Supplementary Appendix

Supplement to: Chua K-P, Bicket MC, Bohnert ASB, et al. Buprenorphine dispensing after elimination of the waiver requirement. N Engl J Med 2024;390:1530-2. DOI: 10.1056/NEJMc2312906

This appendix has been provided by the authors to give readers additional information about the work.

Supplemental Appendix

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Appendix 1. Methodological details

Data source. The IQVIA Longitudinal Prescription Database is a comprehensive national database that captures prescriptions dispensed from 92% of U.S. retail pharmacies and the majority of prescriptions dispensed from mail-order and long-term care pharmacies. The database includes prescriptions across all methods of payment, including cash. Data are at the prescription level and are not projected to national totals. The database includes information on all prescriptions dispensed from over 50,000 of the approximately 60,000 retail, mail-order, and long-term care pharmacies in the U.S. In most cases, prescription information derives directly from pharmacies, but in some cases, information derives from software vendors and "switches" (i.e., software companies that process claims submitted by pharmacies to insurers). Data are updated weekly. Upon receipt, IQVIA initiates an extensive quality control process that includes standardization of patient, product, prescriber, payer, and outlet identifiers through IQVIA's reference files; removing duplicate transactions; ensuring prescription dates are valid; and active monitoring of pharmacy status to ensure data reporting stability and demographic accuracy. The database only includes paid claims (i.e., those for dispensed prescriptions).

The database does not capture dispensing from pharmacies in the Veterans Administration or the Indian Health Service, or dispensing from pharmacies that are only open to patients of a particular health system (e.g., pharmacies for Kaiser Permanente). Moreover, the database does not capture medications administered or directly dispensed during a visit, such as injections of extended-release buprenorphine billed to a patient's medical rather than pharmacy benefit. The database does capture buprenorphine prescriptions written in Opioid Treatment Programs if the prescriptions were filled in a pharmacy captured by the IQVIA database.

The database includes an encrypted provider identifier that stays constant across years. The provider identifier comes from IQVIA's provider reference file, which contains information on 6.5 million health care professionals, of which approximately 2.3 million are authorized to write prescriptions. The provider reference file is derived from multiple inputs, including the American Medical Association, National Provider Identifier, Drug Enforcement Agency, and State License Number. As with all IQVIA reference files, quality control for the provider reference file relies on standard business rules along with intelligence from external data users.

The database also includes a non-identifiable patient identifier. IQVIA relies on a trusted third party to ensure confidentiality and accuracy of this identifier. The identifier is derived from first and last name, date of birth, sex, address, and other inputs. The identifier remains unchanged over time and across IQVIA databases and has no missingness.

Ethical approval. Because IQVIA data are de-identified, the Institutional Review Board of the University of Michigan Medical School exempted analyses from human subjects review. Informed consent was not required.

Sample. We used IQVIA's market definition to identify dispensed buprenorphine prescriptions (Uniform System of Classification category 78340). This definition includes buprenorphine products approved for opioid use disorder but excludes those approved to treat pain, such as buprenorphine patches. Among 30,859,898 buprenorphine prescriptions dispensed to U.S. patients during January 1, 2022 – December 31, 2023, we excluded 1,032 (0.003%) written by

veterinarians and 152,387 (0.5%) written by clinicians with a missing provider identifier variable. The final sample included the remaining 30,706,479 prescriptions.

Statistical analysis. To calculate the monthly number of buprenorphine prescribers, we counted the number of unique provider identifiers across all buprenorphine prescriptions dispensed during the month. When counting the monthly number of patients with any buprenorphine dispensing (i.e., at least one dispensed buprenorphine prescription), we assigned patients to the month during which the prescription was filled. For example, if a patient filled a buprenorphine prescription January 15, 2023 that extended to February 15, 2023, that patient would be included in the January patient count but not the February 2023 patient count (assuming the patient did not fill another buprenorphine prescription in February 2023). Similarly, when counting the monthly number of patients initiating buprenorphine, we assigned patients to the month during which the "new prescription" was filled. A new prescription was defined as a buprenorphine prescription dispensed to a patient who had not filled buprenorphine prescriptions in the 180 days to 1 day before the dispensing date.

To assess for abrupt level and slope changes in monthly outcomes during January 2023, we fitted linear segmented regression models with the following specification for month t:[2]

$$Y_t = \beta_0 + \beta_1 * month_t + \beta_1 * post_t + \beta_2 * monthsafter_t + e_t$$

In this regression, β_0 is the intercept. The term month, the coefficient of which represents the monthly rate of change (slope) before January 2023, is a continuous term with values of 1-24 (1 = January 2022 and 24 = December 2023). The term post represents the change in the intercept of observations during January 2023 (the "level change"). This term is an indicator that equaled 0 for January-December 2022 and 1 for January-December 2023. The term monthsafter represents the change in the monthly rate of change in observations after January 2023 (the "slope change"). This term equaled 0 for months 1-13, 1 for month 14, 2 for month 15, and so on. Finally, e_t is a normally distributed error term.

We assessed for autocorrelation using the Cumby-Huizinga test in Stata's actest package.[3] Based on this test, we used Newey-West standard errors with 6 lags in all models. Like Huber-White robust standard errors, Newey-West standard errors are robust to heteroskedasticity, but unlike Huber-White robust standard errors, they are also robust to autocorrelation.[4] Analyses were conducted using R version 4.2.2 and Stata 17.1/MP.

Appendix 2. Additional analyses

Our analysis suggests that after elimination of the buprenorphine waiver requirement, the number of buprenorphine prescribers increased but the number of patients with buprenorphine dispensing changed little. We conducted several analyses to explore the reasons for this finding. First, we explored the possibility that established prescribers shared responsibility for buprenorphine prescribing with their previously non-waivered colleagues, thus increasing the pool of buprenorphine prescribers without increasing the number of patients. If this were occurring frequently, we reasoned that the number of prescribers from whom patients received buprenorphine prescriptions would increase substantially between 2022 and 2023. Moreover, we reasoned that the proportion of patients with buprenorphine prescriptions from multiple prescribers at the same practice address would also increase substantially. However, as shown in the table below, the mean number of prescribers from whom patients received buprenorphine prescriptions changed little between 2022 and 2023, and the proportion of patients with buprenorphine prescriptions from multiple prescribers at the same practice address only increased modestly. Thus, while some prescribers may now be sharing responsibility for buprenorphine prescribing with their previously non-waivered colleagues, our analyses suggest that this practice may not yet be widespread.

Outcome	**2022 (n = 1,426,050 patients with buprenorphine dispensing)**	**2023 (n = 1,483,628 patients with buprenorphine dispensing)**
Mean (SD) number of prescribers from whom patients received buprenorphine prescriptions during the year	1.9 (1.4)	2.0 (1.5)
Number (%) of patients with buprenorphine prescriptions from multiple prescribers at the same practice address	201,810 (14.2%)	254,312 (17.1%)

Second, we explored the possibility that new prescribers in 2023 only prescribed buprenorphine to a small number of patients, perhaps because they have not yet had enough time to build a panel of patients with buprenorphine use or because they predominantly work in settings in which they may only sporadically see patients with opioid use disorder, such as the emergency department, inpatient setting, or pediatric care setting. This possibility was more strongly supported by our analyses. Of the 109,306 unique prescribers accounting for buprenorphine dispensing during 2023, 50,475 were “new” prescribers, defined as prescribers who had not accounted for any buprenorphine dispensing in the 2020-2022 IQVIA Longitudinal Prescription Database. New prescribers only accounted for buprenorphine dispensing to a mean (SD) of 5.7 (34.7) patients in 2023, compared to 45.1 (125.8) patients among the other 58,831 prescribers in 2023.

Appendix 3. Sensitivity analyses

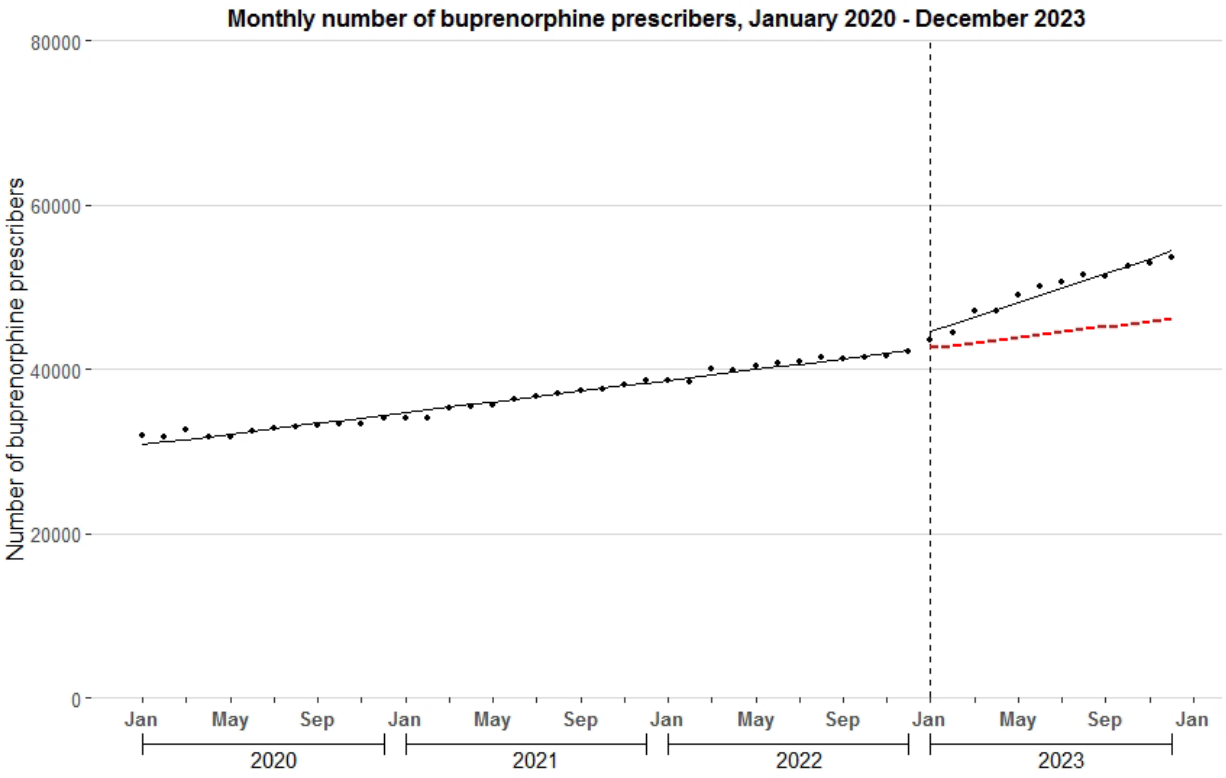
We conducted two sensitivity analyses. First, rather than use linear regression, we used Poisson regression. As shown in **Table S1,** conclusions regarding level and slope changes in January 2023 were qualitatively unchanged.

Second, we expanded the time series to data from January 2020 through December 2023. As shown in **Table S1** and **Figure S1a-Figure S1c**, conclusions regarding level and slope changes in January 2023 were qualitatively unchanged, except that there was a slope decrease in the monthly number of patients with buprenorphine dispensing, unlike in the main analysis, in which there was no slope change. As shown in **Figure S1b**, one potential explanation is that the monthly number of patients with buprenorphine dispensing increased during 2020-2021 and began to flatten in 2022. This flattening was not captured by the fitted line during 2020-2022, which continuously sloped upwards. By limiting to data from 2022-2023 in the main analysis, we were better able to capture the flattening trend before policy implementation. We also were able to limit the study to a period during which health care utilization patterns were less disrupted by the COVID-19 pandemic compared with 2020-2021.

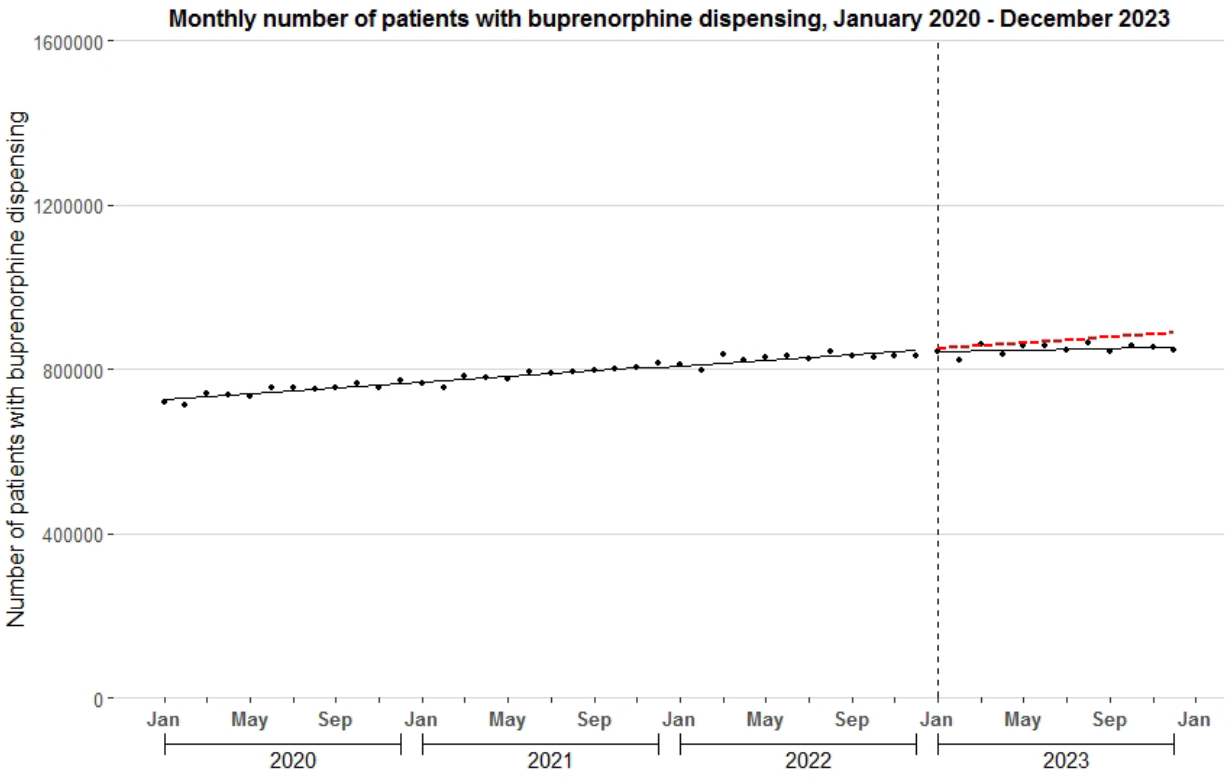
We also note that in the sensitivity analysis using linear models and data from 2020-2023, the coefficient for month for the monthly number of new patients initiating buprenorphine (i.e., the monthly rate of change during January 2020-December 2022) was not different from zero. In contrast, the coefficient for month was negative in the main analysis, which used linear models and data from 2022-2023. This difference in pre-intervention slopes might be driven by outliers in the 2020-2023 data (e.g., the high value in January 2020). Moreover, despite this difference, there was a level increase but no slope change in the monthly number of new patients initiating buprenorphine in both the main analysis and the sensitivity analysis.

Figure S1. Graphs of outcomes in sensitivity analysis using data from 2020-2023. A) Monthly number of buprenorphine prescribers; B) Monthly number of patients with buprenorphine dispensing; C) Monthly number of patients initiating buprenorphine. Initiation was defined as filling a buprenorphine prescription for the first time in a 180-day period. The solid lines are fitted lines from linear segmented regression models evaluating for level and slope changes in outcomes during January 2023 (vertical dashed line). The red dashed line is the counterfactual trend, or the trend that would have occurred had trends from January 2020-December 2022 continued through December 2023.

A.



B.


Monthly number of patients with buprenorphine dispensing, January 2020 - December 2023
Number of patients with buprenorphine dispensing
1600000
1200000
800000
400000
0
Jan
May
Sep
Jan
May
Sep
Jan
May
Sep
Jan
May
Sep
Jan
2020
2021
2022
2023

C.

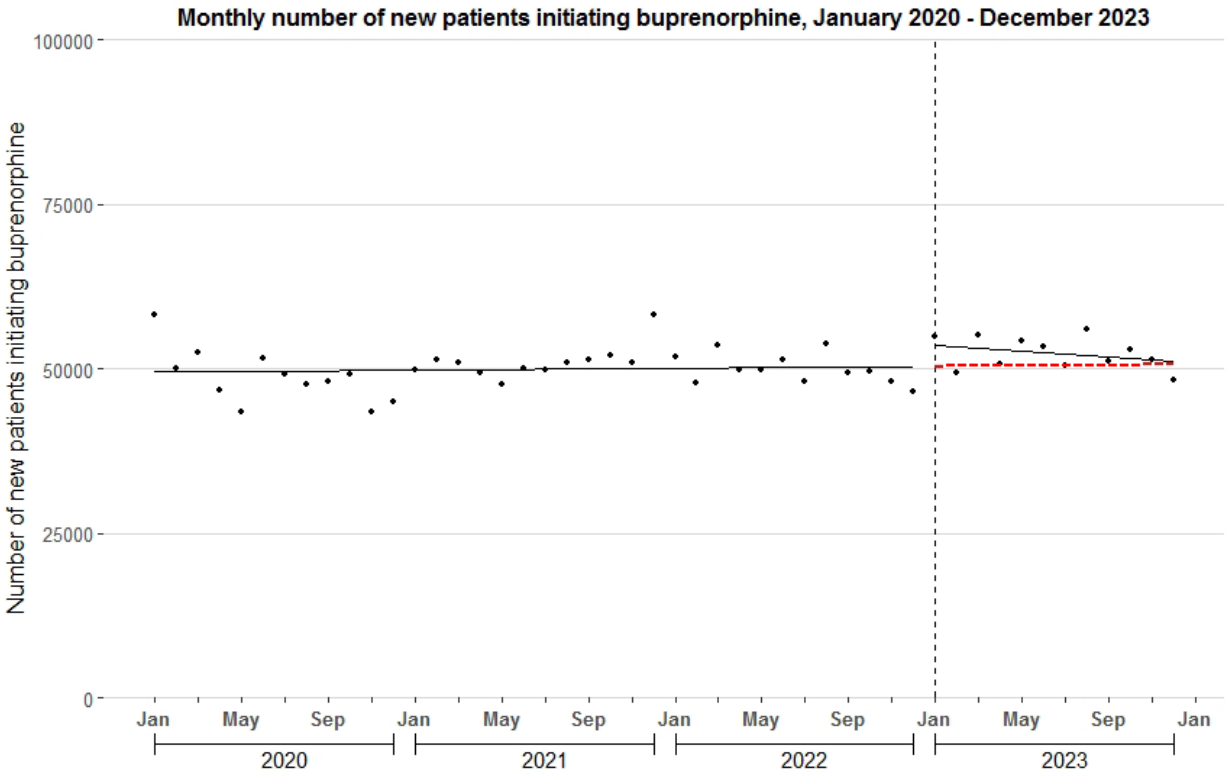

Monthly number of new patients initiating buprenorphine, January 2020 - December 2023
Number of new patients initiating buprenorphine
100000
75000
50000
25000
0
Jan
May
Sep
Jan
May
Sep
Jan
May
Sep
Jan
May
Sep
Jan
2020
2021
2022
2023

Table S1. Results from sensitivity analyses

MONTHLY NUMBER OF BUPRENORPHINE PRESCRIBERS				
Analysis	**Intercept (95% CI)**	**Month (95% CI)**	**Post (95% CI)**	**Monthsafter (95% CI)**
Main analysis: linear model and data from January 2022-September 2023	38,888.6 (38,101,2, 39,061.7)	307.2 (244.6, 369.8)	1,938.3 (989.7, 2,886.9)	589.4 (392.5, 768.3)
Sensitivity analysis: linear model and data from January 2020-September 2023	30,786.5 (30,183.4, 31,385.6)	327.5 (302.3, 352.7)	1,937.3 (758.2, 3,116.3)	569.1 (407.0, 731.2)
Sensitivity analysis: Poisson regression and data from January 2022-September 2023	38,616.3 (38,160.4, 39,077.6)	1.008 (1.006, 1.009)[a]	1.048 (1.026, 1.071) [a]	1.011 (1.006, 1.015) [a]
MONTHLY NUMBER OF PATIENTS WITH BUPRENORPHINE DISPENSING				
Analysis	**Intercept (95% CI)**	**Month (95% CI)**	**Post (95% CI)**	**Monthsafter (95% CI)**
Main analysis: linear model and data from January 2022-September 2023	813,595.9 (802,787.2, 824,313.5)	1,982.4 (602.6, 3,362.1)	2,683.1 (-6,750,7, 12,117.0)	-856.9 (-2,942.5, 1,228.8)
Sensitivity analysis: linear model and data from January 2020-September 2023	727,192.2 (720,563.4, 733,821.0)	3,396.5 (3,028.9, 3,764.2)	-7,417.4 (-20,075.2, 5,240.3)	-2,271.0 (-3,691.3, -850.7)
Sensitivity analysis: Poisson regression and data from January 2022-September 2023	813,667.7 (803,704.9, 823,754.0)	1.002 (1.001, 1.004)[a]	1.003 (0.993, 1.013)[a]	0.999 (0.997, 1.001)[a]
MONTHLY NUMBER OF PATIENTS INITIATING BUPRENORPHINE				
Analysis	**Intercept (95% CI)**	**Month (95% CI)**	**Post (95% CI)**	**Monthsafter (95% CI)**
Main analysis: linear model and data from January 2022-September 2023	51,664.2 (50,151.9, 53,136.6)	-258.6 (-481.1, -36.2)	5,244.5 (3,374.7, 7,114.3)	34.2 (-335.7, 404.0)
Sensitivity analysis: linear model and data from January 2020-September 2023	49,480.2 (46,600.4, 52,359.9)	23.8 (-102.5, 145.0)	3,191.0 (326.8, 6,055.3)	-248.2 (-574.1, 77.6)
Sensitivity analysis: Poisson regression and data from January 2022-September 2023	51,664.7 (50,243.4, 53,126.2)[a]	0.995 (0.991, 0.999)[a]	1.108 (1.070, 1.148)[a]	1.001 (0.994, 1.008)[a]

[a]Reports incidence rate ratios for a one-month increase These ratios were calculated by exponentiating coefficients.

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