REASONS FOR EXCLUDING TRAMADOL, BUPRENORPHINE, AND METHADONE

Tramadol was excluded for 2 reasons: (1) Tramadol was classified as a schedule substance in August 2014. Hence, prior to this period, it was not captured in the prescription monitoring program. (2) Tramadol's MME conversion ratio is very small. One will need extremely high doses of tramadol to receive 90 MMEs. The mean daily MME for tramadol was 21.5 compared to 57.4 for non-excluded opioids. In the dataset, only 82 person months of HD-LTOT attributable to tramadol compared to 4,018,726 person months of HD-LTOT attributable to all other opioids except tramadol, methadone, and buprenorphine.

Methadone was excluded because it has a high MME conversion ratio (see CDC MME conversion tables), which means even seeming modest doses of methadone result in very high daily MMEs (this is one reason that methadone is prescribed to individuals who need very high doses of opioids for long periods of time). As seen in our data set, methadone doses only formed about 0.77% of all opioid patients and 1.7% of all opioid prescriptions. Yet, in an average month between 63%–75% of patients on methadone were HD-LTOT (Appendix Figure 2B below), compared to 8%–12% among all other non-excluded opioid patients (Figure 2A from the main manuscript). This suggested to us that population prescribed methadone is very different than other opioid pain reliever patient population. Thus, we elected to exclude methadone, out of an abundance of caution for study validity.

Lastly, we did not have information on buprenorphine because these data were not shared with us by the North Carolina Controlled Substances Reporting System (CSRS). If we were to have data on buprenorphine, we would have still likely excluded them because unlike other opioids it is a partial mu-receptor agonist, and hence it has a ceiling effect thereby reducing the likelihood of an overdose. The majority of buprenorphine present in the CSRS is from opioid use disorder treatment, and its use for pain management is very small.

CONTROLLED INTERRUPTED TIME SERIES (CITS) AND SINGLE INTERRUPTED TIME SERIES (ITS) MODEL EXPLANATIONS:

The CITS model is be written[20] as:

$$\text{Outcome}_{\text{policy (p) X group (A or B) X time (t)}} = \beta0 + \beta1*\text{time}_t + \beta2*\text{level}_p + \beta3*\text{posttrend}_{p*t} + \beta4*\text{group}_k + \beta5*\text{time}_t*\text{group}_k + \beta6*\text{level}_p*\text{group}_k + \beta7*\text{posttrend}_{p*t}*\text{group}_k + \beta_{8\text{-}n}*\text{Confounders} + e$$

where, time (t) is a continuous variable (1,2,3,…n) for the entire monthly series; level is a binary step function variable (0 or 1) for the presence or absence of a specific policy (p); posttrend is a another time variable for the time after the policy implementation (pre-policy, its value is zero); and group (k) is a variable that distinguishes the policy group (opioids) from the control group (benzodiazepines or stimulants). β0=monthly outcome rate in the control group at time 1; β1=the pre-policy trend (slope) of the outcome in the control group; β2=absolute change in the control outcome rate immediately after policy implementation; β3=the pre- and post-policy outcome trend difference for policy 'p' at time 't' in the control group; β4=the difference between outcome rate in the intervention group and control at time 1 (close to zero); β5=the pre-policy outcome trend difference between intervention group and control; β6=the absolute outcome change difference between intervention group and control immediately after policy implementation; β7=the pre- and post-policy trend difference between intervention group and control; $\beta_{8\text{-}n}$=combined term for all confounder coefficients.

Of main interest to us are β6 and β7 that show the immediate and sustained effects of the SOPI, respectively.[20]

The single ITS model can be written as:

$$\text{Outcome}_{\text{policy (p) X time (t)}} = \beta0 + \beta1*\text{time}_t + \beta2*\text{level}_p + \beta3*\text{posttrend}_{p*t} + \beta_{4\text{-}n}*\text{Confounders} + e$$

where, time (t) is a continuous variable (1,2,3,…n) for the entire monthly series; level is a binary step function variable (0 or 1) for the presence or absence of a specific policy (p); and posttrend is a another time variable for the time after the policy implementation (pre-policy, its value is zero). $\beta 0$=monthly outcome rate at time 1; $\beta 1$=the pre-policy trend (slope) of the outcome; $\beta 2$=absolute change in the outcome rate immediately after policy implementation; $\beta 3$=the pre- and post-policy outcome trend difference for policy 'p' at time 't'; β_{4-n}=combined term for all confounder coefficients.

Appendix Table 1. Dispensed Opioids, North Carolina Controlled Substances Reporting System: January 2010–March 2017

Variable	2010	2011	2012	2013	2014	2015	2016	2017 (January –March)	Total
HD-LTOT patients (>=90 MMEs/day for at least 90 days)									
Number	54,896	60,913	70,422	77,132	80,190	83,483	81,639	53,269	206,255
Percent (%) of all opioid patients	2.3	2.5	2.7	3.0	3.2	3.2	3.3	5.4	2.1
Total number of patients who received an opioid prescription	2403,721	2,403,719	2,617,113	2,556,372	2,517,584	2,605,868	2,460,967	988,680	9,913,580
All opioid prescriptions	7,577,907	7,543,423	8,310,530	8,308,978	8,157,022	8,044,868	7,589,091	1,872,887	57,404,706
MME per day									
Mean (SD)	60.5 (73.1)	56.9 (73.8)	57 (72.6)	57 (73)	57.4 (68.9)	57.4 (69.8)	56.1 (72.8)	55.5 (73.6)	57.4 (72)
Median (IQR)	40 (48)	39.1 (35)	40 (35)	40 (35)	40 (35)	40 (35)	40 (35)	40 (35)	40 (35)
MME per dispensed prescription									
Mean (SD)	956.3 (1,749.5)	939.8 (1,763.2)	967 (1,716.4)	1,008.8 (1,705.9)	1,035.3 (1,670)	1,060.2 (1,627.9)	1,047 (1,561.2)	995.8 (1,446)	1,002.3 (1,679.4)
Median (IQR)	450 (862.5)	400 (750)	450 (862.5)	450 (1,050)	450 (1,050)	525 (1,020)	600 (1,170)	600 (1,020)	450 (1,050)
Days' supply									
Mean (SD)	15.3 (13)	15.6 (13)	16 (13)	16.7 (13)	17.2 (13)	17.7 (13)	18 (13)	17.7 (12)	17 (13)
Median (IQR)	10 (26)	10 (25)	12 (25)	14 (25)	15 (25)	15 (25)	19 (25)	15 (25)	14 (25)

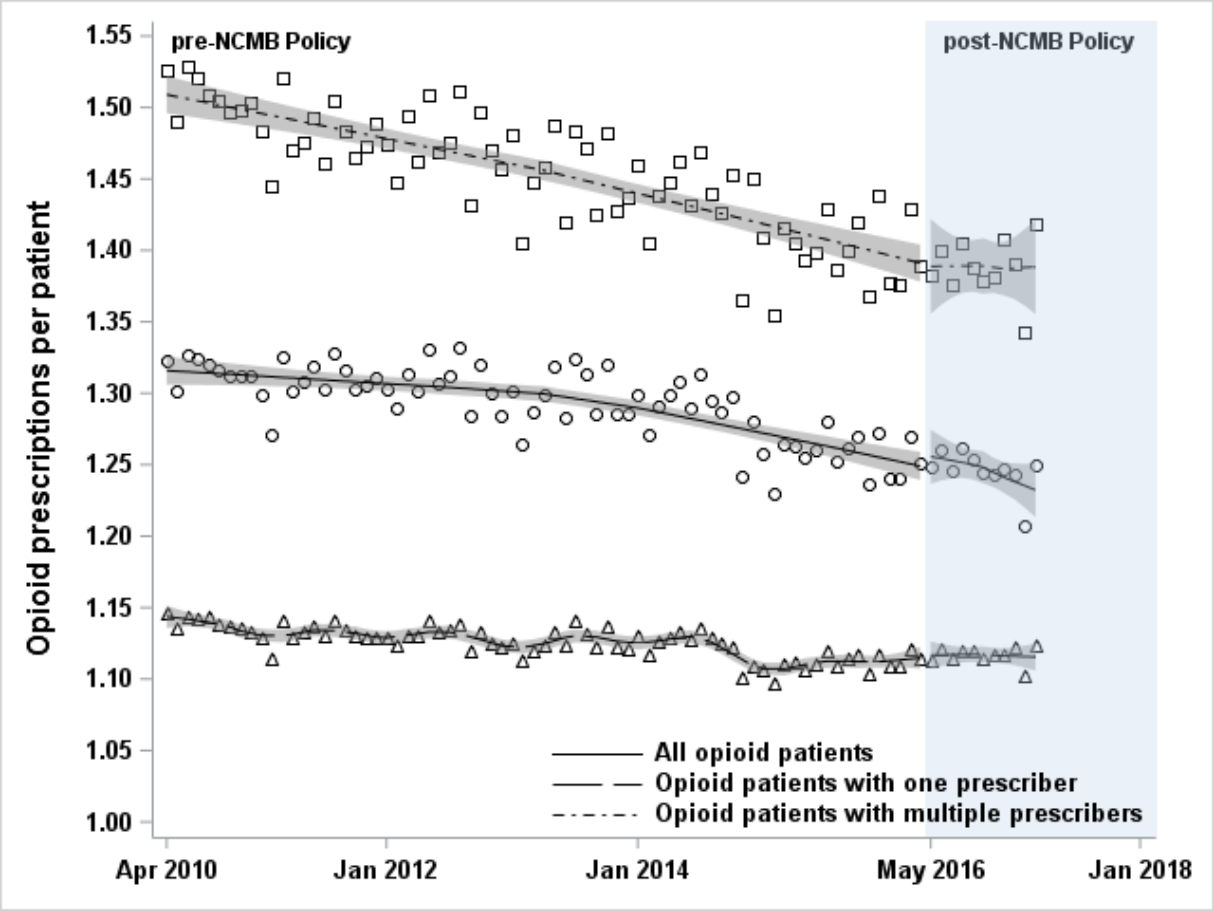
HD-LTOT, high dose long term opioid therapy; MME, morphine milligram equivalents.

Appendix Table 2. Pre- and Post-SOPI Means of All Opioid Patients and Patients Receiving HD-LTOT, North Carolina: April 2010–March 2017

Variable	Pre-SOPI monthly means (April 2010–April 2016)			Post-SOPI monthly means (May 2016–March 2017)			Overall (April 2010–March 2017)		
	Single prescriber patients	Multiple prescriber patients	All patients	Single prescriber patients	Multiple prescriber patients	All patients	Single prescriber patients	Multiple prescriber patients	All patients
Number of opioid patients	252,714	263,568	516,282	260,125	236,569	496,694	253,685	260,032	513,717
NC population filling opioids, %	2.6	2.7	5.3	2.6	2.3	4.9	2.6	2.6	5.2
Number of HD-LTOT patients	4,375	42,953	47,328	6,697	44,555	51,253	4,680	43,162	47,842
Opioid patients with HD-LTOT, %	1.7	16.2	9.1	2.6	18.8	10.3	1.8	16.6	9.3
Number of opioid prescriptions	284,407	382,828	667,235	290,466	328,480	618,946	285,201	375,711	660,912
Mean opioid prescriptions per patient	1.1	1.5	1.3	1.1	1.4	1.2	1.1	1.4	1.3
Number of gradually tapered HD-LTOT patients	141	1,838	1,979	244	2,031	2,275	154	1,864	2,018
HDLTOT gradually tapered, %	3.2	4.3	4.2	3.6	4.5	4.4	3.3	4.3	4.2
Number of rapidly tapered HD-LTOT patients	354	3,656	4,010	474	3,841	4,315	370	3,681	4,050
HDLTOT rapidly tapered, %	8.2	8.6	8.5	7.1	8.6	8.4	8.1	8.6	8.5
Number of discontinued HD-LTOT patients	388	1,730	2,118	441	1,845	2,286	395	1,745	2,140
HD-LTOT discontinued, %	8.9	4.0	4.5	6.7	4.1	4.4	8.6	4.0	4.5

HD-LTOT, high dose long term opioid therapy; NC, North Carolina; SOPI, safe opioid prescribing initiative.

Appendix Figure 1. Association of NCMB SOPI with average opioid prescriptions per opioid patient among all opioid patients in NC: 2010–2017



Sensitivity Analyses:

Anticipatory and lagged policy effects:

For these analyses, the inflection point for the SOPI effects was tested in March, April, and June 2016. Results of the CITS analyses are presented in Appendix Table 3 below.

Appendix Table 3. Sensitivity Analyses to Examine Anticipatory and Lag Effects in the Association of Safe Opioid Prescribing Initiative (SOPI) With Opioid Prescribing Outcomes Among All Opioid Patients in NC: 2010–2017

Anticipatory or lag month/ Outcomes /Control series	Immediate absolute change (β_6) after SOPI (95% CI)	Sustained trend changes (β_7) after SOPI (95% CI)
March		
Proportion of NC population with opioids		
Benzodiazepines	–0.5178 (–0.7851, –0.2505)	0.0307 (–0.0093, 0.0707)
Stimulants	–0.5869 (–0.8568, –0.3170)	0.0084 (–0.0320, 0.0489)
Average opioid Rx per patient		
Benzodiazepines	–0.0006 (–0.0223, 0.0211)	–0.0012 (–0.0044, 0.0020)
Stimulants	–0.0052 (–0.0026, 0.0153)	–0.0017 (–0.0048, 0.0014)
April		
Opioid patients/100 NC population		
Benzodiazepines	–0.4558 (–0.7420, –0.1696)	0.0230 (–0.0190, 0.0650)
Stimulants	–0.5230 (–0.8123, –0.2337)	0.0005 (–0.0419, 0.0429)
Average opioid Rx per patient		
Benzodiazepines	0.0056 (–0.0176, 0.0289)	–0.0020 (–0.0054, 0.0014)
Stimulants	–0.0015 (–0.0236, 0.0206)	–0.0022 (–0.0054, 0.0010)
June		
Opioid patients/100 NC population		
Benzodiazepines	–0.5772 (–0.8646, –0.2898)	0.0364 (–0.0064, 0.0792)
Stimulants	–0.5064 (–0.7932, –0.2196)	–0.0012 (–0.0439, 0.0415)
Average opioid Rx per patient		
Benzodiazepines	0.0018 (–0.0249, 0.0213)	–0.0012 (–0.0046, 0.0022)
Stimulants	–0.0071 (–0.0290, 0.0148)	–0.0015 (–0.0048, 0.0018)

SOPI, Safe Opioid Prescribing Initiative; NC, North Carolina.

Moderate dose long term opioid therapy (MD-LTOT) analyses:
We conducted single ITS analyses to examine the association of SOPI with MD-LTOT rate per 100 opioid patients, and rates of discontinuation and rapid and gradual tapering among MD-LTOT patients. Results are presented in Appendix Table 4 below.

Appendix Table 4. Association of Safe Opioid Prescribing Initiative (SOPI) With Opioid Prescribing Outcomes Among All Opioid Patients and Moderate Dose Long Term Opioid Therapy (MD-LTOT) Patients in North Carolina: 2010–2017

Outcomes	Immediate absolute change after SOPI (95% CI)	Difference between post- and pre-SOPI monthly trends (95% CI)
All patients		
MD-LTOT rate/ 100 opioid patients	1.8195 (0.7472, 2.8918)	–0.4938 (–0.6432, –0.3444)
MD-LTOT patients		
Discontinuation rate/100 HD-LTOT patients	1.0553 (–0.1670, 2.2776)	–0.0523 (–0.2407, 0.1361)
Rapid tapering rate/ 100 HD-LTOT patients	1.7431 (0.6814, 2.8048)	–0.1765 (–0.3053, –0.0083)
Gradual tapering rate/ 100 HD-LTOT patients	0.6100 (0.3557, 0.8643)	–0.0319 (–0.0681, 0.0043)

HD-LTOT, high dose long term opioid therapy; SOPI, Safe Opioid Prescribing Initiative.

Difference-in-differences (DiD) analyses using quarter-over-quarter cohort approach:
In these analyses, we identified all HD-LTOT individuals in the first quarter (January through March0 of a calendar year. Then these individuals are followed till the first quarter of the subsequent calendar year and individuals who are dropped from the HD-LTOT population are identified, and the reason for the dropping out is identified as well in terms discontinuation or tapering (Appendix Table 5 below).

Using these data, we conducted log-binomial regression to estimate risk ratios and 95% CIs adjusted for annual statewide unemployment rate. To estimate the risk differences with 95% CI, we used linear regression with adjustment for annual statewide unemployment rate.

Appendix Table 5. Overall Population for the DiD Analyses

Calendar year	SOPI	HD-LTOT patients from January–March of calendar year	Dropped in January–March of the next calendar year			
			Dropped	Gradual tapering	Rapid tapering	Discontinued
2010	No	36,439	13,155	225	3,747	9,183
2011	No	47,123	15,226	298	4,189	10,739
2012	No	53,130	16,776	329	4,786	11,661
2013	No	61,983	20,131	431	5,585	14,115
2014	No	65,142	20,425	491	5,415	14,519
2015	No	68,089	22,152	564	5,858	15,730
2016	Yes	70,137	27,019	870	7,825	18,324

Notes: The risk ratios (RR) and risk differences (RD) compare the risk of being dropped in the subsequent year (and dropped due to discontinuation or tapering) among the 2016 first quarter HD-LTOT patients to the risk of being dropped in the subsequent year among the 2010–2015 first quarter HD-LTOT patients. Overall, the DiD analyses suggest that the risk of discontinuation, rapid tapering, and gradual tapering all increased after SOPI was implemented in 2016 (Appendix Table 6).

Appendix Table S6. Difference in Differences Analyses to Examine the Association of SOPI Implementation in 2016 Compared to Prior Years on the Risk Being Dropped by Discontinuation and Tapering in the Subsequent Year

Outcomes	Adjusted RR (95% CI)[a]	Adjusted RD (95% CI)[a]
Discontinuation	1.19 (1.14, 1.23)	4.33% (3.49, 5.17)
Rapid tapering	1.37 (1.32, 1.43)	3.19% (2.83, 3.55)
Gradual tapering	1.52 (1.45, 1.59)	0.46% (0.42, 0.50)
Dropped	1.24 (1.20, 1.29)	7.98% (6.76, 9.20)

[a]Adjusted for annual statewide unemployment rate.

RR, risk ratio; RD, risk difference.

Methadone analyses (figures on next page):
Analytic datasets were created by restricting datasets to methadone only. Single ITS analyses were conducted in the same way as those for the non-excluded opioids (excluded opioids include tramadol, buprenorphine, and methadone) using May 2016 as the first month when SOPI is considered as effective. Results suggest that the methadone prescribing rate in NC was decreasing pre-SOPI and continued to decrease at the same rate post SOPI, and there was no immediate decline in the month of May 2016 as seen for the non-excluded opioids (Appendix Figure 2A). Like the non-excluded opioids, the percentage of methadone patients receiving HD-LTOT declined after SOPI implementation (Appendix Figure 2B). The association of SOPI with all other outcomes among methadone patients was similar to that among the non-excluded opioid patient results presented in the main manuscript section (Appendix Figures 2C–2F).

Appendix Figure 2A–2F. Association of SOPI with overall prescribing outcomes among methadone patients and tapering and discontinuation among methadone HD-LTOT patients in NC: single interrupted time series analyses, 2010–2017.

2a-2c **2d-2f**