attainment found as well. PF misuse was largely restricted to those 18 to 49 years (87%), with no such misuse in those 65 and older.

Clinically, individuals who misused PF in the present study knowingly did so (see Limitations), whether by itself or in combination with other opioids and/or drugs of abuse. Thus, some recommendations to reduce illicit fentanyl-related harms such as drug checking kits to identify adulteration with illicit fentanyl (Bardwell & Kerr, 2018), are unlikely to be as effective in those intentionally misusing prescription fentanyl. In contrast, medication-assisted treatment is an important tool for healthcare professionals concerned about PF misuse specifically or NFPO misuse more generally in patients (Lagisetty et al., 2017; Theisen-Toupal, Ronan, Moore, & Rosenthal, 2017). Community-based interventions to increase dispensing of naloxone and train high-risk individuals in its use is warranted to reduce overdose (Rowe, Wheeler, Stephen Jones, Yeh, & Coffin, 2018). Also, heightened screening and monitoring for individuals in healthcare professional recovery programs seems warranted, given healthcare professionals in recovery have often engaged in polysubstance use with multiple opioids. Screening for fentanyl and related compounds require addition of a separate panel to occupational drug panels because such compounds are not detected by commercial morphine- or oxycodone-specific opiate immunoassays (Milone, 2012). Finally, education about proper medication storage and disposal (to prevent theft for misuse) and education about the risks of diversion could help reduce the supply of PF for misuse.

4.1 Limitations

These results may be limited by self-report and self-selection bias, given both the nature of the NSDUH survey. Furthermore, the cross-sectional data do not allow for causal inference in the pathways leading to PF misuse. Also, participants who unknowingly used fentanyladulterated drugs were extremely unlikely to report this as PF misuse (Amlani et al., 2015), and individuals misusing illicit fentanyl were also unlikely to report this as misuse on the NSDUH, meaning that the sample endorsing past-year PF misuse is certainly a subsample of all US individuals exposed to fentanyl. Finally, these data do not differentiate carfentanil (a more potent fentanyl derivative typically used in veterinary medicine) from fentanyl and do not capture those who use fentanyl derivatives. More epidemiological research is needed on carfentanil given its increasing role in overdose deaths (O'Donnell,

Gladden, Mattson, & Kariisa, 2018) and relative resistance to reversal using single naloxone dosing.

4.2 Conclusions

While those engaged in PF misuse are uncommon, comprising 2% of the subpopulation engaged in opioid misuse overall, PF misuse is a clear signal of severe opioid use disorder and overdose risk. The majority of those who misused PF in the past year also reported past-year benzodiazepine misuse and SUD, with over 75% having a non-alcohol SUD diagnosis. They also have much higher rates of heroin use, heroin-related SUD, other opioid-related SUD and a significantly greater number of opioid classes misused than individuals who NFPO medication. Treatment of individuals engaged in PF misuse will need to attend not only to their significant opioid involvement but also to their heavy polysubstance use. More research is warranted to examine the shared and unique characteristics between individuals who misuse PF, illicitly manufactured fentanyl and other opioids. A variety of screening, prevention and intervention techniques are needed to identify and treat this complex and high-risk sub-population in the US.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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HIGHLIGHTS

- This study aimed to identify the correlates of past-year fentanyl misuse in the US.
- Heroin use (44.3%) and SUD (38.2%) often occurred with past-year fentanyl misuse.
- This group also had very high rates of non-alcohol substance use disorder (78.7%).
- Fentanyl misuse was associated frequent prescription opioid use disorder (53.7%).
- Those with past-year fentanyl misuse are heavily opioid and polysubstance involved.

Physical Health, Mental Health and Substance Use Correlates of Past-Year Fentanyl Misuse

Table 1:

	Fentanyl Misuse (n = 153)	Other Prescription Opioid Misuse (n = 5,880)	Population Controls (No Prescription Opioid Misuse) (n = 108,010)	Fentanyl Misuse vs. Population Controls		Fentanyl Misuse vs. Other Prescription Opioid Misuse	
	% (95% CI)	% (95% CI)	% (95% CI)	p	RRR (95% CI)	p	RRR (95% CI)
Physical Health							
PY Hospitalization	21.3 (13.8–31.3)	13.0 (11.8–14.3)	9.5 (9.1–9.8)	0.26	1.51 (0.73–3.11)	0.45	1.29 (0.66–2.51)
PY ED Visit	48.6 (39.0–58.4)	38.5 (36.9–40.1)	25.8 (25.4–26.3)	0.20	1.36 (0.84–2.20)	0.94	0.98 (0.61–1.57)
Poor Self-Reported Health	24.9 (17.0–34.9)	17.2 (15.4–19.1)	12.8 (12.5–13.2)	0.58	1.37 (0.45–4.19)	0.76	1.18 (0.40–3.52)
Mental Health							
PY Major Depression	25.0 (17.2–34.8)	17.8 (16.2–19.5)	6.7 (6.5–6.9)	0.71	0.88 (0.44–1.75)	0.62	0.83 (0.39–1.75)
PY Serious Psychological Distress	49.0 (37.4–60.6)	29.3 (27.8–30.9)	9.7 (9.4–10.0)	0.017	2.51 (1.19–5.30)	0.22	1.58 (0.76–3.29)
PY Suicidal Ideation	21.0 (14.7–29.0)	14.0 (12.6–15.5)	3.5 (3.4–3.7)	0.81	1.08 (0.58–2.00)	0.46	0.81 (0.45–1.44)
Substance Use							
30-day Binge Drinking	47.5 (35.7–59.6)	48.9 (47.0–50.9)	23.6 (23.1–24.1)	0.44	1.20 (0.67–2.45)	0.46	0.80 (0.43–1.47)
PY Marijuana	64.2 (51.6–75.1)	47.0 (44.7–49.3)	12.2 (11.8–12.5)	0.65	1.21 (0.53–2.72)	0.24	0.62 (0.28–1.39)
PY Cocaine	34.0 (26.7–42.2)	13.7 (12.4–15.0)	1.3 (1.2–1.4)	0.26	0.74 (0.44–1.25)	0.15	0.68 (0.40–1.15)
PY Benzodiazepine Misuse	65.5 (53.8–75.5)	21.5 (20.3–22.9)	1.2 (1.1–1.2)	< 0.001	26.24 (12.55–54.91)	< 0.001	4.10 (2.02–8.33)
PY Stimulant Misuse	36.6 (25.5–49.4)	15.1 (14.1–16.2)	1.4 (1.3–1.5)	0.001	3.55 (1.77–7.08)	0.10	1.71 (0.89–3.26)
PY Heroin	44.3 (34.8–54.4)	4.4 (3.7–5.1)	0.1 (0.08–0.13)	< 0.001	35.06 (17.30–71.06)	< 0.001	7.14 (3.67–13.88)
PY Alcohol Use Disorder	29.3 (19.6–41.3)	22.0 (20.7–23.4)	5.0 (4.8–5.2)	0.40	1.42 (0.61–3.31)	0.97	1.02 (0.45–2.28)
PY Non-Alcohol SUD	78.7 (68.3–86.4)	27.5 (26.0–29.0)	1.6 (1.5–1.7)	< 0.001	20.64 (9.38–45.45)	0.001	3.84 (1.80–8.19)

Source: 2015–16 NSDUH surveys

Notes: Analyses were adjusted for sex, race/ethnicity, age group, income, education, employment status and population density in area of residence

Abbreviations: 95% CI = 95% confidence interval; RRR = Relative risk ratio; PY = Past-year; SPD = Serious psychological distress; SUD = Substance use disorder

Table 2:

Opioid Misuse Characteristics in Those with Past-Year Fentanyl Misuse and Other Prescription Opioid (Non-Fentanyl) Misuse

	Fentanyl Misuse (n = 153)	Other Prescription Opioid Misuse (n = 5,880)	<i>p</i> -value	Fentanyl Misuse vs. Other Prescription Opioid Misuse
	% (95% CI)	% (95% CI)		AOR (95% CI)
Past-Year Prescription Opioid Misuse Initiation ^a	2.6 (0.9–7.3)	18.4 (17.1–19.8)	0.015	0.26 (0.09–0.76)
30-day Prescription Opioid Misuse Frequency			0.20	
No Episodes	44.1 (33.2–55.6)	71.1 (69.2–72.9)		-----reference-----
1–2 Episodes	8.9 (4.2–17.8)	11.7 (10.3–13.3)		1.31 (0.60–2.89)
3–5 Episodes	4.5 (1.6–12.0)	7.6 (6.7–8.5)		0.64 (0.19–2.11)
6–19 Episodes	23.9 (14.9–35.9)	6.4 (5.5–7.4)		3.37 (1.61–7.04)
20–30 Episodes	18.7 (10.6–30.9)	3.3 (2.7–4.0)		4.33 (1.61–11.66)
Past-Year Prescription Opioid Misuse Type			0.50	
Nonmedical Misuse	36.0 (25.9–47.5)	47.3 (45.1–49.5)		-----reference-----
Medical Misuse	31.5 (21.9–43.0)	38.1 (36.0–40.2)		0.97 (0.49–1.91)
Mixed Misuse	32.5 (24.4–41.7)	14.6 (13.3–16.0)		1.25 (0.72–2.16)
Non-Pain Relief Motives	78.2 (67.9–85.8)	51.2 (49.0–53.4)	0.13	1.76 (0.83–3.74)
Past-Year Opioid SUD	53.7 (42.6–64.4)	15.6 (14.3–16.9)	0.002	2.84 (1.52–5.30)
Past-Year Heroin SUD	38.2 (28.6–48.8)	3.1 (2.6–3.7)	< 0.001	8.42 (4.74–14.92)

Source: 2015–16 NSUDH Data

Abbreviations: 95% CI = 95% confidence interval; AOR = Adjusted odds ratio; SUD = Substance use disorder

^aPast-year prescription opioid misuse initiation denotes the proportion of individuals in the subgroup who began opioid misuse within the past 12 months, with no prior history of opioid misuse.