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APPENDIX

Missing Data

North Carolina (NC) Controlled Substances Reporting System (CSRS) data captured 94.4% of Medicaid controlled substance claims during our study period. We examined Medicaid claims not captured by the CSRS to assess the potential for bias stemming from systematic missingness. There was no statistical difference between captured vs. non-captured Medicaid claims with regard to time, sex, and comorbid burden. There were negligible, but statistically significant, differences in Medicaid claim capture rate with regard to subject age and rural residence. Based on this evidence we assumed that non-capture of Medicaid prescription claims by the CSRS did not introduce bias into our analysis. Therefore, the main consequence of imperfect CSRS capture was conservative estimates for the prevalence of the study outcome of controlled substance (CS) circumvention biased toward the null.

Continuous Medicaid coverage

Continuous NC Medicaid coverage was defined as having gaps in coverage of no greater than 31 days. Because our definition of continuous enrollment allowed non-consecutive month-long gaps in coverage, we examined the prevalence of month-long coverage gaps in our analytic cohort to assess the level of turbulence in NC Medicaid coverage. High coverage turbulence would likely bias study estimates through inclusion of monthly observations of controlled substance use for which data was not actually measureable. Nearly 93% of study subjects had zero month-long lapses in coverage, while 6.6% had one month of coverage gap, and less than 1% had two non-consecutive months of no NC Medicaid coverage. This level of Medicaid coverage turbulence was consistent with commonly used definitions of continuous Medicaid

enrollment that allow one month of coverage gap for every 12 months of observation.[1,2] A sensitivity analysis was performed excluding the 7% of subjects with one or two coverage gap months. Differences in findings between the sensitivity and base analyses were negligible, so we report results for the full base analytic cohort.

Controlled Substance Drug Product Selection

We included only NC Medicaid claims and NC CSRS records in study analyses for the CS drug products that contributed to a patient's NC Medicaid lock-in program (LIP) eligibility and were subject to NC LIP restrictions. These opioid and benzodiazepine drug products were identified using the First Databank Hierarchical Ingredient Codes: H3A, H3H, H3J, H3M, H3N, H3U, and H3X. All tramadol products were then excluded as these were non-controlled substances at the time of the study period.

It is important to note that antitussive and other cough/cold opioid preparations were not included. Additionally, opioid products for the medication assisted treatment of opioid use disorders, such as the common buprenorphine product Suboxone, were also not included in our analyses. The only buprenorphine product that was included was the long-acting transdermal formulation, Butrans, which was solely indicated for the treatment of chronic pain.

Modeling Approach and Specification

Two generalized estimating equations (GEE) were performed to estimate the association of NC Medicaid LIP enrollment with the two study outcomes: likelihood of a circumvented opioid or benzodiazepine fill in a given month, and the number of circumvented opioid and benzodiazepine fills in a given month. Study data were structured to allow GEE analyses by measuring time-varying variables, including outcome measures, in calendar month increments.

We modeled the binary circumvention outcome using a modified Poisson regression approach in which we specified a Poisson distribution family and log link.[3-5] This was advantageous for numerous reasons. A modified Poisson GEE model allows estimation of relative risk of the outcome, as opposed to odds ratios produced by logistic regression. Relative risks have a more intuitive interpretation than odds ratios and are more accurate and conservative estimators of the relationship between an independent variable and a common outcome than odds ratios. The modified Poisson approach is also more robust to omitted variable bias than logistic regression. The estimated probabilities of a circumvented CS fill presented in Exhibit 4 of the manuscript were obtained through post-estimation prediction of the modified Poisson GEE model at values of zero and one of the NC LIP enrollment binary independent variable.

The second GEE model used a Poisson count model approach to estimate incidence rate ratios of circumvented CS prescription fills. Post-estimation prediction was performed to obtain average number of monthly circumvented CS prescription fills, which are presented in Exhibit 4 of the manuscript.

In both GEE models, we selected a one month autoregressive correlation structure based on examination of the quasi-likelihood information criterion (QIC).[6] We also specified Huber-White robust standard errors in both models. In addition to being necessary to obtain relative risk estimates in the modified Poisson approach, robust standard errors in GEE ensured valid standard errors even in the face of a misspecified correlation structure. Robust standard errors in GEE also account for within-person correlation, which prevents artificially narrow confidence intervals around model estimates.

The full specification of the GEE models, which also controlled for patient- and policy-level characteristics, is displayed in Appendix Exhibit 1. Full model output from both GEE models is presented in Appendix Exhibit 2.

Appendix Exhibit A1: Specification of the generalized estimating equation analytic models

Model 1 (Binary circumvention): Distribution=Poisson, link=log, corr=autoregressive (1 month)

Model 2 (Count circumvention): Distribution=Poisson, link=log, corr=autoregressive (1 month)

$$\text{Circumvention outcome} = \beta_0 + \beta_1 X_{\text{LIP enrollment}} + \beta_2 X_{\text{LIP enrollment*month}} + \beta_3 X_{\text{LIP delay}} + \beta_4 X_{\text{LIP delay*month}} + \beta_5 X_{\text{month}} + \beta_6 X_{\text{LIP period}} + \beta_7 X_{\text{LIP period*month}} + \beta_8 X_{\text{LIP eligibility:opioid}} + \beta_9 X_{\text{LIP eligibility:benzo}} + \beta_{10} X_{\text{LIP eligibility:pharmacy}} + \beta_{11} X_{\text{LIP eligibility:none}} + \beta_{12} X_{\text{Age}} + \beta_{13} X_{\text{Female}} + \beta_{14} X_{\text{Black}} + \beta_{15} X_{\text{Other/unknown race}} + \beta_{16} X_{\text{Metropolitan county}} + \beta_{17} X_{\text{Pharmacy supply:11-25}} + \beta_{18} X_{\text{Pharmacy supply:26-50}} + \beta_{19} X_{\text{Pharmacy supply 51-100}} + \beta_{20} X_{\text{Pharmacy supply:>100}} + \beta_{21} X_{\text{Border county}} + \beta_{22} X_{\text{Chronic pain}} + \beta_{23} X_{\text{Anxiety}} + \beta_{24} X_{\text{Substance use}} + \beta_{25} X_{\text{Depression}} + \beta_{26} X_{\text{Other mental illness}} + \beta_{27} X_{\text{Charlson:1}} + \beta_{28} X_{\text{Charlson:}\geq 2} + \beta_{29} X_{\text{Prescription burden}} + \varepsilon$$

Note: Corr=correlation; LIP=Lock-in program; benzo=benzodiazepine.

Appendix Exhibit A2: Full model output estimating the effect of the lock-in program on controlled substance circumvention behavior

	Any circumvented fill			Number of circumvented fills		
Variable	RR	(95% CI)	P-value	IRR	(95% CI)	P-value
Key independent variable						
LIP enrollment (Key IV)	3.55	(3.13, 4.03)	<0.001	4.40	(3.76, 5.15)	<0.001
LIP policy variables						
LIP enrollment * month	1.00	(0.99, 1.01)	0.675	1.01	(0.99, 1.02)	0.274
LIP enrollment delay	1.28	(1.13, 1.46)	<0.001	1.25	(1.06, 1.47)	0.008
LIP enrollment delay * month	1.02	(1.00, 1.03)	0.031	1.02	(1.00, 1.05)	0.036
Month	1.00	(0.99, 1.01)	0.766	0.98	(0.97, 1.00)	0.025
LIP policy period	0.81	(0.73, 0.91)	<0.001	0.88	(0.77, 1.01)	0.074
LIP policy period * month	0.99	(0.98, 1.00)	0.099	1.00	(0.98, 1.01)	0.645
LIP eligibility route						
Opioid use	1.01	(0.87, 1.16)	0.928	1.10	(0.92, 1.31)	0.283
Benzodiazepine use	1.52	(1.29, 1.79)	<0.001	1.78	(1.47, 2.16)	<0.001
Pharmacy use	1.10	(1.01, 1.21)	0.028	1.18	(1.03, 1.35)	0.018
No eligibility criteria met	0.94	(0.72, 1.22)	0.628	0.96	(0.68, 1.36)	0.834
Predisposing characteristics						
Age	0.994	(0.99, 1.00)	0.001	0.99	(0.99, 1.00)	0.017
Female	0.94	(0.86, 1.02)	0.144	0.88	(0.78, 1.00)	0.053
Race (White referent)						
Black	0.99	(0.90, 1.10)	0.892	0.97	(0.83, 1.13)	0.658
Other	0.96	(0.82, 1.11)	0.551	0.91	(0.74, 1.12)	0.368
Enabling characteristics						
Metropolitan residence	1.01	(0.93, 1.10)	0.806	1.03	(0.91, 1.17)	0.602
County pharmacy supply (<10 referent)						
11-25	1.05	(0.95, 1.17)	0.343	1.03	(0.89, 1.19)	0.673
26-50	1.10	(0.99, 1.22)	0.071	1.06	(0.92, 1.23)	0.414
51-100	1.07	(0.96, 1.20)	0.220	1.04	(0.89, 1.22)	0.623
>100	1.22	(1.07, 1.39)	0.004	1.33	(1.08, 1.65)	0.008
Border county	1.00	(0.93, 1.07)	0.925	1.01	(0.90, 1.14)	0.817
Need characteristics						
Chronic non-cancer pain[1]	1.33	(1.06, 1.68)	0.013	1.48	(1.11, 1.96)	0.008
Anxiety disorder	1.12	(1.04, 1.22)	0.003	1.11	(0.98, 1.25)	0.100
Substance use disorder	1.01	(0.94, 1.08)	0.874	1.03	(0.93, 1.15)	0.573
Depression	1.07	(0.99, 1.16)	0.071	1.11	(0.99, 1.24)	0.070
Other mental illness	1.05	(0.98, 1.13)	0.195	1.03	(0.93, 1.15)	0.542
Charlson Comorbidity Index score						
0 (referent)						
1	1.00	(0.92, 1.09)	0.979	0.98	(0.87, 1.11)	0.753
≥2	1.14	(1.03, 1.25)	0.010	1.15	(0.99, 1.34)	0.074
Prescription drug burden	1.00	(0.99, 1.00)	0.473	1.00	(0.99, 1.01)	0.417

Note: RR=relative risk; CI=confidence interval; IRR=incidence rate ratio; LIP=Lock-in program. RR were obtained through generalized estimating equation (GEE) modeling with monthly measures using Poisson distribution, log link, and autoregressive (1 month) correlation structure with robust standard errors. IRR were obtained through GEE using Poisson distribution, log link, and autoregressive correlation structure with robust standard errors.

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