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BRIEF REPORT

Impact of Alternative Ways to Operationalize Buprenorphine Treatment Duration on Understanding Continuity of Care for Opioid Use Disorder

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Medications for opioid use disorder (OUD), including buprenorphine, methadone, and naltrexone, are effective approaches to address the opioid crisis (Wakeman, 2022). Buprenorphine, an opioid agonist medication, is attractive as a first-line treatment for OUD, given its favorable safety profile, fewer clinical barriers to initiation and retention in real-world contexts, and greater potential for widespread usage (Shulman et al., 2019).

Buprenorphine treatment continuity (i.e., whether someone remains in treatment) is indicative of the quality of addiction care because it means that patients are not experiencing gaps in treatment which may, in turn, increase the risk of overdose (Gibbons et al., 2022) and other problematic outcomes (Gibbons et al., 2022; Dupouy et al., 2017). Treatment continuity, as a clinical concept, affects definitions of other commonly used treatment outcomes, including treatment duration, discontinuation, and retention, and thus affects researchers' and clinicians' understanding of the quality of buprenorphine treatment received.

Because of its impact on our understanding of OUD treatment, how researchers decide to measure treatment continuity is critical. One common way that treatment continuity is measured is episode duration, or how long people receive buprenorphine before a gap in refilling a subsequent prescription occurs. Duration is operationalized as the maximum allowable gap in the supply of remaining medication before a new episode begins. Longer allowable gaps without a refill produce episode durations that are longer. However, the choice of the maximum allowable gap in the existing literature is inconsistent, ranging from 5 to 30 days and sometimes even longer (e.g., 90 days) (Samples et al., 2018; Hui et al., 2017; Gomes et al., 2022; Olfson et al., 2020; Saloner et al., 2017).

In this analysis, we demonstrate how varying the operationalization of buprenorphine episode duration will change the statistical inferences drawn about treatment continuity and, therefore, conclusions drawn about the quality of care. We show this variation using

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an illustrative example, comparing buprenorphine treatment duration between female and male patients. OUD may affect health and treatment outcomes differentially for females and males, given important biological, environmental, and sociocultural differences (Becker et al., 2017). But results have been inconsistent when comparing treatment retention — one measure of treatment continuity — between females and males, with some showing better treatment retention for females and others showing better retention for males (Huhn et al., 2019). Given the results presented here, these inconsistent findings may be attributable to how treatment episode durations were operationalized.

Methods

We utilized buprenorphine prescription records from the IQVIA Real World Longitudinal Prescription Data (LRx). We analyzed a random sample, containing 867,788 patients with 28,335,185 dispensed buprenorphine prescriptions for OUD between January 2010 and December 2020. The population coverage of IQVIA LRx has increased over time to include 74–92% of retail pharmacy prescriptions, 60–80% of traditional and specialty mail orders, and 50–70% of long-term care.

To extract buprenorphine prescription records for treating OUD, we first filtered data based on the market product names. We selected all records involving "Bunavail," "buprenorphine/naloxone," "buprenorphine," "Probuphine," "Sublocade," "Suboxone," "Subutex," and "Zubsolv." To attempt to exclude medication prescribed for pain treatment, we further restricted the data based on the Uniform System of Classification (USC) code. We included prescription records with USC as "drug dependence" and excluded ones with "crude/bulk medicinal" and "morphine/opium, injectable." The USC was developed by IQVIA and is widely accepted in North America as the standard for defining the usage of pharmaceutical products (IQVIA, 2018).

To illustrate the influence of different ways of operationalizing a treatment episode's duration, we chose a wide range of values as allowable gaps. Similar to previous studies (Samples et al., 2018; Gomes et al., 2022; Olfson et al., 2020; Saloner et al., 2017; Dong et al., 2022), the start of a new buprenorphine episode was defined as the date when a prescription was filled after an allowable gap (we chose 7, 14, 30, or 60 days) without buprenorphine supply. If two or more prescription records overlapped, we carried the overlapping days supplied forward to calculate the episode duration. We also constructed a sensitivity analysis for buprenorphine treatment episodes without carrying forward the medications on overlapping days.

We examined how different operationalizations could affect the estimated duration of a buprenorphine treatment episode. To visualize trends over time, we presented the observed median episode duration values, then fitted lines using polynomial smoothing functions with R-squared values and corresponding 95% confidence intervals. Additionally, we used quantile regression to examine whether there were statistically significant differences in the median episode duration between females and males each year. We repeated the regression analysis using episodes constructed with different allowable gaps.

We summarized the sociodemographic characteristics (i.e., age, sex, race/ethnicity, region, and payment type) associated with the constructed episodes. All *P*-values were two-sided. Data were analyzed using R software version 4.2.1 (R Core Team, 2022), and the analysis code is available at https://doi.org/10.5281/zenodo.7375434.

Results

Using 7 days as the allowable gap without buprenorphine supply, we identified 3,192,879 treatment episodes. When allowing larger gaps, more prescriptions could be consolidated, resulting in a decrease in the number of discrete episodes. For example, using 60 days as the gap, there were 1,485,831 episodes, a 53.5% decrease in the number of episodes when compared to using 7 days as the gap. On average, females contributed to 42% of the treatment episodes across all analyses. We report the demographic characteristics for buprenorphine treatment episodes in Table S1.

Episode duration increased, as anticipated, when using a larger allowable gap. As shown in Fig. 1A, 30 days was the median episode duration throughout the study period when using 7 days as the gap in both female and male patients. The yearly median episode duration across all patients increased to 42 days (range: 37–47) using 14 days as the gap, 63 days (60–74) using 30 days as the gap, and 89 days (78–111) using 60 days as the gap.

When comparing the episode duration between females and males in each year, there were no differences with a 7-day allowable gap, as both groups had a median episode duration of 30 days. However, when using 14 days as the gap, females had a significantly longer

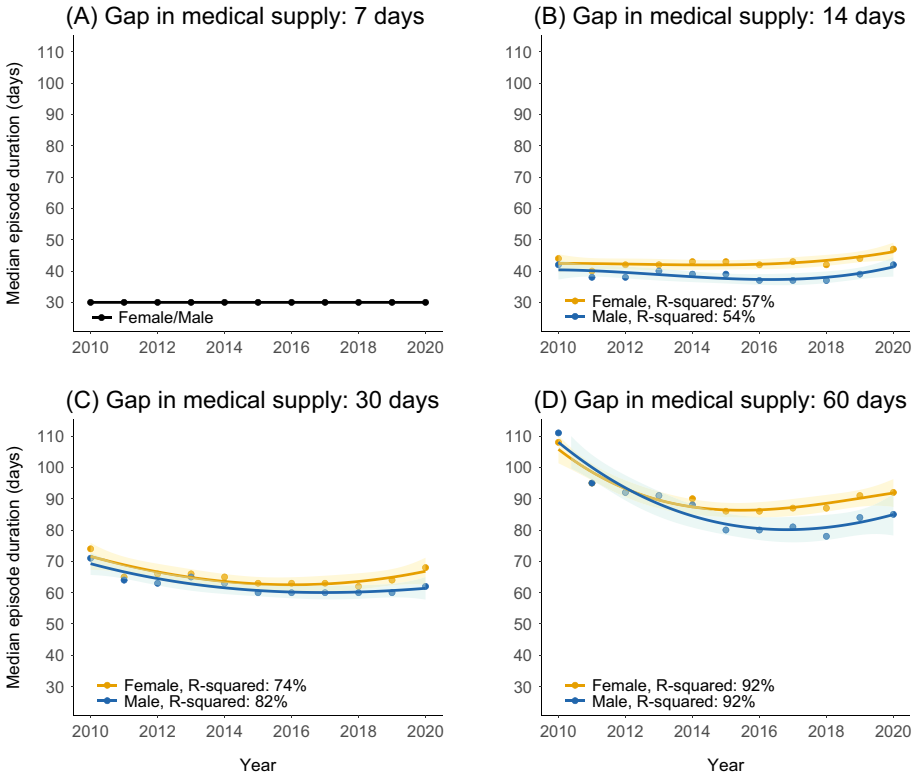

Fig. 1 Trends of buprenorphine episode duration in the USA based on the different maximum allowed gap durations (7, 14, 30, or 60 days), stratified by sex, 2010–2020. Lines were fitted based on polynomial smoothing functions and presented with 95% confidence intervals using the shaded areas and the corresponding R-squared values. Raw data points and fitted lines can be found at https://doi.org/10.5281/zenodo.7375434

median episode duration than males every year, with the largest difference seen in 2017 (Fig. 1B). When we changed the gap to 30 days, females had significantly longer episodes than males except in 2011 (P-value = 0.272) and 2013 (P-value = 0.255), and the largest difference occurred in 2020 (Fig. 1C). With a 60-day allowable gap, we did not detect any statistically significant difference between females and males in the median episode duration until 2015 (Fig. 1D). From 2015 to 2020, females had significantly longer episodes than males, and the largest difference was in 2018 (P-value < 0.001). We present the detailed test results in Table S2.

In the sensitivity analysis, where medications on overlapping days were not carried forward to construct treatment episodes, the results were overall consistent with the findings in the primary analysis. There were similar variations of the trends in the median episode duration for females and males when using different operationalizations of episode duration (Fig. S1).

Discussion

We demonstrated that different ways of operationalizing treatment duration could affect the conclusions drawn about whether there are differences in treatment continuity between females and males, pointing to the importance of how such operationalizations can drastically affect our understanding of OUD treatment with buprenorphine. Our study also contributes to the literature by quantifying buprenorphine treatment duration over time for females and males using a nationally representative sample.

Our analysis shows that an investigator using the 7-day gap may conclude there are no meaningful differences in buprenorphine episode duration in any year between females and males. In contrast, another using a 14-day or 30-day gap between prescriptions would conclude there are differences in all or most years. A third using the 60-day gap would conclude that differences had only emerged recently.

The lack of consensus on how to operationalize buprenorphine episode duration makes it challenging to have meaningful discussions about key treatment outcomes, such as continuity of care, and translate research findings into effective practice changes. Therefore, researchers should interpret study findings with an awareness of the potential consequences of choosing a specific measure (e.g., episode duration) and operationalization of that measure (e.g., maximum allowable gap before defining a new episode), including how it may impact conclusions drawn about commonly used treatment outcomes (i.e., treatment engagement rate (Olfson et al., 2020), retention, risk of overdose (Stringfellow et al., 2022; Lim et al., 2022)).

Choosing an allowable gap should be empirically defined, based on identifying at which point a gap in buprenorphine supply clearly increases risks, but too little research of this nature has been done. A recent study showed that a period of 15 consecutive days without buprenorphine could increase the risk of opioid overdose for an individual by 1.56 to 4.30 times, depending on buprenorphine formulation and dosage during that brief window (Gibbons et al., 2022). If it only takes a 15-day gap to experience increased overdose risk, then any analysis where a longer gap is allowed is perhaps wrongly attributing overdoses that occur during that gap to an "in treatment" period. Such problems could arise for other outcomes as well — remission or recovery from OUD, changes in use status, and other health conditions — for which there is a lack of standards on definitions, measures, and operationalizations.

Study limitations include that the estimated durations were based on prescriptions dispensed rather than actual use. Given the illustrative purposes of the study, presented trends in buprenorphine treatment duration and differences observed between sexes were not adjusted for potential confounders. Additionally, we did not investigate the causes of sex differences in buprenorphine treatment duration. A large body of literature has revealed that beyond biological differences in responses to substance use (Becker et al., 2017), females and males with OUD could face unique challenges to achieving long-term recovery (Huhn et al., 2019; Huhn & Dunn, 2020; Bawor et al., 2015). These factors may affect buprenorphine treatment continuity differently in female and male patients. We chose sex disparities as an example in this analysis; however, gender identity may be both a more informative marker and also represent a distinct form of disparity separate from sex (Huhn & Dunn, 2020). Ethnic and racial disparities exist in duration, even when using different gaps (Dong et al., 2022), highlighting the need for sensitivity analyses.

Future research should seek to empirically identify the maximum gap in treatment that can occur before problematic outcomes occur and whether it differs between groups with different characteristics or identities. Establishing such a validated cut-off point for these outcomes could be used as the standard operationalization for allowable gaps in medication supply. In lieu of better empirical data, sensitivity analyses with different measures and operationalizations could facilitate generating more robust results.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11469-022-00985-w.

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Data Availability Data and code are available in an online repository that is archived for this article: https://zenodo.org/record/7375434.

Declarations

Conflict of Interest The authors declare no competing interests.

Ethical approval This research study was conducted retrospectively from anonymized data obtained from IQVIA. The Mass General Brigham Institutional Review Board determined this study exempt from review.

References

Bawor, M., Dennis, B. B., Bhalerao, A., et al. (2015). Sex differences in outcomes of methadone maintenance treatment for opioid use disorder: A systematic review and meta-analysis. *Canadian Medical Association Open Access Journal, 3*(3), E344–E351.

Becker, J. B., McClellan, M. L., & Reed, B. G. (2017). Sex differences, gender and addiction. *Journal of Neuroscience Research, 95*(1–2), 136–147.

Dong, H., Stringfellow, E.J., Russell, W.A., Jalali, M.S. (2022). Racial and ethnic disparities in buprenorphine treatment duration in the US. *JAMA Psychiatry,* e223673. https://doi.org/10.1001/jamapsychiatry.2022.3673.

Dupouy, J., Palmaro, A., Fatséas, M., et al. (2017). Mortality associated with time in and out of buprenorphine treatment in French office-based general practice: A 7-year cohort study. *The Annals of Family Medicine, 15*(4), 355–358.

Gibbons, J. B., McCullough, J. S., Zivin, K., Brown, Z. Y., & Norton, E. C. (2022). Association between buprenorphine treatment gaps, opioid overdose, and health care spending in US medicare beneficiaries with opioid use disorder. *JAMA Psychiatry, 79*(12), 1173.

Gomes, T., Campbell, T. J., Kitchen, S. A., et al. (2022). Association between increased dispensing of opioid agonist therapy take-home doses and opioid overdose and treatment interruption and discontinuation. *JAMA, 327*(9), 846–855.

Huhn, A. S., & Dunn, K. E. (2020). Challenges for women entering treatment for opioid use disorder. *Current Psychiatry Reports, 22*(12), 1–10.

Huhn, A. S., Berry, M. S., & Dunn, K. E. (2019). Sex-based differences in treatment outcomes for persons with opioid use disorder. *The American Journal on Addictions, 28*(4), 246–261.

Hui, D., Weinstein, Z. M., Cheng, D. M., et al. (2017). Very early disengagement and subsequent re-engagement in primary care office based opioid treatment (OBOT) with buprenorphine. *Journal of Substance Abuse Treatment, 79*, 12–19.

IQVIA. The Uniform System of Classification (USC). Published 2018. https://zenodo.org/record/7429288. Accessed 19 Nov 2022.

Lim, T. Y., Stringfellow, E. J., Stafford, C. A., et al. (2022). Modeling the evolution of the US opioid crisis for national policy development. *Proceedings of the National Academy of Sciences, 119*(23), e2115714119.

Olfson, M., Zhang, V. S., Schoenbaum, M., & King, M. (2020). Trends in buprenorphine treatment in the United States, 2009–2018. *JAMA, 323*(3), 276–277.

R Core Team. (2022). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria.

Saloner, B., Daubresse, M., & Alexander, G. C. (2017). Patterns of buprenorphine-naloxone treatment for opioid use disorder in a multi-state population. *Medical Care, 55*(7), 669.

Samples, H., Williams, A. R., Olfson, M., & Crystal, S. (2018). Risk factors for discontinuation of buprenorphine treatment for opioid use disorders in a multi-state sample of Medicaid enrollees. *Journal of Substance Abuse Treatment, 95*, 9–17.

Shulman, M., Wai, J. M., & Nunes, E. V. (2019). Buprenorphine treatment for opioid use disorder: An overview. *CNS Drugs, 33*(6), 567–580.

Stringfellow, E. J., Lim, T. Y., Humphreys, K., et al. (2022). Reducing opioid use disorder and overdose deaths in the United States: A dynamic modeling analysis. *Science Advances, 8*(25), eabm8147.

Wakeman, S. (2022). Shifting focus to evidence-based management of substance use disorders. *Annals of Internal Medicine, 175*(5), 753–754.