Electronic Advisories Increase Naloxone Prescribing Across Health Care Settings

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BACKGROUND: Naloxone is a life-saving, yet underprescribed, medication that is recommended to be provided to patients at high risk of opioid overdose.

OBJECTIVE: We set out to evaluate the changes in prescriber practices due to the use of an electronic health record (EHR) advisory that prompted opioid prescribers to co-prescribe naloxone when prescribing a high-dose opioid. It also provided prescribers with guidance on decreasing opioid doses for safety.

DESIGN: This was a retrospective chart abstraction study looking at all opioid prescriptions and all naloxone prescriptions written as emergency department (ED) discharge, inpatient hospital discharge, or outpatient medications, between July 1, 2018, and February 1, 2020. The EHR advisory went live on June 1, 2019.

SUBJECTS: Included in the analysis were all adult patients seen in the abovementioned settings at a large county hospital and associated outpatient clinics.

MAIN MEASURES: We performed an interrupted time series analysis looking at naloxone prescriptions and daily opioid dosing in morphine milligram equivalents (MMEs), before and after initiation of the EHR advisory.

KEY RESULTS: The EHR advisory was associated with changes in prescribers’ behavior, leading to increased naloxone prescriptions and decreased prescribed opioid doses.

CONCLUSIONS: EHR advisories are an effective systems-level intervention to enhance the safety of prescribed opioids and increase rates of naloxone prescribing.

KEY WORDS: computerized clinical decision support; electronic medical record; electronic health record; harm reduction; naloxone; opioid; overdose; take home.

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INTRODUCTION

Since the start of the opioid epidemic in the late 1990s, almost 500,000 people have died from an opioid-involved overdose in the USA.1,2 Provisional data from 2021 suggest a 15% increase in US overdose deaths, with a staggering 100,000 deaths in that year alone.3 The number of emergency department (ED) visits for opioid use disorder and opioid overdoses has continued to increase during the COVID-19 global pandemic.4,5 While overdose deaths solely due to prescription opioids and heroin have decreased in recent years, the concomitant rise of synthetic opioids—fentanyl, in particular—has driven a striking increase in opioid overdose deaths.6,7 Nevertheless, prescription opioids were implicated in nearly 18% of all opioid-related overdose deaths in 2020,8 and research has shown that a high percentage of people who use illicit drugs were previously prescribed an opioid medication.9,10 Thus, the population of people using prescribed opioid medications remains a high-risk group for overdoses.

Studies have demonstrated an increased risk of overdose with higher daily doses of prescribed opioid medications.11-13 Based on this accumulated evidence, the Centers for Disease Control and Prevention (CDC) released a practice guideline in 2016 that recommended “carefully reassess[ing] evidence of individual benefits and risks when considering increasing dosage to ≥50 morphine milligram equivalents (MMEs)/day”.14 Caution must be advised before applying this dose recommendation broadly: recent observational studies show that rapid tapering of chronic opioid prescriptions is associated with increased risks in overdose and mental health crises.15,16 These new data are currently being incorporated into revised CDC opioid prescribing guidelines. Naloxone, a full opioid antagonist, has been shown to reduce mortality associated with opioid overdoses with minimal adverse effects.17 Take-home naloxone (THN) programs provide home naloxone kits for individuals at high risk of overdose, enabling expeditious reversal of opioid overdose in the out-of-hospital setting. THN programs have been shown to be effective in decreasing mortality among high-risk individuals,18,19 and have been successfully implemented in emergency departments and hospital medicine wards.20-23 Although THN programs often target patients with use of illicit opioids, programs that include co-prescriptions of naloxone for patients on prescribed opioids have also shown feasibility and effectiveness.24,25

Naloxone dispensing rates remain low across all states.26 Barriers to patients receiving THN still exist, resulting in significant underuse of naloxone and subsequent loss of life...
and increased hospitalizations. Barriers to prescription of THN include inadequate provider knowledge and training as well as misconceptions, such as the belief that patients using prescribed opioids do not need THN and that naloxone is not efficacious, and that having naloxone on-hand increases high-risk behaviors. Structural barriers to THN prescription include lack of institutional workflows.

Computerized clinical decision support systems are powerful tools to modify provider behaviors. Although poorly designed prompts in the electronic health record (EHR) can lead to “alert fatigue,” alerts that are designed to promote specific, actionable evidence-based interventions, are aimed at the appropriate users, and do not fire inappropriately, have been shown to be acceptable to EHR users, and can lead to practice improvements. EHR prompts have effectively increased prescription of THN after opioid overdoses when discharged from the ED, and in higher-risk patients being co-prescribed opioids by primary care clinicians.

On June 1, 2019, a best practice advisory (BPA) was initiated in the EHR at the Grady Health System to encourage clinicians to engage in opioid best practices, including co-prescription of naloxone and prescription of opioids with dosing below 50 MME per day. The aim of our study is to characterize and evaluate provider actions affected by the BPA. The primary objective is to determine the changes in provider practices of naloxone prescribing due to implementation of two EHR-based reminder tools. The secondary objectives are to determine trends in opioid prescribing over time, looking specifically at opioid dosing changes attributable to the BPA implementation versus those attributable to secular changes in prescribing practices.

We hypothesized that the BPA would be associated with changes in providers’ behavior: namely, an increase in the rate of naloxone prescriptions and a decrease in the doses of opioids being prescribed.

**Methods**

**Study Design, Setting, and Patients**

We performed a retrospective study examining EHR evidence of opioid prescriptions written between July 1, 2018, and February 1, 2020. All opioid prescriptions written for adult patients over the age of 18, who were seen and evaluated in the Grady Health System in the following clinical contexts, were included: the ED, inpatient hospital wards, outpatient clinics located within the main hospital, and outpatient clinics at satellite sites. For the ED and inpatient wards, discharge medication prescriptions were included in the analysis; prescriptions written for on-site administration were excluded.

Buprenorphine prescriptions were removed from the dataset, as these prescriptions were written exclusively by a specialty clinic that provided naloxone to patients directly without the use of a written prescription.

**Variables**

Patient age, gender, and race were entered into our dataset as they appeared within the EHR. Prescriber type and specialty were similarly recorded as they appeared in EHR data fields. MMEs were calculated based on standard conversions; when prescriptions were written with a taper or an “as needed” dosing instruction, the maximum daily MME dose was assumed. This study was approved by the Emory University IRB and the Grady Office of Research Administration.

**EHR Notification**

The notification, or best practice advisory (BPA), evaluated here is a pop-up message that appears on the screen when an EHR user signs an opioid prescription for which the EHR calculates the daily MME to be >50. The BPA prompts the user to prescribe concomitant intranasal naloxone if they proceed with the opioid prescription. The message also notifies prescribers that MME values <50 are recommended and calculates the MME of the prescription in real-time for the clinician’s knowledge and awareness. This advisory was designed by clinicians and information technologists working as a team to reduce risks of harm due to opioids and was devised based on CDC guidelines for opioid prescribing. The advisory is shown in Figure 1.

**Statistical Analysis**

Categorical variables (e.g., whether or not naloxone was prescribed) were described using frequencies and percentages. Patient age and total MMEs were described using medians and interquartile ranges (IQR). Bivariate associations between time period and patient characteristics were conducted using the Mann-Whitney U and χ² test. The primary research question—i.e., whether the rate of naloxone prescription and MMEs >50 changed following the implementation of the EHR BPA—was evaluated using an interrupted time series analysis implemented as fixed-effects segmented regressions. This analysis enables the evaluation of the immediate effect of the BPA intervention, secular changes over time, and changes to the secular trends following the BPA while adjusting for covariates. Both analyses used a binary logistic regression. Covariates in the adjusted analysis included age, gender, race, type of provider, and type of encounter. Nurse practitioners, physician assistants, and certified nurse midwives were combined into an “other” category due to small cell sizes. p-values and 95% confidence intervals were computed using bias-corrected and accelerated bootstrapped estimates (10,000 resamples). Natural cubic splines were used to allow for potential non-linear effects of age. Initial analyses revealed autocorrelations to be minimal. The regressions were repeated using Newey-West robust standard errors to evaluate the consistency across methods; the results did not change. An additional exploratory analysis was conducted on the conditional quantiles of the MME distribution.
Assuming maximal variance for a binomially distributed outcome \((\pi = 0.5); i.e., the worst-case scenario for statistical power\), the present sample \((N = 36,739)\) in the pre-BPA period and \(N = 25,955\) in post-BPA period, is sufficiently powered (80\%) to detect an overall increase in 1.39\% in absolute terms (an odds ratio of 1.05). Analyses were conducted using R v. 4.1 (R Core Team, 2022).

## RESULTS

A total of 62,693 encounters resulting in opioid prescriptions were included in the analysis. Patient characteristics are presented in Table 1. The sample had a median age of 48 years (IQR: 34–59), and was 51.1\% male, 48.9\% female, 79.9\% Black, 12.1\% White, 5.8\% Hispanic, 0.9\% Asian, 0.5\% multiracial, 0.3\% Native American, and 0.6\% “other.” The majority of patients (94\%) were seen by physicians, and there was an approximately even split between inpatient (34.8\%), outpatient (34.7\%), and ED (30.4\%) patients. Gender did not differ by study period. All other variables exhibited small differences between the pre- and post-intervention periods.

The results of the interrupted time series regression (ITR) evaluating the rate of naloxone prescriptions are presented in Table 2. The rate of naloxone prescription significantly increased following the BPA initiation (OR = 5.66, 95\% CI: 4.11–7.78, \(p < .001\)). This finding remained significant following adjustment for the study covariates (OR = 8.21, 95\% CI: 5.89–11.43, \(p < .001\)). This finding is depicted in Figure 2A, B. There was also a significant interaction term...

### Table 1 Characteristics of the Sample

| Characteristic          | Full sample \((N = 62,693)\) | Pre-intervention \((N = 36,738)\) | Post-intervention \((N = 25,955)\) | \(p^*\)  |
|-------------------------|-------------------------------|-----------------------------------|-----------------------------------|------|
| Age, M (IQR)            | 48 (34–59)                    | 48 (34–59)                        | 49 (34–60)                        | <.001 |
| Gender, N (%)           |                               |                                   |                                  | .66  |
| Female                  | 30677 (48.9)                  | 18004 (49.0)                      | 12673 (48.8)                      |       |
| Male                    | 32016 (51.1)                  | 18734 (51.0)                      | 13282 (51.2)                      | <.001 |
| Race, N (%)             |                               |                                   |                                  |      |
| Native American         | 159 (0.3)                     | 98 (0.3)                          | 61 (0.2)                          | <.001 |
| Asian                   | 567 (0.9)                     | 328 (0.9)                         | 239 (0.9)                         |       |
| Black                   | 50105 (79.9)                  | 29422 (80.1)                      | 20683 (79.7)                      | <.001 |
| Hispanic                | 3610 (5.8)                    | 2049 (5.6)                        | 1561 (6.0)                        |      |
| Multi-racial            | 290 (0.5)                     | 159 (0.4)                         | 131 (0.5)                         |      |
| Other                   | 347 (0.6)                     | 241 (0.7)                         | 106 (0.4)                         |      |
| White                   | 7615 (12.1)                   | 4441 (12.1)                       | 3174 (12.2)                       | <.001 |
| Type of provider, N (%) |                               |                                   |                                  | <.001 |
| Dentist                 | 2636 (4.2)                    | 1825 (5.0)                        | 811 (3.1)                         |      |
| Other/APP               | 1036 (1.7)                    | 685 (1.9)                         | 351 (1.4)                         |      |
| Physician               | 58917 (94.0)                  | 34165 (92.9)                      | 24752 (95.4)                      |      |
| Podiatrist              | 104 (0.2)                     | 63 (0.2)                          | 41 (0.2)                          | <.001 |
| Encounter type, N (%)   |                               |                                   |                                  | <.001 |
| ED                      | 19048 (30.4)                  | 11103 (30.2)                      | 7945 (30.6)                       |      |
| Inpatient               | 21816 (34.8)                  | 12476 (34.0)                      | 9340 (36.3)                       |      |
| Outpatient              | 21739 (34.7)                  | 13159 (35.8)                      | 8580 (33.1)                       |      |
| Naloxone, N (%)         | 1354 (2.2)                    | 272 (0.7)                         | 1082 (4.2)                        | <.001 |
| MME, M (IQR)            | 22.5 (20–30)                  | 22.5 (20–35)                      | 22.5 (20–25)                      | <.001 |
| MME≥50, N (%)           | 6641 (10.6)                   | 4305 (11.7)                       | 2336 (9.0)                        | <.001 |

\(p^*\)-values were computed using the Mann-Whitney U for age and MME, and \(\chi^2\) test for the categorical variables.
The results of the ITR evaluating the prescription of opioids with doses >50 MME are presented in Figure 2C, D. The rate of >50 MME prescriptions significantly decreased following the BPA initiation (OR = 0.85, 95% CI: 0.76–0.94, p = .002). This finding remained significant following adjustment for the study covariates (OR = 0.83, 95% CI: 0.72–0.96, p = .01). A review of trends showed that, although the rate of prescriptions >50 MME had already begun declining before the initiation of the BPA, implementation of the BPA was associated with a significant change in slope (p = .04), indicating an additional decline in prescriptions >50 MME that was attributable to the BPA. An analysis of the simple slopes revealed that, prior to BPA initiation, the secular trend was negative and statistically significant (OR for daily change = 0.998, 95% CI: 0.997–0.999, p = .001). However, following BPA initiation, the secular trend was no longer significant (OR = 1.0, 95% CI: 0.99–1.01, p = .70).

To further explore the changes in opioid dosing following BPA initiation, we evaluated the conditional quantiles of the MME distribution using quantile regression. The adjusted effect of the intervention on MME quantiles is presented in Figure 3. For the lower quantiles (lower than the 75th percentile), the intervention had little effect. For the upper quantiles (greater than the 75th percentile, which corresponds to approximately 30 MME), slopes were negative and significant. This suggests that the intervention may reduce the largest MMEs prescribed, while having little impact on prescriptions with lower daily MMEs.
In this set of analyses, we examined the effect of an EHR advisory on prescribers’ behavior, specifically, the co-prescription of naloxone and the dosage of prescribed opioid in MME/day. Our analyses supported our hypothesis that the BPA was associated with a change in providers’ behavior, including increased rates of naloxone prescribing.

The ITR revealed that this significant and impressive change (OR = 8.21) occurred alongside a secular trend that saw increases in naloxone prescribing independent of the EHR alert. Although the post-alert overall rate of naloxone prescribing remained low (4.2% of all opioid prescriptions), this represents a co-prescribing rate of 47% for eligible opioid prescriptions—those with daily MME $\geq 50$—and an increase from the baseline co-prescribing rate of 6.0% of eligible opioid prescriptions prior to the implementation of the alert.

Previous work on naloxone prescribing to patients who presented to EDs with opioid overdoses or opioid use disorder showed similar, consistent increases. Our results correlate well with these findings, also showing increases in naloxone prescribing that were sustained at the end of the study period. Naloxone prescribing rates in our study remained lower than in a recent, similar study evaluating an EHR prompt enacted within the Kaiser Permanente Southern California health system. Some likely reasons for this disparity are the higher rates of prescriptions written by trainees at Grady, which implies a larger percentage of “rotators” as well as less experienced clinicians, and fewer opportunities for training and orientation within a comparatively lower-resourced health system.

Our sample was comprised of a majority of African American subjects, which reflects the patient population seen by our health system. Historically, a lower percentage of Black and Latinx patients have been prescribed opioid medications for chronic pain. This aligns with our estimate of MMEs/day in our analysis of a population that is largely African American, and is lower than the MME/day average recorded in other populations. There was no difference between Black and White patients with respect to naloxone prescriptions before or after the BPA. The finding that this EHR alert was effective in guiding prescriber behavior as they cared for this underserved population suggests that such alerts may be effective in combating implicit and explicit bias that contribute to health disparities. Additional importance of this finding comes from the rising rates of overdose mortality among Black patients relative to patients of other racial and ethnic backgrounds, making it imperative that healthcare systems utilize tools to address dangerous opioid use that reach Black communities.

The EHR alert was also associated with a decrease in MME/day prescription doses. Here, the effect of time and the effect of the BPA itself were significant in the ITR analysis, confirming a secular trend in opioid prescribing, as well as the efficacy of the alert, similar to our finding with naloxone prescribing. The BPA was only associated with a decrease in daily dosing for the highest dosing quantiles. That is, approximately the 75th percentile and above were observed to decrease following the initiation of the BPA. The lowest quantiles were not observed to change following the BPA. The 75th percentile corresponded to approximately 30 MME/day, lower than the threshold for activating the BPA, which may indicate that mere awareness of the BPA was sufficient to induce a behavioral change among providers. Encounters which would normally result in smaller MME prescriptions were unchanged.

While lower opioid MME doses correspond to lower overdose risk, the recent observation that rapid tapering of chronic opioid prescriptions can lead to adverse outcomes has added caution to a sweeping recommendation towards prescribing lower doses of opioids, particularly for patients on chronic,
stable doses of opioids. However, the patients in this cohort are predominantly being prescribed opioids for acute or subacute pain, with only 14% of patients receiving more than two opioid prescriptions during the time period evaluated. While it is always of importance to balance the harms and benefits of medication prescribing, the specific caution around rapid tapering is unlikely to apply here.

As interventions that are cost-effective and with a broad reach, EHR prompts fare well. They require an initial input of technical expertise but then minimal ongoing efforts, as opposed to training sessions, which require repeated sessions for continued maintenance of behavior change. When well-designed, they take up a minimal amount of clinicians’ time. This study demonstrated the feasibility and efficacy of an EHR prompt within multiple settings of a safety-net teaching hospital, a low-resource institution that is the training site for many “rotators” who may not have a long-term relationship with staff and administration. The EHR prompt was still associated with changes in prescriber behavior. Future studies should be conducted to elucidate provider-, patient-, and systems-level factors associated with successful implementation of this EHR prompt, in order to further refine it and identify best practices that may be applied at other institutions.

Limitations

Several relevant patient characteristics were not included in the present study. For example, whether a patient had been prescribed naloxone in the past, or reported to their prescribing clinician that they had naloxone already, is not captured. Importantly, it is not known whether naloxone was dispensed to patients, only that it was prescribed. Additionally, the risk of overdose is not consistent across populations. People with comorbid respiratory diseases, such as obstructive sleep apnea (OSA), or people who take other respiratory-depressant medications, such as benzodiazepines, have a higher risk of opioid overdose, and it may be appropriate for naloxone co-prescription at a lower daily MME. These factors were not captured by the BPA. Demographic categorizations are limited by how they are represented in the dataset and may be incomplete. For example, during the period analyzed, there were no additional categories of gender in the EHR besides male and female, and limited racial categories. Individuals are represented in the database as they were assigned in the EHR, which may reflect incorrect classifications.

More generally, this was not a randomized controlled trial. While several patient characteristics were statistically controlled, it is nonetheless possible that unmeasured confounding contributed to the observed effects. While the interrupted time series design of the study aims to distinguish the effects of other environmental factors from the effect of BPA, it is possible that other factors contributed to the changes in provider practices that were observed. Lastly, as a single-center study conducted at a large academic medical center, results may not be generalizable to all settings.

The pre-BPA period was associated with a secular decrease in the rate of prescriptions for MMEs exceeding 50, which dissipated following the BPA. Given that the response to the opioid crisis has been continuously evolving, it is likely that multiple policies and cultural shifts contributed to this secular trend.

Conclusions

Having naloxone in-hand on the site of an overdose is lifesaving. The naloxone cascade is complex and includes actions at the policy level, as well as the institutional, individual, and community levels. EHR alerts are an effective tool to help expand naloxone prescription and availability, including for patients from traditionally underserved groups such as Black Americans. As the opioid epidemic continues to claim lives and shows little evidence of slowing, healthcare institutions and professionals should consider deploying similar alerts that aim to promote prescribing behaviors that decrease morbidity and mortality from opioid overdoses.

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Declarations:

Conflict of Interest: The authors have no conflicts of interest to declare.

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