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Perceptions and practices addressing diversion among US buprenorphine prescribers

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ABSTRACT

Background: While there has been a dramatic increase in prescribing of buprenorphine for the treatment of opioid use disorder in the US, little is known about prescribers' attitudes and practices regarding buprenorphine diversion and how they relate to prescriber characteristics.

Methods: A national random sample of buprenorphine prescribers (N = 1174) completed surveys from July 2014 to January 2017. Analyses examined relationships between prescriber and practice characteristics and prescriber perceptions and approaches regarding diversion.

Results: Among this sample of buprenorphine prescribers, 79.0% (N = 898) reported assessing all patients for risk of buprenorphine diversion and misuse. A third of prescribers described diversion as a significant or very significant concern in their community. The majority of prescribers reported seeing patients on average at least every other week during the first 60 days of treatment, and the majority reported testing urine for buprenorphine to assess for diversion. Perceptions of diversion being a greater problem in their community (AOR 1.212, 95% CI 1.073–1.369) and use of medication counts (AOR 1.006, 95% CI 1.003–1.009) were associated with increased likelihood of terminating patients when diversion was suspected, while having expertise in addiction (AOR 0.526, 95% CI 0.406–0.682) or psychiatry (AOR 0.714, 95% CI 0.558–0.914) were associated with decreased odds of terminating treatment for suspected diversion.

Conclusions: Buprenorphine prescribers report diversion is an important issue, and most prescribers report that they assess patients for diversion, though specific practices differ based on prescriber and practice characteristics.

1. Introduction

Given the dramatic rise in the prevalence of opioid use disorders (OUD) in the U.S. (Han et al., 2015; Martins et al., 2017), there is a clear and urgent need to expand access to evidence-based treatment. The most effective treatment for OUD is pharmacotherapy with formulations of buprenorphine and buprenorphine/naloxone (hereafter collectively termed buprenorphine) and methadone (Mattick et al., 2014; Nielsen et al., 2016; Nielsen et al., 2017). Recent data also strengthen support for long-acting naltrexone (Lee et al., 2017; Tanum et al., 2017). In the US, methadone and buprenorphine can be dispensed in federally approved opioid treatment programs (OTPs), and

since 2003, buprenorphine can also be prescribed by waivered prescribers in health care settings outside OTPs. Buprenorphine prescriptions in the US have substantially increased, and Medicaid spending for buprenorphine increased from $380.9 million in 2011 to $753.9 million in 2016 (Clemans-Cope et al., 2017). This increase suggests more individuals are receiving treatment, but concerns have also emerged about increased diversion of buprenorphine, defined as unauthorized rerouting or misappropriation of prescribed buprenorphine to someone other than the person for whom it was intended (Lofwall and Walsh, 2014). Diversion concerns are often cited by providers as a barrier to incorporating buprenorphine treatment into their practice (Andrilla et al., 2017). Thus, there is a crucial need to understand prescriber

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attitudes and identify practices addressing diversion.

Diversion of prescribed buprenorphine is an important and complicated clinical issue for prescribers. On the one hand, it is an illegal behavior involving a controlled substance they are prescribing; on the other hand, it is a marker of non-adherence to treatment, a common problem in all areas of medicine (Kardas et al., 2013; Nieuwlaat et al., 2014). Reasons for diversion vary. Patients may sell buprenorphine to supplement their income or to obtain their opioid of choice (Allen and Harocopos, 2016). Use of diverted buprenorphine among out-of-treatment individuals is clinically concerning but may be related to lack of access to formal treatment (Bazazi et al., 2011). For instance, among those who have used diverted buprenorphine in Appalachia Kentucky, the most robust risk factor was failing to access buprenorphine treatment in healthcare settings (Lofwall and Havens, 2012). Use of diverted buprenorphine does not guarantee that the person is taking the medication appropriately and may be associated with less positive clinical outcomes than when buprenorphine is provided as part of a treatment plan with ongoing monitoring. In rarer cases, individuals may misuse buprenorphine for euphoric effects, especially when more preferred substances are not available (Cicero et al., 2014; Kenney et al., 2017). International reports indicate that buprenorphine can be misused, though higher rates typically occur when the buprenorphine-mono-product is more widely available (Lofwall and Walsh, 2014).

Although there are numerous strategies providers can use to assess and mitigate diversion, including using the lowest effective dose of medication and informing patients about diversion, specific practices have been emphasized in buprenorphine prescribing guidelines (Substance Abuse and Mental Health Services Administration, 2004). The American Society of Addiction Medicine's National Practice Guideline on OUD treatment specifies that "recommended strategies include frequent office visits (weekly in early treatment), urine drug testing, including testing for buprenorphine and metabolites, and recall visits for pill counts (page 7)." Urine testing encompasses testing for buprenorphine and the metabolite norbuprenorphine because detection of only the parent compound may suggest an adulterated sample (Donroe et al., 2017; Suzuki et al., 2017). Although it is possible for patients to circumvent urine testing and other measures, these represent some of the key recommended practices to assess for diversion.

However, little is known about actual prescriber practices to address diversion. A 2008–2009 survey reported buprenorphine prescribers take a mean of 4.4 steps, including prescribing lowest effective dose and urine screens, to try to mitigate diversion (Yang et al., 2013). More detailed data and analyses on this issue, and examining impact of prescriber and practice characteristics, are critical to assessing current practices and attitudes as buprenorphine prescribing increases. In the present analyses, we assessed attitudes and practices regarding diversion, focusing on the specific practices recommended by the ASAM guideline. Analyses were conducted in a random sample of US buprenorphine prescribers and examined the relationships between prescriber characteristics with diversion practices and attitudes.

2. Methods

2.1. Sample

As the first wave of a longitudinal study, a national random sample of buprenorphine prescribers was drawn from the May 2014 issue of the Drug Enforcement Agency's Controlled Substances Act (CSA) Active Registrants database, which lists all civilian physicians holding a DEA X-license to prescribe buprenorphine in the 50 US states and the District of Columbia. Prescribers were sampled within each state, proportional to their state's representation within the DEA database, with 8031 prescribers randomly selected for screening by telephone (see Fig. 1 for participant recruitment). To be eligible, physicians were required to be currently treating at least one OUD patient with buprenorphine and to be practicing within the sampled state. Screening identified 3553
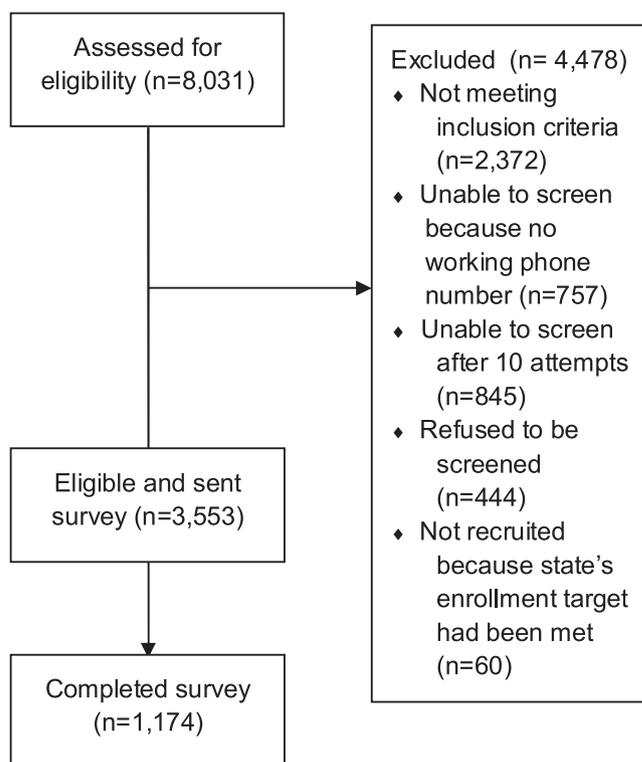

Fig. 1. Study flow diagram.

eligible prescribers. Eligible prescribers were mailed a letter describing the study and, about one week later, they were express-mailed a study packet (i.e., survey, consent forms, postage-paid return envelope). Participants received $100. Participation was encouraged with a postcard reminder, a follow-up telephone call, and the mailing of a second packet to non-respondents. From July 2014 to January 2017, 33.0% (n = 1174) of eligible prescribers participated in the study. All procedures were approved by the University of Kentucky's Institutional Review Board.

2.2. Dependent variables

Five diversion-related dependent variables and four encompassing practices for detecting and deterring diversion and one focused on responding to diversion were measured. The first mention of diversion in the survey defined it as "patients selling, giving away, or trading their medication", and the related issue of buprenorphine misuse was defined in the survey as "not taking medication as prescribed." First, *assessment of diversion risk* was measured by an item asking "In the past year, for what percentage of your buprenorphine patients did you assess patients for medication misuse and diversion?" Responses were dichotomized into two groups—those reporting assessing all patients (=1) and those not assessing all patients (=0). Second, frequency of office visits during the early phase of treatment was measured by an item that asked, "For patients in treatment for 1–2 months following induction, how frequently do you typically see those patients?" Analyses used the categories of weekly or more, every other week, or monthly or fewer. Third, *urine drug screening for buprenorphine* was measured by an item that asked "Do you usually require that urine specimens be tested for buprenorphine? Reponse options were 'Yes, always,' "Yes, but only if misuse/diversion is suspected," and "No." Reponses were dichotomized to always testing for buprenorphine (=1) versus not always testing/not ever testing (=0). Third, prescribers were asked "In the past year, for what percentage of your buprenorphine patients did you initiate random film/pill counts based on your concerns about possible medication diversion (e.g., selling, giving away, or trading medication)?"

Table 1
Practices and perceptions related to diversion in a national sample of buprenorphine prescribers.

	Mean (SD) or % (n)[a]	Available n
Practices for detecting and mitigating diversion		
Assessment of diversion risk		
Assesses 100% of buprenorphine patients for diversion	79.0% (898)	1136
Assesses < 100% of buprenorphine patients for diversion	21.0% (238)	
Frequency of office visits during the first 60 days of treatment		1131
Weekly or more frequently	26.6% (301)	
Every other week	35.5% (401)	
Once a month or less	37.9% (429)	
Urine drug screening		1139
Urine drug screen always tests for buprenorphine	79.1% (901)	
Urine drug screen does not always test for buprenorphine or no screen	20.9% (238)	
Percentage of patients with random medication counts initiated because of diversion concerns	31.4 (38.6)	1134
Response to diversion		
Willingness to terminate treatment with patients who divert buprenorphine[b]	4.2 (1.0)	1159
Magnitude of the diversion problem in the community[c]	1.3 (0.9)	1133
Practice characteristics		
Buprenorphine practice setting		1155
Delivers buprenorphine in individual practice	50.8% (587)	
Delivers buprenorphine not in individual practice	49.2% (568)	
Office visit payment type		1141
Only accepts cash	19.5% (223)	
Accepts private insurance but not Medicaid	23.8% (272)	
Accepts Medicaid	51.9% (592)	
All other types of payment	4.7% (54)	
Current number of buprenorphine patients	49.3 (48.1)	1121
Years of prescribing buprenorphine	6.7 (3.9)	1124
Waiver type		1174
Up to 100 patients	57.8% (678)	
Up to 30 patients	42.2% (496)	
Prescriber characteristics		
Medical specialty		1149
Addiction (psychiatry or medicine)	21.6% (248)	
Psychiatry	27.2% (312)	
All other specialties	51.3% (589)	
Membership in American Society of Addiction Medicine (ASAM) and/or American Academy of Addiction Psychiatry (AAAP)		1151
Yes	37.0% (426)	
No	63.0% (725)	
Age in years	55.5 (11.4)	1160
Gender		1165
Female	22.9% (267)	
Male	77.1% (898)	
Race/ethnicity		1148
White	76.5% (878)	
Non-white	23.5% (270)	

[a] Percentages may not sum to 100% due to rounding.
[b] Willingness to terminate treatment ranged from 1 = strongly disagree to 5 = strongly agree. [c] Magnitude of diversion in the community ranged from 0 = not a significant problem to 3 = extremely significant problem.

Lastly, the response to the diversion measure focused on treatment termination, with an item that asked prescribers the extent to which they agreed with the statement, "I will terminate treatment with any patient who diverts the buprenorphine that I have prescribed to them," where 1 = strongly disagree and 5 = strongly agree.

2.3. Independent variables

Independent variables measured the perceived magnitude of diversion in the prescriber's community, buprenorphine practice characteristics, and prescriber characteristics. Prescribers were asked to characterize the magnitude of diversion in their communities as "not a significant problem" (=0), "a moderately significant problem" (=1), "a significant problem" (=2), or "an extremely significant problem" (=3). Practice characteristics included whether prescribers delivered buprenorphine treatment in individual medical practice (1 = yes, 0 = no), types of payment accepted for office visits, number of current buprenorphine patients, and years of prescribing buprenorphine. Accepted payments consisted of four mutually exclusive groups: cash only (reference group), private insurance but not Medicaid, Medicaid (with or

without accepting private insurance), and all others. Waiver type (1 = 100 patients, 0 = 30 patients) was extracted from the May 2014 DEA database. Prescriber characteristics included medical specialty, membership in American Academy of Addiction Psychiatry (AAAP) or American Society of Addiction Medicine (ASAM) versus those who belonged to neither organization, age in years, gender, and race/ethnicity. Medical specialty consisted of three mutually exclusive groups: having credentials in addiction treatment (i.e., addiction medicine or psychiatry), psychiatry (without mention of addiction), and all others (reference group). Race/ethnicity grouped prescribers into those who were white (reference group) and those who were non-white.

2.4. Data management and statistical analysis

Study data were entered into the University of Kentucky's portal for REDCap (Research Electronic Data Capture), which is a secure, web-based application (Harris et al., 2009). All analyses were conducted in Stata 15.0 (StataCorp, College Station, TX). Descriptive statistics were calculated for all variables. To consider the issue of multicollinearity, we examined variance inflation factors (VIFs) in the regression model of

willingness to terminate treatment for diversion, which included the most covariates. The average VIF was 1.30 and only one variable had a VIF that exceeded 2.00, suggesting that multicollinearity was not a substantial issue in the models (O'brien, 2007).

Missing survey data rates ranged from 0.8% for gender (n = 9) to 4.5% (n = 53) for the current number of buprenorphine patients. To reduce the risk of bias associated with complete case analysis (Allison, 2009), multiple imputation by chained equations was implemented (White et al., 2011). Our specification included all independent and dependent variables with the appropriate link function (e.g., logistic regression if dichotomous, Poisson regression if a count, etc.). We used the "augment" option to address the problem of perfect prediction when imputing categorical variables (StataCorp, 2017; White et al., 2010). The multivariate models, using "mi estimate," pooled the results from 20 imputed datasets and used the type of regression appropriate for the level of measurement (i.e., logistic regression for assessment of diversion risk and urine drug screening, negative binomial regression for medication counts, and the logit version of the ordinal regression model for frequency of office visits and treatment termination for diversion (Long, 1997). Each model was estimated with robust standard errors to adjust for the clustering of prescribers within states. In addition to noting when $p < .05$, all p-values were also evaluated using the Benjamini-Hochberg false discovery rate (FDR) approach, which addresses the issue of multiple comparisons (Benjamini and Hochberg, 1995).

3. Results

Among this sample of buprenorphine prescribers, 79.0% (N = 898) reported that they assessed all patients for the risk of diversion and misuse, and 79.1% (N = 901) reported that urine drug screening tested for the presence of buprenorphine (Table 1). During the first 60 days of treatment, 35.5% of prescribers typically saw patients twice per month, and 26.6% saw patients every week or more frequently. There was considerable variability in the percentage of patients for whom medication counts were initiated (mean = 31.4, SD = 38.6). One-third of this sample (33.6%; n = 381) indicated that they had not initiated medication counts for any patients because of diversion concerns in the past year. Willingness to terminate patients for diversion was high, with 50.7% (n = 588) of prescribers indicating strong agreement and another 29.6% (n = 343) reporting agreement with this approach. About half (49.3%; n = 559) of the sample indicated that diversion was a moderately significant problem in their community, another 23.9% (n = 271) reported it was a significant problem, and 11.8% (n = 134) reported diversion was an extremely significant problem.

The logistic regression model of assessment of diversion risk, as measured by assessing all patients in the past year for diversion/misuse risk, appears in the first column of Table 2. Prescribers' perceptions about the magnitude of diversion in their community were positively associated with diversion risk assessment, such that a one-unit increase in the perceived magnitude of the community's diversion problem was associated with a 18.8% increase in the odds of always assessing patients for diversion risk ($p = .0032$). The number of years of prescribing buprenorphine was negatively associated with the odds of assessing all patients for diversion; each additional year of experience was associated with a 5.8% decrease in the odds of assessing for diversion risk ($p = .0011$). Compared to white prescribers, minority prescribers were 45.9% less likely to report assessing all patients for diversion ($p = .0001$).

The ordinal regression model for office visits with the prescriber during the early phase of treatment appears in the second column of Table 2. Perceived magnitude of diversion was positively associated with office visits; physicians who perceived greater diversion reported seeing patients more frequently (AOR = 1.202, 95% CI = 1.060–1.361; $p = .0039$). Compared to cash-only practices, prescribers who accepted Medicaid reported seeing patients significantly more frequently during

the early phase of treatment (AOR = 1.814, 95% CI = 1.213–2.711, $p = .0037$). Addiction specialists (AOR = 1.762, 95% CI = 1.245–2.493, $p = .0014$) and psychiatrists (AOR = 1.817, 95% CI = 1.366–2.418, $p < .0001$) both reported seeing patients significantly more frequently than physicians from other specialties.

In the logistic regression model for urine drug screening that tests for the presence of buprenorphine, five variables were statistically significant. Perceived diversion in the community was positively associated with the odds of including a urine drug screen that always tests for buprenorphine; each one-unit increase in this scale was associated with a 27.8% increase in the odds of always testing for the presence of buprenorphine ($p = .0123$). The current number of patients was positively associated with the likelihood of always testing; each additional patient was associated with a 1.7% increase in the odds of testing for buprenorphine ($p < .0001$). Prescribing experience was negatively associated with the likelihood of testing; an additional year of experience was associated with a 10.6% decrease in the odds of testing for buprenorphine ($p < .0001$). Physicians holding the 100-patient waiver had 64.1% increased odds to test for buprenorphine than physicians with the 30-patient waiver ($p = .0052$). Psychiatrists had 44.9% decreased odds to report testing for buprenorphine when compared to physicians from other specialties (p = .0002).

In the negative binomial regression model of the percentage of patients with medication counts initiated, there was a positive association between the perceived magnitude of diversion and medication counts (IRR 1.186, 95% CI 1.081–1.302, $p = .0003$). Members of ASAM/AAAP reported a significantly higher rate of medication counts (IRR 1.358, 95% CI 1.173–1.573, $p < .0001$) than physicians who were not members of either organization.

Table 3 displays the ordinal logistic regression model of response to diversion as measured by willingness to terminate treatment. Prescribers with greater percentages of patients with medication counts reported greater willingness to terminate patients from treatment for diverting their medication (AOR 1.006, 95% CI 1.003–1.009, $p < .0001$). Willingness to terminate patients was significantly greater among prescribers who perceived diversion as a more significant problem within their community (AOR 1.212, 95% CI 1.073–1.369, $p = .0020$). Addiction specialists (AOR 0.526, 95% CI 0.406–0.682, $p < .0001$) and psychiatrists (AOR 0.714, 95% CI 0.558–0.914, $p = .0075$) were less willing to terminate treatment compared to prescribers from non-addiction/non-psychiatry specialties.

4. Discussion

This study examined perceptions of and practices to assess and mitigate diversion in a large sample of US buprenorphine prescribers. The vast majority of prescribers report routinely assessing patients for diversion. This approach is consistent with the view held by half of the prescribers that diversion poses a moderately significant problem and a third of prescribers who felt it was a significant or very significant problem in their community. Consistent with a prior study indicating that buprenorphine prescribers take multiple measures to mitigate diversion (Yang et al., 2013), in our analyses, most prescribers test for buprenorphine in urine drug screens and see patients relatively frequently early in treatment. The majority reported initiating medication counts for one or more patients in the past year to assess for diversion. This study also shows that, as buprenorphine prescribing has dramatically increased in this country, the majority of prescribers report using recommended practices to assess for diversion.

In examining a wide range of prescriber characteristics, perceived magnitude of diversion in the community was associated with all four diversion mitigation practices of always assessing for diversion, seeing patients frequently early in treatment, using urine screens to test for buprenorphine, and implementing medication counts. Underlying attitudes and beliefs have been shown to be associated with concern about dangers of diversion (Schuman-Olivier et al., 2013). In this case,

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Table 3

Ordinal regression model examining prescriber factors and willingness to terminate treatment for concerns of diversion (N = 1174).

	AOR (95% CI)
Diversion-related practices	
Assesses all patients for diversion (vs. assesses < 100% of patients)	1.229 (0.917 1.647)
Frequency of office visits in early treatment	0.920 (0.797, 1.062)
Always tests urine screen for buprenorphine (vs. does not always test)	1.143 (0.877, 1.490)
Percentage of patients with medication counts	1.006*** (1.003, 1.009)
Magnitude of the diversion problem in the community	1.212** (1.073, 1.369)
Buprenorphine practice characteristics	
Delivers buprenorphine treatment in individual medical practice (vs. not individual practice)	1.067 (0.784, 1.452)
Payment typology	
Only accepts cash	Reference
Accepts private insurance but not Medicaid	0.935 (0.693, 1.261)
Accepts Medicaid	0.670*[+] (0.474, 0.947)
All other types of payment	0.723 (0.406, 1.286)
Current number of buprenorphine patients	0.999 (0.997, 1.001)
Years of prescribing buprenorphine	0.980 (0.940, 1.021)
Waivered to treat up to 100 patients (vs. 30 patients)	0.933 (0.712, 1.223)
Prescriber characteristics	
Medical specialty	
Addiction (psychiatry or medicine)	0.526*** (0.406, 0.682)
Psychiatry	0.714** (0.558, 0.914)
All other specialties	Reference
Member of ASAM/AAAP (vs member of neither)	0.859 (0.670, 1.100)
Age	1.007 (0.995, 1.018)
Female (vs. male)	1.199 (0.942, 1.527)
Non-white (vs. white)	1.280 (0.963, 1.702)
Threshold 1	−3.700 (-4.499, −2.900)
Threshold 2	−2.115 (-2.806, −1.425)
Threshold 3	−1.209 (-1.870, −0.549)
Threshold 4	0.259 (−0.451, 0.970)

Notes. *p < .05, **p < .01, ***p < .001 (two-tailed tests). [+]p-value exceeds the false discovery rate (FDR) value for statistical significance when adjusting for multiple comparisons. AOR = adjusted proportional odds ratio. CI = confidence interval. Responses to this dependent variable were 1 = strongly disagree, 2 = disagree, 3 = neither agree nor disagree, 4 = agree, and 5 = strongly agree. The model was estimated using the logit version of the ordinal regression model with robust standard errors to adjust for the clustering of prescribers within states. Thresholds represent estimated cutpoints on the underlying latent variable of willingness to terminate patients. Threshold 1 is the estimated cutpoint used to differentiate "strongly disagree" responses from all other categories when values of the independent variables are zero. Threshold 2 is the estimated cutpoint that differentiates the groups "strongly disagree" and "disagree" from the remaining three groups when the independent variables are set at zero. Similar logic applies to Threshold 3 ("strongly disagree, 'disagree' and "neither" vs. "agree" and "strongly agree) and Threshold 4 ('strongly disagree, "disagree,' 'neither,' and "agree vs. "strongly agree). Pooled estimates were calculated from models estimated using 20 imputed datasets (n = 1174).

emphasized by guidelines in these analyses. Additional strategies include using formulations that combine buprenorphine and naloxone, clear policies about diversion communicated to patients and education about harms of diversion, recommending additional supports, and checking state prescription monitoring programs regularly. In addition, when there is concern about diversion, strategies may include using supervised dosing (by clinic staff or potentially other healthcare providers including pharmacy staff), intensifying care (e.g., referral for higher levels of care), referring for concurrent psychotherapeutic interventions, increasing the frequency of visits to ensure medication adherence, and changing medications, all of which may mitigate risk of relapse and decrease diversion. Future research should consider these additional practices. Interestingly, addiction specialty prescribers and psychiatrists were less likely to terminate patients due to concerns of diversion, potentially indicating further training in addiction may confer greater comfort with managing these higher risk behaviors. However, it may also be that providers with further addiction training are more likely to practice in urban and other areas of high patient

concentration, where they are able to refer patients to higher intensity of care, including supervised dosing clinics and inpatient settings. Addressing diversion is a complex clinical dilemma and contextual factors, including availability of services, may need to be explored in the future alongside provider practices addressing diversion.

4.1. Limitations

A number of limitations should be noted. This national survey relied upon a cross-sectional design which cannot be used to make causal inferences. At the time of the study, physicians were the only medical prescribers who were allowed to prescribe buprenorphine. It is unknown whether these results would generalize to nurse practitioners and physician assistants, two groups who can prescribe now after meeting specific requirements (Department of Health and Human Services, 2016). Other unmeasured practice and prescriber characteristics, such as the presence of other clinical staff including nurses and counselors, may be associated with the dependent variables but were not captured in the survey. There are additional limitations based on the survey measures. The question about the urine drug screen did not differentiate whether the test was measuring the presence of buprenorphine versus the metabolite nor-buprenorphine. The measure of urine drug screens collapsed respondents who do not conduct urine drug testing with those that do not always test for buprenorphine, although other survey items suggest that only 5% of the sample do not conduct any urine drug testing. It also is unknown whether physicians are utilizing urine drug screens at every visit. Finally, it is not possible to differentiate whether physicians answered our measure of medication counts with a zero because they had no patients who they suspected of diversion or because they do not ever conduct medication counts.

The limited response rate is a considerable limitation, although it is a common challenge in national surveys of physicians (Keto et al., 2015; Macalino et al., 2009). Our sampling strategy resulted in respondents being well-distributed across the nation, although the proportion from some of the mid-Atlantic states was slightly lower than their representation among all waivered physicians in the DEA database. Because of our focus on current prescribers, physicians with the 100-patient waiver were far more likely to be eligible for the study, and these physicians were more likely to respond (36.5% response rate) than physicians with the 30-patient waiver (29.3% response rate). However, it is worth nothing that, while higher response rates may be assumed to be superior, empirical analyses of response bias have shown that response rates do not have a large impact on point estimates (Davern et al., 2010) or upon the associations between variables (Mealing et al., 2010). Nonetheless, it is impossible to know whether these findings generalize to prescribers who did not participate.

Despite these limitations, this study provides new information regarding prescriber practices to mitigate diversion and the associations with prescriber and practice characteristics. Most buprenorphine prescribers in this national survey reported diversion was at least a moderately significant problem in their community and described routinely assessing for diversion through practices including frequent visits early in treatment, urine screens for buprenorphine, and using medication counts when diversion is suspected. A number of characteristics were associated with these three practices, including beliefs about diversion being a problem in the community. There was some variability in how prescribers approached patients when diversion was suspected, though the majority agreed with termination. This is an area in need of further research. Little is known about patient outcomes if they are terminated for diversion and how this would compare with outcomes if alternative approaches were taken. Future research should examine in detail how providers are assessing for diversion and treatment approaches to diversion in order to inform clinical practice. Additional guidance on how to proceed when diversion is suspected, including recommendations about escalation in treatment/monitoring versus termination, may help prescribers better respond to the challenging issue of

diversion while ensuring access to this treatment that has been shown to save lives and have public health benefits (Auriacombe et al., 2004; Schwartz et al., 2013).

Contributors

Lewei Lin and Hannah Knudsen helped to conceptualize the analysis and drafted the initial manuscript. Hannah Knudsen is the PI for the study that provided the data for this manuscript and conducted the statistical analysis. Sharon Walsh and Michelle Lofwall helped with data interpretation, provided expertise on topic area, and edited the manuscript. Adam Gordon helped interpret findings and edited the manuscript. All authors reviewed and revised the manuscript and approved the final manuscript as submitted.

Conflicts of interest

Lewei Lin, Hannah Knudsen, and Adam Gordon have no conflicts of interest. Michelle Lofwall has received contract research funding from Braeburn Pharmaceuticals, has provided consultation for Indivior, and has received honoraria from PCM Scientific, which received unrestricted educational grant funds from Reckitt Benckiser (now Invidior) for developing and delivering educational presentations on opioid use disorder. Sharon Walsh has received consulting fees and research support from Braeburn Pharmaceuticals, consulting fees from Camurus, honoraria and travel support from Indivior, and honoraria from PCM Scientific, through an unrestricted educational grant from Reckitt Benckiser, as a speaker and conference organizer.

References

Allen, B., Harocopos, A., 2016. Non-prescribed buprenorphine in New York City: motivations for use, practices of diversion, and experiences of stigma. J. Subst. Abuse Treat. 70, 81–86.

Allison, P.D., 2009. Missing data. In: Millsap, R.E., Maydeu-Olivares, A. (Eds.), The SAGE Handbook of Quantitative Methods in Psychology. SAGE Publications, Thousand Oaks, CA, pp. 72–89.

Andrilla, C.H.A., Coulthard, C., Larson, E.H., 2017. Barriers rural physicians face prescribing buprenorphine for opioid use disorder. Ann. Fam. Med. 15, 359–362.

Auriacombe, M., Fatseas, M., Dubernet, J., Daulouede, J.P., Tignol, J., 2004. French field experience with buprenorphine. Am. J. Addict. 13, S17–28.

Bazazi, A.R., Yokell, M., Fu, J.J., Rich, J.D., Zaller, N.D., 2011. Illicit use of buprenorphine/naloxone among injecting and noninjecting opioid users. J. Addict. Med. 5, 175–180.

Benjamini, Y., Hochberg, Y., 1995. Controlling the false discovery rate: a practical and powerful approach to multiple testing. J. R. Stat. Soc. Ser. B Methodol. 57, 289–300.

Cicero, T.J., Ellis, M.S., Surratt, H.L., Kurtz, S.P., 2014. Factors contributing to the rise of buprenorphine misuse: 2008–2013. Drug Alcohol Depend. 142, 98–104.

Clemans-Cope, L.E., Marni Kenney, Genevieve, M., 2017. Rapid Growth in Medicaid Spending on Medications to Treat Opioid Use Disorder and Overdose. Urban Institute Accessed at: https://www.urban.org/research/publication/rapid-growth-medicaid-spending-medications-treat-opioid-use-disorder-and-overdose.

Davern, M., McAlpine, D., Beebe, T.J., Ziegenfuss, J., Rockwood, T., Call, K.T., 2010. Are lower response rates hazardous to your health survey? An analysis of three state telephone health surveys. Health Serv. Res. 45, 1324–1344.

Department of Health and Human Services (DHHS), 2016. Medication Assisted Treatment for Opioid Use Disorders. Fed. Regist. 81. Department of Health and Human Services, Washington, DC.

Donroe, J.H., Holt, S.R., O'Connor, P.G., Sukumar, N., Tetrault, J.M., 2017. Interpreting quantitative urine buprenorphine and norbuprenorphine levels in office-based clinical practice. Drug Alcohol Depend. 180, 46–51.

Han, B., Compton, W.M., Jones, C.M., Cai, R., 2015. Nonmedical prescription opioid use and use disorders among adults aged 18 through 64 years in the United States, 2003–2013. JAMA 314, 1468–1478.

Harris, P.A., Taylor, R., Thielke, R., Payne, J., Gonzalez, N., Conde, J.G., 2009. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. J. Biomed. Inf. 42, 377–381.

Kardas, P., Lewek, P., Matyjaszczyk, M., 2013. Determinants of patient adherence: a review of systematic reviews. Front. Pharmacol. 4, 91.

Kenney, S.R., Anderson, B.J., Bailey, G.L., Stein, M.D., 2017. The relationship between diversion-related attitudes and sharing and selling buprenorphine. J. Subst. Abuse Treat. 78, 43–47.

Keto, J., Jokelainen, J., Timonen, M., Linden, K., Ylisaukko-oja, T., 2015. Physicians discuss the risks of smoking with their patients, but seldom offer practical cessation support. Subst. Abuse Treat. Prev. Policy 10, 43.

Lee, J.D., Nunes, E.V., Novo, P., Bachrach, K., Bailey, G.L., Bhatt, S., Farkas, S., Fishman, M., Gauthier, P., Hodgkins, C.C., King, J., Lindblad, R., Liu, D., Matthews, A.G., May, J., Peavy, K.M., Ross, S., Salazar, D., Schkolnik, P., Shmueli-Blumberg, D., Stablein, D., Subramaniam, G., Rotrosen, J., 2017. Comparative effectiveness of extended-release naltrexone versus buprenorphine-naloxone for opioid relapse prevention (X:BOT): a multicentre, open-label, randomised controlled trial. Lancet 391, 309–318.

Lofwall, M.R., Havens, J.R., 2012. Inability to access buprenorphine treatment as a risk factor for using diverted buprenorphine. Drug Alcohol Depend. 126, 379–383.

Lofwall, M.R., Walsh, S.L., 2014. A review of buprenorphine diversion and misuse: the current evidence base and experiences from around the world. J. Addict. Med. 8, 315–326.

Long, J.S., 1997. Regression Models for Categorical and Limited Dependent Variables. SAGE, Thousand Oaks, CA.

Macalino, G.E., Sachdev, D.D., Rich, J.D., Becker, C., Tan, L.J., Beletsky, L., Burris, S., 2009. A national physician survey on prescribing syringes as an HIV prevention measure. Subst. Abuse Treat. Prev. Policy 4, 13.

Martins, S.S., Sarvet, A., Santaella-Tenorio, J., Saha, T., Grant, B.F., Hasin, D.S., 2017. Changes in US lifetime heroin use and heroin use disorder: prevalence from the 2001–2002 to 2012–2013 National Epidemiologic Survey on Alcohol and Related Conditions. JAMA Psychiatry 74, 445–455.

Mattick, R.P., Breen, C., Kimber, J., Davoli, M., 2014. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. Cochrane Database Syst. Rev. 2, Cd002207.

Mealing, N.M., Banks, E., Jorm, L.R., Steel, D.G., Clements, M.S., Rogers, K.D., 2010. Investigation of relative risk assessments from studies of the same population with contrasting response rates and designs. BMC Med. Res. Methodol. 10.

Nielsen, S., Larance, B., Degenhardt, L., Gowing, L., Kehler, C., Lintzeris, N., 2016. Opioid agonist treatment for pharmaceutical opioid dependent people. Cochrane Database Syst. Rev. 5, Cd011117.

Nielsen, S., Larance, B., Lintzeris, N., 2017. Opioid agonist treatment for patients with dependence on prescription opioids. JAMA 317, 967–968.

Nieuwlaat, R., Wilczynski, N., Navarro, T., Hobson, N., Jeffery, R., Keepanasseril, A., Agoritsas, T., Mistry, N., Iorio, A., Jack, S., Sivaramalingam, B., Iserman, E., Mustafa, R.A., Jedraszewski, D., Cotoi, C., Haynes, R.B., 2014. Interventions for enhancing medication adherence. Cochrane Database Syst. Rev. 11, CD000011.

O'brien, R.M., 2007. A caution regarding rules of thumb for variance inflation factors. Qual. Quant. 41, 673–690.

Schuman-Olivier, Z., Connery, H., Griffin, M.L., Wyatt, S.A., Wartenberg, A.A., Borodovsky, J., Renner, J.A., Weiss, R.D., 2013. Clinician beliefs and attitudes about buprenorphine/naloxone diversion. Am. J. Addict. 22, 574–580.

Schwartz, R.P., Gryczynski, J., O'Grady, K.E., Sharfstein, J.M., Warren, G., Olsen, Y., Mitchell, S.G., Jaffe, J.H., 2013. Opioid agonist treatments and heroin overdose deaths in Baltimore, Maryland, 1995–2009. Am. J. Public Health 103, 917–922.

StataCorp, 2017. Stata Multiple-imputation Reference Manual, Release 15. StataCorp, College Station, TX.

Substance Abuse and Mental Health Services Administration (SAMHSA), 2004. Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction Tip 40. Substance Abuse and Mental Health Services Administration, Rockville, MD.

Suzuki, J., Zinser, J., Issa, M., Rodriguez, C., 2017. Quantitative testing of buprenorphine and norbuprenorphine to identify urine sample spiking during office-based opioid treatment. Subst. Abuse 38, 504–507.

Tanum, L., Solli, K.K., Latif, Z.-E.H., Benth, J.Š., Opheim, A., Sharma-Haase, K., Krajci, P., Kunøe, N., 2017. The effectiveness of injectable extended-release naltrexone vs daily buprenorphine-naloxone for opioid dependence: a randomized clinical noninferiority trial. JAMA Psychiatry 74, 1197–1205.

White, I.R., Daniel, R.M., Royston, P., 2010. Avoiding bias due to perfect prediction in multiple imputation of incomplete categorical data. Comput. Stat. Data Anal. 54, 2267–2275.

White, I.R., Royston, P., Wood, A.M., 2011. Multiple imputation using chained equations: issues and guidance for practice. Stat. Med. 30, 377–399.

Yang, A., Arfken, C.L., Johanson, C.-E., 2013. Steps physicians report taking to reduce diversion of buprenorphine. Am. J. Addict. 22, 184–187.