# Evaluation of a state law on opioid-prescribing behaviour and the void affecting codeine-containing antitussive syrup

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## ABSTRACT

**Background** Government opioid policies—such as the North Carolina Strengthen Opioid Misuse Prevention (STOP) Act—have aided in lowering the days' supply of opioid prescriptions. However, what effect do these laws have on codeine-containing antitussive syrup? We aimed to assess the effect of the North Carolina STOP Act on ED opioid prescriptions written for >5 days for acute pain/non-pain diagnoses and whether it had an effect on the prescribing of codeine-containing antitussive syrup.

**Methods** A retrospective study of two emergency departments, with an average annual census of 70 000 and 22 000 patients, from January to August of 2017 and 2018. We applied logistic regression techniques to calculate the odds of an opioid prescription for >5 days. Opioid medication categories were formed to determine relational proportions. Two-tailed z-tests were used to test the difference in proportions.

**Results** Our study included 5366 verifiable opioid prescriptions. The percentage of an opioid prescription for >5 days decreased by 3.3% (95% CI −1.8% to −4.7%, p<0.05) after the North Carolina STOP Act (9.8% to 6.5%; 95% CI 5.5% to 7.5%, p<0.05). There was no statistically significant change in the prescribing of codeine syrup for >5 days pre-STOP and post- STOP Act, respectively (91.5% and 90.4%; difference=−1.1%, p=0.83).

**Conclusion** The North Carolina STOP Act was associated with a reduction in the overall percentage of opioid prescriptions for >5 days for acute pain/non-pain diagnoses. However, there was no statistically significant effect on the prescribing of codeine-containing antitussive syrup.

## Key messages

**What is already known on this subject?**

- The opioid epidemic has stimulated global governments to make policies that guide the prescribing of opioid medications.
- Prior research studies on opioid-prescribing policies report these policies impact the prescribing behaviour of practitioners and increase the responsible prescribing of opioids.
- The current studies and policies, however, only focus on pain-related conditions and currently do not contain language that guides the prescription of opioids for non-pain-related conditions, such as codeine-containing antitussive syrup for cough.

**What this study adds**

- Our study adds to the literature as it further supports the use of government policies to guide the prescribing of opioids; however, it also adds a new suggestion that these current policies may have a minimal effect on the prescribing of codeine-containing antitussive syrup, a commonly prescribed and abused opioid, which could perpetuate the opioid epidemic.
- Our study supports the inclusion of non-pain related conditions—such as cough—when developing well-encompassing opioid-prescribing guidelines as this will not exclude specific common opioids that are currently prescribed and abused—such as codeine-containing antitussive syrup.

## INTRODUCTION

The opioid epidemic has caused negative health consequences to the global society and has been declared a global issue by the International Narcotics Control Board.[1] A 2019 report from the European Monitoring Centre for Drugs and Drug Addiction stated that the UK, at this time, had 341 576 high-risk opioid users.[2] Rises in deaths from oxycodone have been tracked in Canada and Australia since the early 2000s. Germany was estimated to have upwards of 1.9 million people addicted to opioids in 2011.[1] Specifically, in the USA, approximately 42 000 Americans died of opioid overdoses in 2016. To address the opioid epidemic, US state governments have begun to create guidelines for opioid prescriptions. Recently these guidelines have focused on emergency departments (EDs) across the nation. This is likely due to the high frequency of patients presenting to the ED with pain and studies reporting the association of an initial ED opioid prescription with recurrent opioid use.[3–6] These guidelines typically include the review of a patient in a prescription drug monitoring programme system prior to writing a narcotic prescription, and days' supply limitation of opioids that varies from state to state.[7–9]

We found published literature on several studies evaluating these policies for their effects on prescriber behaviour.[10–12] Most studies found an association between the opioid policy and an overall decrease in opioid prescriptions and/or reduction in the number of days' supply of opioid prescriptions over the policy limit. These policies primarily focus



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on pain because the major indication for opioids is pain. In countries such as the UK, codeine can be purchased with a prescription or over the counter for pain control.[13] In fact, in 2016, the UK was the second largest manufacturer and consumer of codeine in the world. However, codeine-containing antitussive syrups have contributed to the opioid epidemic in Bangladesh, Nigeria and the USA based on the 2019 International Narcotics Control Strategy Report.[14] We found no published literature mentioning codeine-containing antitussive syrup prescribing laws. This merits concern because codeine continues to be prescribed despite the lack of evidence supporting its clinical efficacy and the guidelines recommending against its use as an antitussive.[15 16]

We aimed to assess the effect of the North Carolina General Assembly House Bill 243—Strengthen Opioid Misuse Prevention (STOP) Act of June 2017 on the prescribing of opioids greater than 5 days for acute pain/acute non-pain diagnoses. More specifically, we aimed to determine what effect, if any, the North Carolina STOP Act had on the days' supply of codeine-containing antitussive syrup.

## METHOD

### Study design and setting

The sites for this study were two EDs in North Carolina, USA. One is a 58-bed ED with an average annual visit of 70 000 patients, and the other is a 15-bed ED with an average annual visit of 22 000 patients. Both EDs are staffed by the same group of providers.

Our study was approved by our institutional review board, and patients or the public was not involved in the design/execution. The study design was a retrospective chart review. We used evidence-based methods for chart reviews to optimally mitigate bias and produce robust results and conclusions.[17] An electronic medical record was used to extract stored data for this study. The data analyst for both EDs performed the data extraction and assisted in the construction of the dataset. So, the methodology behind the extraction is similar to the systematic data collection for formal internal and external metrics reporting for each ED. Both EDs use the EPIC Systems Corporation software as an electronic medical record system.

### Selection of participants

Prescriptions from discharged adult patients (>17 years old) from both EDs were included in our study. All opioid prescriptions for these patients were included in the study if they were written for ED encounters between the months of January and August for the years 2017 and 2018. Data from 2016 January-August were extracted and used for comparison when necessary. Opioids used for the treatment of opioid abuse were excluded and did not have a high frequency in the initial dataset. Opioids written for chronic diagnoses/conditions were excluded from the study because the North Carolina STOP Act specifically applies to acute pain, not chronic pain. The research team, which includes an emergency physician, made the presumption that if a patient presented to the ED for chronic pain or a chronic non-pain diagnosis, it would be specified in their 10th Revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) description given by the provider at discharge. Therefore, we defined an acute pain and acute non-pain diagnosis as any diagnosis without 'chronic' specified in the primary ICD-10 code and description. Any cancelled prescription or prescription with missing data for which the days' supply could not be calculated was excluded. Duplicate records were also excluded from our study.

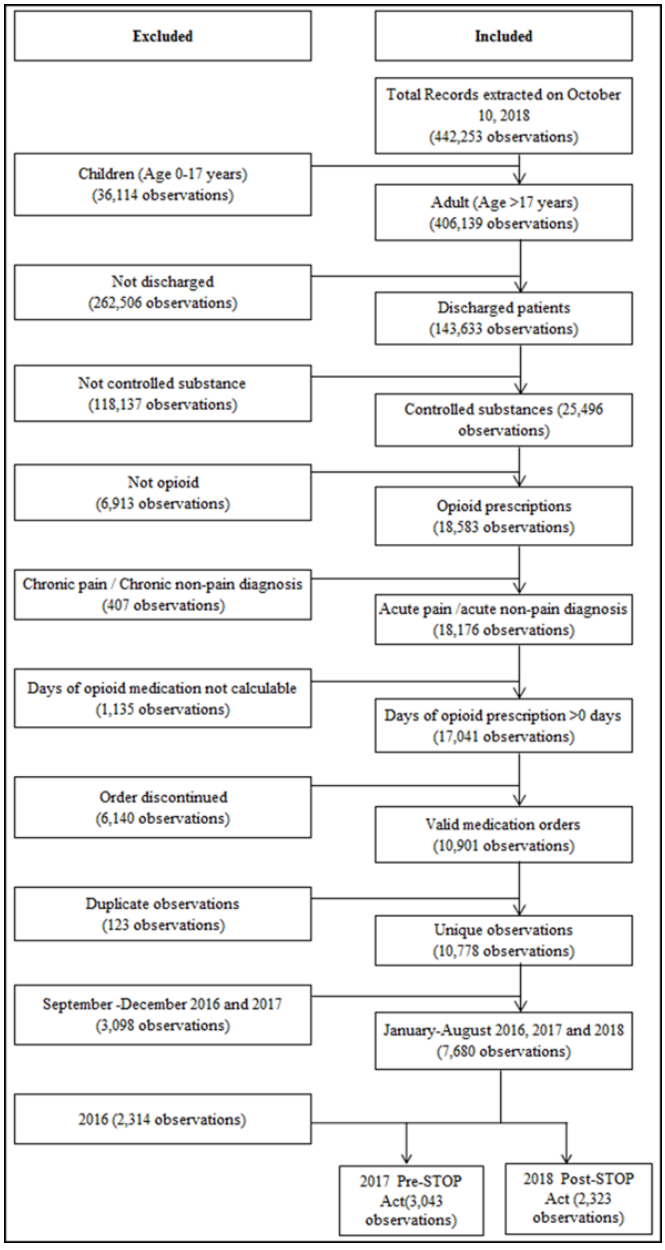


**Figure 1** Consolidated Standards of Reporting Trials diagram showing the inclusion and exclusion of prescriptions—or observations—for the study at each stage and based on the inclusion and exclusion criteria. The initial dataset started with 442 253 prescriptions, and after the application of the inclusion and exclusion criteria, the final dataset used for analysis contained 5366 verifiable prescriptions—3043 and 2323 for 2017 and 2018, respectively. STOP, Strengthen Opioid Misuse Prevention.

We used SAP BusinessObjects software to extract the data from EPIC. The data analyst used filters to extract an initial dataset with controlled substance prescriptions written for discharged adult patients in the ED from our target time periods. We used Microsoft Excel 2016 MSO to review and identify the unique opioids and indicate the appropriate records. A filter was then used to remove chronic pain and chronic non-pain diagnosis. Filters were also used to remove prescriptions with missing data necessary for calculations and cancelled prescriptions. STATA

**Table 1** Characteristics of study participants

| Characteristics of patients in the ED | Pre-STOP act, n (%) (n=3043) | Post-STOP act, n (%) (n=2323) |
|---|---|---|
| Opioid prescription >5 days | 296 (9.7) | 152 (6.5) |
| Mean age (SD) (years | 44.1 (15.6) | 45.7 (16.2) |
| Median age (range) years | 43 (18–102) | 44 (18–98) |
| Elderly (age ≥65 years of age) | 333 (10.9) | 332 (14.3) |
| Female | 1617 (53.1) | 1226 (52.8) |
| Race | | |
| White or Caucasian | 1740 (57.2) | 1411 (60.7) |
| Black or African–American | 867 (28.5) | 596 (25.7) |
| Other race | 436 (14.3) | 316 (13.6) |
| ED discharge disposition: home with self-care | 3016 (99.1) | 2305 (99.2) |
| Suburban ED site | 2075 (68.2) | 1517 (65.3) |
| Rural ED site | 968 (31.8) | 806 (34.7) |

ED, emergency department; STOP, Strengthen Opioid Misuse Prevention.

V.12 software was then used to remove the duplicates. We used the duplicates to assess the validity of the data through a chart review.

## Intervention

We defined the intervention as the enactment of the supply limitation policy set forth by the North Carolina STOP Act, which occurred on 1 January 2018. Among other initiatives, the North Carolina STOP Act has a time limitation supply on first-time opioid prescriptions for non-surgical acute pain to a maximum of 5 days.[9] We used the January–August 2017 time period to define the pre-STOP Act period and data from January–August 2018 to define the post-STOP Act period. We excluded September–December 2017 because there were no comparison data in 2018 at the time of the study.

## Measurements

We calculated the days' supply worth of opioids with two standard Microsoft Excel formulas, one for unit/pill and another for liquid, since the data for unit/pill and liquid opioids were stored in a standard structured format for all prescriptions. The accuracy of these formulas was confirmed through a review of random records. The proportion of opioid prescriptions greater than 5 days was then calculated for each of the study periods.

We extracted the opioid prescriptions greater than 5 days and made a second dataset. All opioids in this subset were categorised by their active opioid medication. For example, oxycodone-acetaminophen 5–325 mg and oxycodone 10 mg were classified into the category oxycodone. From here, we calculated the individual percentage of opioid prescriptions for greater than 5 days for each opioid, pre-STOP and post-STOP Act, to determine if there was a change. We did this by dividing the number of individual opioid prescriptions for greater than 5 days by the total number of prescriptions written for that respective opioid in that time period.

As part of our results, we also categorised the diagnoses receiving greater than 5 days of opioids into basic categories. The categories were created after reviewing all the unique ICD-10 diagnoses in this subset of the data. An instruction manual was made to standardise the categorisation process. One researcher performed the categorisation, and an additional categorisation was performed by a physician blinded to the purpose of the study. Any discrepancy was further investigated with a chart review and a final classification was made.

## Outcomes

Our study aimed to determine if there was an association between an acute pain-focused opioid prescription policy and the reduction of opioid prescriptions for greater than 5 days and what effect, if any, it had on the prescribing of codeine-containing antitussive syrup. Our first outcome was the change in proportion of all opioid prescriptions over 5 days after the implementation of the North Carolina STOP Act, 1 January 2018 (post-STOP). The second outcome was the change in the proportion of individual opioids written for greater than 5 days after the North Carolina STOP Act was implemented. We were interested in this outcome because an opioid with a high percentage of prescriptions for greater than 5 days pre-STOP and post-STOP ACT represents a potential lack of efficacy in the policy for that opioid.

## Analysis

Prescriptions of opioid medication for more than 5 days for acute pain and non-pain diagnoses was one of the outcomes of interest. The key predictor variable for this particular outcome was whether the date of the prescription was before (January–August 2017) or after (January–August 2018) the implementation of the STOP Act of North Carolina.

We calculated descriptive statistics to assess variations in patient characteristics pre-STOP and post-STOP Act implementation. We also used frequencies to assess the most common characteristics of prescription-related variables, including ED diagnosis (ICD-10 diagnosis) and opioid category. We used binary logistic regression to estimate the odds of prescription opioids for more than 5 days for patients with acute pain and non-pain diagnoses. We assessed two main logistic regression models. The first model was the crude model, where only the key independent variable (period of prescription, pre-STOP or post-STOP Act) was the predictor variable. In the second model, we added control variables, including age, sex, department (suburban and rural) and ED disposition to the first model. We added the control variables in the second model to assess whether patient characteristics influenced the relationship between the outcome and the key independent variable.

We estimated effects of each of the control variables on the outcome independently and compared the generated estimates with those from the second model to assess any moderation effects inherent in each variable. After estimation, we used the delta method to generate CIs for the estimates of the predicted outcomes and to test for differences in the estimates for pre-STOP and post-STOP Act. The delta method, which is appropriate in large samples, is a numeric approximation based on a Taylor series expansion.[18] We used STATA V.2012 to conduct data analysis.[19]

We classified all diagnoses for prescriptions greater than 5 days of opioids into 11 categories, including abdominal/pelvis, chest, dental, HEENT (head, eyes, ears, nose, throat), musculoskeletal, renal, respiratory, skin, systematic disease, trauma and others. We classified opioids prescribed for these diagnoses into nine categories, including codeine—pill, codeine—syrup, diphenoxylate, fentanyl, hydrocodone, hydromorphone, morphine, opium and oxycodone. To determine any difference in proportions between the study periods, we used the two-tailed z-test.

**Table 2** Logistic regression model estimates of the effect of patient characteristics on the odds of being prescribed opioid medication for >5 days

| | Adjusted estimates | | |
|---|---|---|---|
| **Characteristics of ED patients/variable** | **OR** | **P value** | **95% CI** |
| Opioid prescription >5 days post-STOP Act compared with pre-STOP Act | 0.60 | <0.01 | 0.50 to 0.80 |
| Elderly (age ≥65 years of age) | 1.50 | 0.01 | 1.10 to 1.90 |
| Female | 1.40 | <0.01 | 1.10 to 1.70 |
| Race | | | |
| White or Caucasian (referent) | – | – | – |
| Black or African–American | 1.30 | 0.03 | 1.03 to 1.60 |
| Other race | 1.30 | 0.13 | 0.90 to 1.70 |
| Home with self-care | 0.50 | 0.12 | 0.20 to 1.20 |
| Suburban ED site | 0.90 | 0.53 | 0.80 to 1.20 |

ED, emergency department.

## RESULTS

### Characteristics of the final dataset

We extracted 442 253 records of medication orders for patients treated from January 2016 to August 2018. After implementing the exclusion criteria, there were 7680 verifiable ED opioid prescriptions written on discharge—23 143 043, and 2323 in 2016, 2017 and 2018, respectively. This ultimately amounted to the inclusion of 5366 records in our study—January-August 2017 and 2018. Figure 1 demonstrates the data inclusion/exclusion processing diagram used to select the final set of records. On chart review, we found that all 123 duplicate records had accurate data and would have been appropriate for inclusion if the records were not a duplicate. The results of this chart review, combined with the use of standard processes for more formal data extraction, support the validity of our dataset. No opioid prescription in our dataset was written for a subsequent visit for which opioids were prescribed on a prior visit for the same diagnosis. The descriptive characteristics for the pre-STOP and post-STOP Act were similar and can be found in table 1. The remainder of this section only includes data from 2017 (pre-STOP Act) and 2018 (post-STOP Act).

### Effect of North Carolina STOP Act on Days' Supply of Opioids

Logistic regression results show that there were no differences between crude and adjusted estimates. Therefore, only the adjusted estimates are discussed in this section (table 2). As shown in figure 2, the results show a reduction in the percentage of discharge opioid prescriptions greater than 5 days post-STOP Act from 9.8% (95% CI 8.7% to 10.8%) to 6.5% (95% CI 5.5% to 7.5%). The OR for receiving a prescription for greater than 5 days post-STOP Act was 0.6 (95% CI 0.5 to 0.8, p<0.05).

### Opioid composition in the dataset and the proportion of opioid days' supply over the policy limit

Oxycodone, hydrocodone, morphine and codeine-containing syrup were most commonly prescribed for greater than 5 days for both pre-STOP and post-STOP Act. Approximately 91.5% of all codeine syrup prescriptions were written for greater than 5 days pre-STOP Act, with minimal change occurring after the policy was implemented, 90.4% representing a difference of 1.1%. This is high compared with hydrocodone (pre-STOP=13.2%, post-STOP=5.5%) and oxycodone (pre-STOP=4.2%, post-STOP=3.7%) (table 3). Hydrocodone was the only opioid to have a statistically significant decrease post-STOP Act.

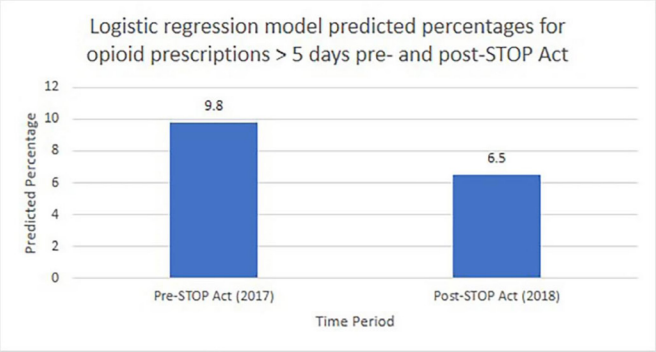


**Figure 2** Bar graph showing the predicted percentages of opioid prescriptions written for greater than 5 days for the two target periods, January–August 2017 (pre-STOP Act) and January–August 2018 (post-STOP Act). The graph shows there was a 3.3% (95% CI −4.7% to −1.8%, p<0.05) reduction in the predicted percentages from the pre-STOP Act period (9.8%; 95% CI 8.7% to 10.8%, p<0.05), to the post-STOP Act period (6.5%; 95% CI 5.5% to 7.5%, p<0.05). STOP, Strengthen Opioid Misuse Prevention.

### Categorical diagnosis characteristics for opioids over the policy limit

The most frequent categorical diagnosis was respiratory for both study periods (online supplemental appendix A). On further analysis, codeine syrup was the most common opioid prescribed for respiratory diagnoses pre-STOP and post-STOP Act (78.7% and 76.6%, respectively).

## DISCUSSION

This study shows the association of a pain-focused opioid policy with a reduction in the days' supply of opioids above a specified limit, and the minimal effect it has on a commonly abused opioid, codeine-containing antitussive syrup. Based on the literature review, this is the first study to evaluate the North Carolina STOP Act; therefore, it contributes to the study of the effect of new opioid legislation in different parts of the world. Similar studies are important to healthcare providers, policy makers and lawmakers because other countries have investigated and taken action against the growing abuse of codeine-containing syrup.[20] For example, Australia has upscheduled their codeine-containing products.[21] Our study also offers insight to the effects of government policies against the opioid epidemic. The knowledge gained from this study can be used to form effective government and hospital policies and to amend current policies on opioids.

The most interesting finding from this study is the minimal effect the North Carolina STOP Act had on codeine syrup prescribed for greater than 5 days. This poses a potential problem because this opioid appears to be unaffected by the policy.

**Table 3** Per cent reduction in each opioid medication supply for greater than 5 days pre-STOP and post-STOP Act*

| Opioid name | 2017 Pre-STOP | 2018 Post-STOP | Difference (%) | P value |
|---|---|---|---|---|
| Codeine syrup | (75/82), (91.5%) | (47/52), (90.4%) | −1.1 | 0.83 |
| Hydrocodone | (106/801), (13.2%) | (28/509), (5.50%) | −7.7 | <0.01 |
| Morphine | (19/102), (18.6%) | (16/88), (18.2%) | −0.4 | 0.94 |
| Oxycodone | (84/1981), (4.2%) | (60/1640), (3.7%) | −0.5 | 0.37 |

*The numerator is the total number of prescriptions for >5 days for each opioid during each time period, and the denominator is the respective total number of opioid prescriptions written for each opioid during each time period—[number of opioid×prescriptions>5 days]/(total number of opioid×prescriptions) (% in brackets).
STOP, Strengthen Opioid Misuse Prevention.

Despite its popularity as a drug of abuse around the world, to our knowledge, there are few studies that assess the contribution of codeine-containing antitussive syrups toward the opioid crisis. This creates a need for further studies understanding the prevalence of codeine syrup abuse and the providers prescribing it. Of note, our study also found no statistically significant reduction in oxycodone or morphine prescription over 5 days.

The individual categorical diagnoses for greater than 5 days were similar to diagnoses for opioids found in other studies.[22 23] The individual categorical diagnoses prescribed for greater than 5 days showed no significant change in their proportions between the study periods (online supplemental appendix A). This finding demonstrates a similar presentation of diagnoses for the two study periods, making it unlikely that each period encountered a characteristically different population (table 1). Our results found that respiratory diagnoses were the most common diagnoses associated with a prescription greater than 5 days, and codeine syrup was the most frequent opioid prescribed for respiratory diagnoses. Since codeine syrup is usually prescribed for cough, it is a safe assumption that it was prescribed for cough in the setting of a respiratory condition. This is significant because there are data supporting the ineffectiveness of codeine-containing syrup as an antitussive medication.[16 24 25] Current pain-focused policies limiting opioid supplies should evaluate their policies' application to opioids, such as codeine-containing cough syrup, for non-pain diagnoses. Furthermore, using alternatives to codeine syrup for cough could decrease the supply of opioids in circulation without harming patients.

This issue may not appear to be paramount, now, but as current pain-focused policies reduce the abuse of other common opioids, we may see an increase in the abuse of codeine-containing antitussive syrup. Decreasing the circulation of codeine syrup for non-evidence-based indications through future legislation may have a long-term effect on its contribution to the opioid crisis. With little knowledge of its effect on the opioid epidemic and the current permittance for a non-evidence-based indication, the prescribing of codeine-containing antitussive syrup should be monitored. Furthermore, if the overall goal is to decrease opioid misuse and abuse, government policies should be applicable towards opioid prescriptions for pain and non-pain diagnoses.

This study had some limitations. Although it associates the reduction in opioid prescriptions greater than 5 days with a day's supply limiting policy, it does not prove causation. Our study also assumed that patients getting opioid prescriptions would have the reasons for the prescriptions as the primary ICD-10 code. It is possible that the diagnosis necessitating the opioid was a secondary or subsequent ICD-10 code. In this same context, our definition of acute pain and acute non-pain diagnoses was broad and not restrictive. However, in spite of these limitations, the literature still corroborated our diagnoses as common diagnoses for opioid prescriptions. The STOP Act was implemented on 1 January 2018, and laws and policies need sufficient lag time to realise their full effects. However, continuous assessment of public health laws is instrumental in monitoring their effects and identifying challenges and areas for improvement to make them more effective and sensitive to the current needs of the community. Lastly, a minute amount of data came from patients presenting in the pre-North Carolina STOP and post-North Carolina STOP Act, which may have an effect on the statistical independence of the data.

In conclusion, the North Carolina STOP Act was associated with a reduction in the number of opioid prescriptions greater than 5 days written by ED providers. However, codeine-containing antitussive syrup appears to be immune to the North Carolina STOP Act policy, revealing a potential problem that can work against initiatives aimed at stopping the opioid epidemic. The effect of this can be far greater in areas of the world where codeine-containing antitussive syrup has a higher prevalence. Physicians may be doing more harm than good by prescribing codeine syrup as an antitussive. Alternative and more conservative therapies for cough are likely to be safer for patients in the ED and less likely to have an encouraging effect on the opioid epidemic.

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**Contributors** WMP, CBA and EMA all contributed significantly to this research study. CBA and WMP performed the literature review for this study. WMP conceived the idea of the study and its design. With the help of WMP, EMA extracted the data and was an integral part in the construction of the final database using quality control methods. The statistical analysis plan was created by CBA and WMP. CBA primarily executed this analysis. WMP primarily composed the manuscript and takes responsibility for the paper as a whole.

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**Ethics approval** Our study was approved by the University of North Carolina at Chapel Hill Institutional Review Board. Our study approval number is 19–0078.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** No data are available. Data contains patients' history of present illness and are not available to anyone outside of the respective healthcare system.

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