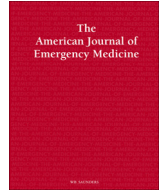




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Trends in naloxone prescribed at emergency department discharge: A national analysis (2012–2019)

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ABSTRACT

Background: While having access to naloxone is recommended for patients at risk for opioid overdose, little is known about trends in national naloxone prescribing rates in emergency departments (EDs) both for co-prescription with opioids and for patients who presented with opioid abuse or overdose. This study aims to evaluate the change in naloxone prescribing and opioid/naloxone co-prescribing at discharge using national data. **Methods:** We conducted an IRB exempt retrospective review of data collected by the National Hospital Ambulatory Medical Care Survey from 2012 to 2019. The primary outcome was trend in rate of naloxone prescribing at discharge from ED visits. We also computed the proportion of visits where naloxone was both administered in the ED and prescribed at discharge, where naloxone and opioids were co-prescribed at discharge, and where an opioid was administered during the ED visit and naloxone was prescribed at discharge. All data were summarized using descriptive statistics and Spearman's Rho (SR) or Pearson's correlation (PR) were used to describe trends.

Results: There was an estimated total of 250,365 patient visits where naloxone was prescribed at discharge with an increasing rate over time (0% of all ED visits in 2012 to 0.075% in 2019, $p = 0.002$). There were also increases in naloxone being both administered in the ED and prescribed at discharge (PC: 0.8, $p = 0.02$) as well as in naloxone and opioid co-prescribing (SR: 0.76, $P = 0.03$). There was an increase in utilization of opioids during the ED visit and naloxone prescribing at discharge for the same visit (SR: 0.80, $p = 0.02$).

Conclusion: There are increases in naloxone prescribing at discharge, naloxone and opioid co-prescribing, and opioid utilization during the same visit where naloxone is prescribed at discharge. Future studies should be done to confirm such trends, and targeted interventions should be put into place to increase access to this life-saving antidote.

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1. Introduction

Opioid overdose mortality rates involving both medically and non-medically obtained opioids have been increasing, with over 100,000 deaths occurring annually in the US [1]. Naloxone, an opioid antagonist, is a powerful part of a larger harm reduction strategy. Timely administration of naloxone by bystanders is critical to survival after opioid overdose, and with the increased prevalence of illicit fentanyl, hypoxic complications can occur rapidly, prior to emergency medical service (EMS) arrival [2].

Since 2001, legal changes have been adopted to allow greater naloxone accessibility, including naloxone standing orders at pharmacies and

third-party prescribing [3]. Naloxone distribution has been implemented in community settings through Overdose Education and Naloxone Distribution (OEND), and increasingly in hospital settings, with proven success at reducing deaths [4]. An estimated 9% of take-home naloxone is being used within 3 months to reverse an overdose [5]. In addition, the U.S. Food and Drug Administration (FDA) and several states have made recommendations or mandates for co-prescribing of naloxone with opioid analgesics to patients at high risk of overdoses [6,7]. Modeling algorithms predict that increasing naloxone availability alone over a 5 year period, would lead to the largest reduction in opioid overdose deaths (4.3%), surpassing needle exchange, medication-assisted therapy, and psychosocial treatment [8].

Emergency departments (EDs) are in a unique position to prescribe naloxone at discharge to people at risk for opioid overdose [9]. This would most likely occur following an ED evaluation after an opioid overdose. With the rate of ED visits for opioid overdoses increasing

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(approximating 1 in 300 visits [10]), in addition to the large number of opioid prescriptions from the ED (over 80 opioid prescriptions per 100 patients reported in 2012, not necessarily high dose [11]), there is another valuable opportunity for take home naloxone.

Rates of opioid and naloxone co-prescribing are as low as <0.1% in various care settings [12–14]. However, still little is known about the rate and trends in national naloxone prescribing rates in EDs both for co-prescription with opioids and for patients who presented with opioid abuse or overdose. This study aims to evaluate the change in naloxone prescribing at discharge and opioid/naloxone co-prescribing at discharge using data from the National Hospital Ambulatory Medical Care Survey (NHAMCS) from 2012 to 2019, a timeframe that was before the COVID-19 pandemic.

2. Methods

We conducted a retrospective review of publicly available data collected by the NHAMCS from 2012 to 2019. All data were deidentified. The study was exempt from IRB review since it is not considered human subjects research.

2.1. Study design, setting, and population

NHAMCS is a nationally representative survey of acute care visits that is conducted annually by the National Center for Health Statistics (NCHS) using a sample of EDs with the goal of estimating the provision of services in these settings. NHAMCS uses a multi-stage probability design so that the data obtained from the survey sample can be used to approximate the distribution of patient visits across U.S. EDs. Visits are weighted to approximate the number of patients that fit specific visit characteristics defined by the variables collected by the survey. Variables collected include patient demographics (age, gender, race, ethnicity, insurance, etc.), reason(s) for visit, medications administered in the ED and/or prescribed upon discharge, services provided (such as diagnostic tests and procedures performed), patient disposition, among many others. The survey is a patient record form that is completed by trained staff who extract data from patient records for a random sample of visits during randomly assigned reporting periods.

For the purposes of this study, our focus was on patient visits between 2012 and 2019 in which there was documentation of a naloxone prescription at the time of ED discharge. In the NHAMCS databases, under medications, all variations that represented naloxone were captured including “Narcan,” and “naloxone HCl.” There is NHAMCS data available for years prior to 2012, however we did not include those years in our study since those databases were designed only to include information for a maximum of 8 medications that were either given in the ED or prescribed at discharge during a patient visit. Consequently, if >8 medications were used or prescribed at an ED visit, naloxone may have been missed and not documented. Consequently, we decided to start our study using data when there were more medication fields available in the database to allow for better data capture.

2.2. Data abstraction

In the NHAMCS database, one can differentiate whether a patient had a medication administered during their ED visit, prescribed at discharge, or at both by examining the data for each medication summarized by the variables named “GPMED_” where “_” can represent any number from 1 to 30, as that is the maximum number of medications given at a patient visit the NHAMCS captures. To complete our study, we used the data selection tool in IBM SPSS software to select only those visits for each year where naloxone was prescribed at ED discharge or both administered at the ED visit and prescribed at discharge. We additionally abstracted demographic information for each of these weighted patient visits such as age, residence, gender, ethnicity, race, payor, reason for visit, region, metropolitan status of hospital, academic

status, whether the patient had a documented substance use disorder and the total number of patient visits to the ED for each year.

From this dataset, which only consisted of patient visits that involved naloxone prescribed at discharge, we further abstracted those patients that were prescribed both naloxone and an opioid analgesic at discharge for each year. A summary of opioids that are documented in the NHAMCS database and are included in this study are listed in Appendix 1.

2.3. Outcomes

The primary outcome of our study was the trend in the number of patient visits where naloxone was prescribed at discharge from the ED visits between 2012 and 2019. Secondly, we also aimed to identify the proportion of instances in which naloxone was both administered in the ED and prescribed at discharge, the proportion of instances where naloxone and opioids were co-prescribed at discharge, and the proportion of visits in which an opioid was administered during the ED visit and naloxone was prescribed at discharge.

2.4. Data compilation and analysis

In order to determine if there was a trend in naloxone prescriptions given at ED discharge between 2012 and 2019, we first tabulated the total number of visits per year where naloxone prescriptions (including both of the naloxone codes mentioned above) were given at discharge using the patient weights for each eligible visit. We conducted Shapiro Wilke's test to determine the normality of the data, and used Pearson's correlation or Spearman's rho as applicable to determine if there was a trend. We repeated this analysis looking at rates of naloxone prescribing instead of absolute numbers by dividing the total number of visits where naloxone was given by the total number of patient visits for each year to account for the rising number of ED patient visits per year. Of visits in which naloxone was prescribed at discharge, we also identified the most common diagnoses for patient visits in which patients were discharged with naloxone by tabulating the patient visit weights for common diagnoses and then ranking them based on weight.

For the first secondary analysis, we used the naloxone discharge prescription dataset to further narrow the dataset to contain only those instances in which naloxone was administered during the ED visit and was prescribed at discharge. Using the patient weights for the eligible visits, we were able to compute the estimated number of visits where naloxone was given both at the emergency department and prescribed at discharge and conduct a trend analysis using Pearson's correlation (PC) or Spearman's rho (SR) as applicable. We also did a rate calculation normalizing for the number of ED visits per year to confirm this trend. We repeated the same process for our secondary analysis, tabulating the number of visits for each year where patients were co-prescribed both naloxone and an opioid at discharge and to determine the number of visits where an opioid was administered during an ED visit and naloxone was prescribed at discharge.

Since the NHAMCS database documents each visit (row) as a weighted visit, all analyses were conducted using the unweighted patient samples. These were computed for eligible row visits (i.e. those visits that involved naloxone prescribing) using the “PATWT” column variable for each weighted visit. We used the values in this column to compute the non-weighted representative numbers for each weighted visit for variable of interest. We then used these non-weighted numbers to conduct our analyses.

Descriptive statistics (such as mean, median, standard deviation (SD), interquartile range (IQR) and percent change) were used to summarize all data as applicable, 95% confidence intervals were reported when available, the Mann-whitney *U* test was used to make comparisons when applicable, and all *p*-values were one-tailed (to determine

if there was an increase or decrease over time) and reported at a 0.05 significance level. All analyses were conducted in IBM SPSS version 28.

3. Results

3.1. Demographics

During the study period, most patients (127,805, 51%, 95% CI: [50.9, 51.3]) that were prescribed naloxone at discharge were between ages 25 and 44 years, followed by 45–64 (75,334, 30.1%, 95% CI: [29.9,30.3]). Of the patients that were in the age range 15–24, all of the visits where naloxone was prescribed was prescribed to those aged either 23 or 24. Most patients were male (220,098, 87.9%, 95% CI: [87.8,88.4]), White (166,186, 66.4%, 95% CI: [66.2,66.6]) and were not Hispanic or Latino (217,416, 86.8%, 95% CI: [86.7,86.9]). Many patients that were prescribed naloxone had Medicaid as their primary payor (110,572, 44.2%, 95% CI: [43.9,44.4]), and lived either in the South or West regions of the country (184,297, 73.6%, 95% CI: [73.4,73.8]). Most patients had a documented substance use disorder (155,290, 62.0%, 95% CI: [61.8,62.2]). Please see Table 1 for a complete breakdown of patient baseline demographics.

3.2. General trends in naloxone prescribing

Between 2012 and 2019, there was an estimated total of 250,365 patient visits where naloxone was prescribed at discharge. Upon evaluating change in absolute numbers, we found that there was a strong, increasing linear correlation over time ($PC = 0.897, p = 0.003$). When we looked at the rate of change as a function of total ED visits, we had the same finding ($PC = 0.911, p = 0.002$). At the beginning of the

Table 1
Demographic distribution of patients that were given a prescription for naloxone upon discharge from the emergency department (2012–2019).

Variable	Raw Counts (<i>n</i> = 44)	Estimated Number of Patients (<i>n</i> = 250,365)	Percentage (%)	95% CI
Age				
Under 15	0	0	0	[0,0]
15–24	4	32,166	12.9	[12.7,13.0]
25–44	18	127,805	51.1	[50.8,51.3]
45–64	18	75,334	30.1	[29.9,30.3]
65–74	4	14,137	5.7	[5.6,5.74]
75 and over	0	0	0	0
Sex				
Female	15	49,658	19.8	[19.7,20.0]
Male	29	220,098	87.9	[87.8,88.0]
Race				
White	28	166,186	66.4	[66.2,66.6]
Black	13	64,423	25.7	[25.6,26.0]
Other	3	2669	1.1	[1.0,1.1]
Payor				
Unknown	2	54,823	21.9	[21.7,22.1]
Private Insurance	4	11,632	4.7	[4.6,4.7]
Medicare	10	24,158	9.7	[9.5,9.8]
Medicaid or CHIP or other state-based program	20	110,572	44.2	[44.0,44.4]
Self-pay	3	6560	2.6	[2.6,2.7]
Region				
Northeast	4	15,302	6.1	[6.0,6.2]
Midwest	3	16,408	6.6	[6.5, 6.7]
South	24	92,795	37.1	[36.9,37.3]
West	13	91,501	36.6	[36.4,36.7]
History of Substance Abuse				
Yes	27	155,290	62.0	[61.8,62.2]
No	17	71,618	28.6	[28.4,28.8]

study period (2012), there were an estimated 0% (0) of all patient visits where naloxone was prescribed at discharge and at the end of the study period (2019) there was an estimated 0.075% (113,671) of all patient visits where naloxone was prescribed (mean: 31,295, SD: 39,712). To be noted, years 2012, 2013, and 2014 all had an estimated 0 naloxone prescriptions. Taking into consideration these outliers, we repeated the trend analysis using the rate of prescribing from years 2015–2019 and still found a significant increase over time ($PC: 0.95, p = 0.008$).

The most common diagnoses for which patients were given discharge naloxone included poisoning by overdosing of narcotics and psychodysleptics and opioid related disorders. All naloxone prescribed at discharged occurred in metropolitan settings. There was no significant difference in naloxone prescribed at discharge between academic (median: 1996; IQR: 4123) and non-academic sites (median: 1844; IQR: 5807) ($p = 0.29$).

3.3. Trends in patient visits where naloxone was given both in the ED as well as prescribed at discharge (2012–2019)

There were a total of 111,073 visits in which naloxone was both administered in the ED and prescribed at discharge. Between 2012 and 2014, the number of visits where naloxone was given both in the ED and prescribed at discharge was undetectable. In 2015, there were a total of 3152 such visits and at the end of the study period (2019), there were a total of 36,604 visits. Overall, there was a strong, increasing linear trend in rate of naloxone being both administered in the ED and prescribed at discharge ($PC: 0.8, p = 0.02$), with an average of 13,884 naloxone prescriptions being given per year (SD: 18,593). See Fig. 1, for a visualization of how the number of visits changed over time.

3.4. Trends in patient visits where naloxone and opioids were co-prescribed at discharge (2012–2019)

At the beginning of the study period (2012), there were 0 visits where naloxone and opioids were co-prescribed at discharge, while at the end of the study period (2019), there were 28,621 visits where they were co-prescribed. There were a total of 44,625 visits throughout the study period where they were co-prescribed (Median: 295, IQR: 9983), and there was a strong, increasing trend in rate over time ($SR: 0.76, P = 0.03$) (see Fig. 2).

3.5. Trends in patient visits where opioids were given during the ED visit and naloxone was prescribed at discharge for the same visit (2012–2019)

Overall, there were a total of 76,607 patient visits where opioids were given during the ED visit and naloxone was prescribed at discharge for the same visit during the study period, and there was a strong, increasing trend over time ($SR: 0.80, p = 0.02$) (see Fig. 3). In 2012, there were 0 visits and in 2019, the end of the study period there were 22,070 visits for such an occurrence. Over time, the median number of visits was 1576 with an IQR of 18,330.

4. Discussion

Our study found that between 2012 and 2019, prior to the COVID-19 pandemic, there was an increase in naloxone prescriptions given at ED discharge, consistent with efforts across the US to address the opioid crisis. Our study also found that there also was an increase in naloxone and opioids co-prescribed at discharge, the number of visits where opioids were given in the ED and naloxone was prescribed at discharge, and the number of visits where naloxone was administered during the ED visit and prescribed at discharge.

Although the number of naloxone prescriptions given at discharge has increased over time, it must be noted that the number of prescriptions found in this study is significantly less than the number of patients that come to the ED with an overdose or opioid related complication

Visits where Naloxone was given both in the Emergency Department and prescribed at Discharge (2012-2019)

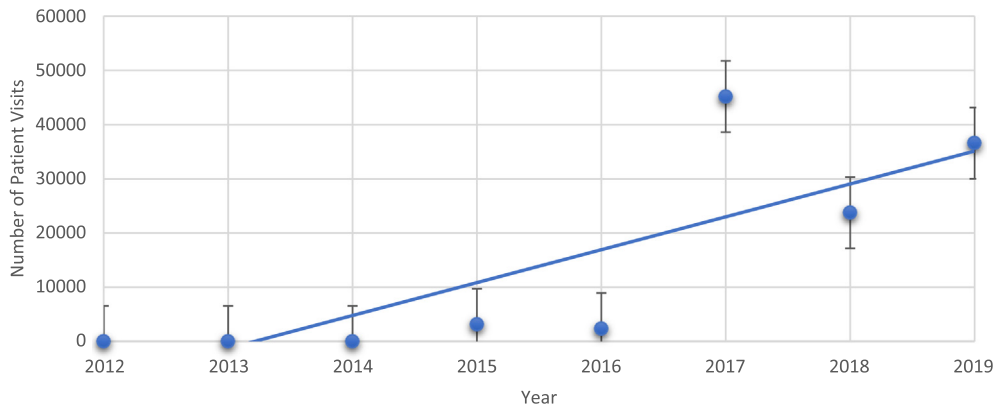


Fig. 1. National trends in naloxone administration in the ED and prescribing at discharge over time.

(notably in the Northeast and Midwest regions). There could be several reasons for this. For one, this study looks specifically at naloxone prescriptions. EDs across the nation distribute naloxone in the form of kits or devices to eligible patients free of charge [15,16]. Such patients would not need a naloxone prescription, and this would not necessarily be captured in NHAMCS and there is little literature on distribution rates to eligible patients. Additionally, this strategy may be preferable to providers than to give a prescription since there can be out of pocket costs associated with naloxone which the patient cannot afford [17]. As shown in our study, most of these patients have Medicaid, but there may be higher out of pockets costs for those who do not have insurance or have private insurance. Additionally, not all pharmacies carry naloxone [18]. Patients may also refuse a prescription for naloxone, or if they were given a naloxone prescription, they may not fill it [25]. There is also the possibility that nationwide, ED are underperforming in terms of providing naloxone prescriptions and distributing kits due to stigma, cost, laws, or other factors. There should be increased interventions at

all levels (federal and local) to ensure that patients have access to naloxone and can afford it. There should also be particular focus on making naloxone accessible to those age groups that are at highest risk, including young adults [19]. A recent study published in JAMA found that drug overdose deaths among adolescents are rising quickly in the setting of fentanyl [20]. A recent initiative in Michigan involved created naloxone vending machines that is publicly available to patients and from which the naloxone is free [21].

It is notable that the number of visits where naloxone was both given in the ED and prescribed at discharge significantly increased, and this is also consistent with the rising rates of opioid related complications. The number of visits where an opioid was given during the ED visit while naloxone was prescribed at discharge and the number of visits where naloxone and opioids were co-prescribed also significantly increased. These findings are of interest and can be counterintuitive for several reasons. It is known that the opioid epidemic began due to the prescribing of opioids for pain. Consequently, over years, due to policies

Visits where Naloxone and Opioids Were Co-prescribed at Discharge (2012-2019)

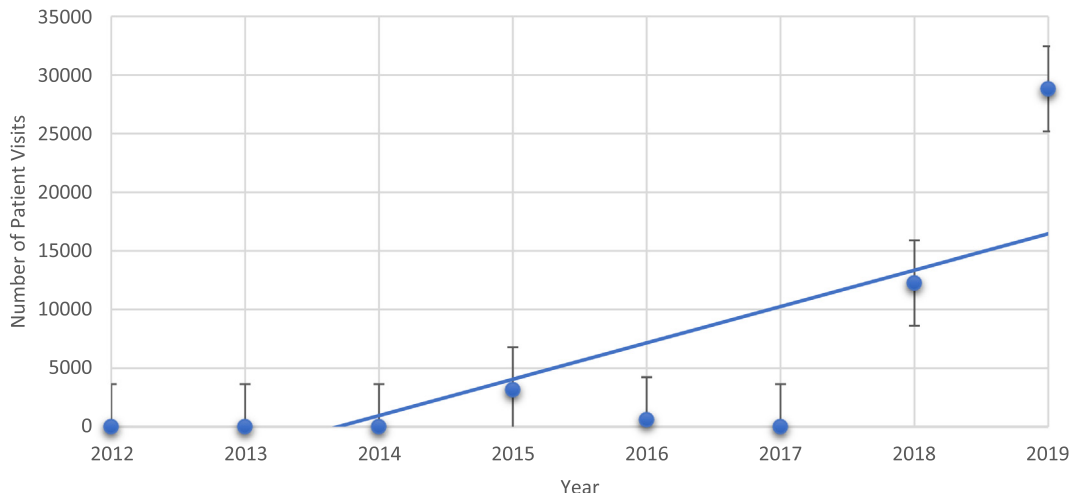


Fig. 2. National trends in naloxone and opioids were co-prescribed at discharge over time.

Visits where opioids were given during the ED visit and naloxone was prescribed at discharge for the same visit (2012-2019)

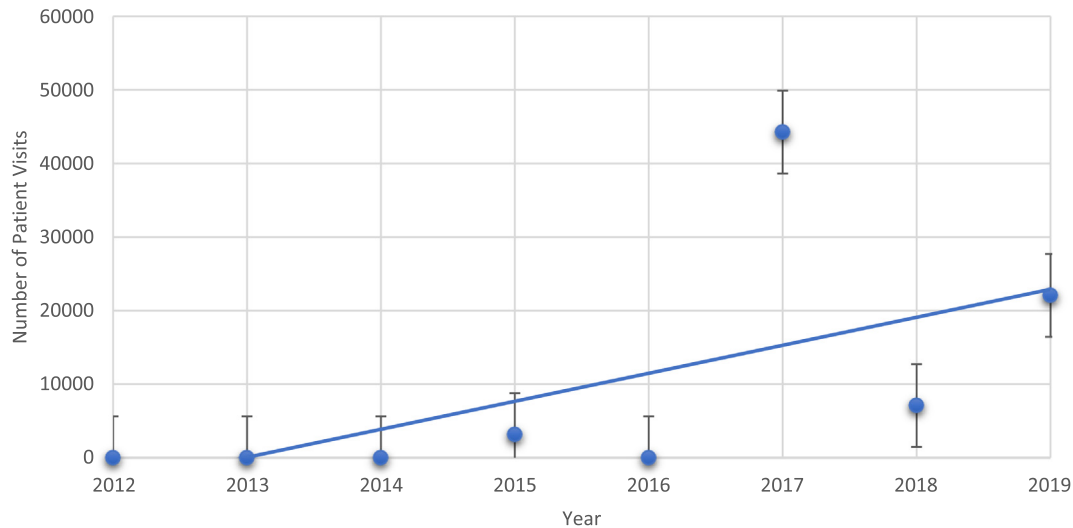


Fig. 3. National trends in visits where opioids were given during the ED visit and naloxone was prescribed at discharge over time.

and regulations put in place at all levels, opioid prescribing across the nation (including in ED settings) have dramatically decreased [6]. Additionally, it should be noted that non-opioid pain medications such as ibuprofen and ketorolac decrease pain at similar levels than opioid medications and have, therefore they can be used in place of traditional opioid medications [22,23]. A majority of the patients in this study were given opioids either at the ED visit or at discharge came to the ED have substance use disorder and had a related complaint. It is possible that several of these patients may have undocumented chronic pain secondary to their complaint for their ED visit, as many studies have shown and are showing that a large proportion of patients with substance use disorders have chronic pain. It is also possible that they were given an opioid during the ED visit to help manage withdrawal, or another secondary complaint related to an acute issue that may have required opioid therapy; however, we were not able to identify this given the limitations of the NHAMCS database. It should also be noted that recent harm reduction initiatives are also pushing for the prescribing naloxone when prescribing an opioid at discharge if providers believe the patient is at high risk for an overdose [24]. This may also be contributing to the rising rates.

Naloxone is a life saving therapy [25]. A meta-analysis of the literature found that bystander naloxone administration can be safe and effective [26]. This can be critical in saving a patient's life even prior to EMS arrival. Consequently, there should be an increased focus on prescribing and/or dispensing it at ED discharge and examining barriers to provision of this evidence based treatment, which can in turn reverse many overdoses and save many lives from being unnecessarily lost.

5. Limitations

There are several limitations to note in this study. The NHAMCS database is limited in the ability to evaluate reasons for naloxone or opioid prescriptions or lack of prescriptions, and also dose, limiting our understanding of physician decision-making. Additionally, the database does not contain information on whether alternative modalities for treatment of pain were attempted but given that the primary patient diagnoses were not pain related, future studies should further investigate this

finding for clarification. It is possible that opioids were used for withdrawal management but given the limitations of the database, we were not able to confirm/refute this. The NHAMCS data also has the benefit of sampling from EDs across the country, however, this limits the ability to understand how state-specific policies have affected specific regions over time. Data from beyond 2019 was not yet available at the time of this study, as a result, all findings reported are pre COVID-19 pandemic and do not represent the impact of the pandemic on naloxone prescribing, which should be investigated in a future study. The NHAMCS database also does not contain data on hospital size or ED census, further limiting our ability to understand factors that may impact naloxone prescribing. Furthermore, it should be noted that changes in NHAMCS occur yearly (in terms of data collection process, data collection instrument, and the hospitals sampled). As a result, this could be one reason why the numbers in our study from 2012 to 2014 are 0. Additionally, these changes could have affected the results between 2015 and 2019 in ways that we are not sure about.

Additionally, while we tabulated naloxone prescriptions provided, we did not account for the number of opportunities where ED providers may have missed giving a naloxone prescription, such as the total number of visits over the years of patients that came to the ED with opioid use complications. Therefore, although there is an increasing trend in absolute numbers, overall this likely only may be a small number of patients we are capturing of those eligible to receive a prescription and consequently the actual rate of distribution could be falling. It should also be noted that the NHAMCS database does not have data on the type of prescriber that prescribed naloxone (e.g. licensed physicians, trainees, physician assistants, nurse practitioners). As a result, from this study, we are not able to understand the impact different caregivers or training levels have on prescribing.

Although naloxone prescriptions have been shown to increase naloxone dispensing [27], the practicality of using naloxone prescriptions as a beneficial harm reduction strategy should be viewed cautiously. Recent studies indicate that only 1% of naloxone prescriptions from the ED are filled within 30 days [28]. This could be due to a number of reasons including lack of access, affordability, or refusal. Additionally, freely available take-home naloxone (THN) without prescriptions, is being piloted at EDs around the country and does not get counted into the

naloxone prescription data [29]. Although that data is not yet available in NHAMCS, this is an interesting area for further study.

6. Conclusion

There is an increasing trend in providing naloxone prescriptions at discharge, but also trends showing increases in visits where naloxone and opioids are co-prescribed, and visits where an opioid is given during the same visit where naloxone is prescribed at discharge. Due to the limitations of the dataset, it is not clear if these represent different approaches to care or different patient populations. Future studies should be done to confirm or refute such trends, and if they are confirmed, targeted interventions should be put into place to address this problem including, but not limited to education initiatives and protocols. Additionally, reasons for providing opioid prescriptions at discharge and ED utilization should be analyzed to further develop targeted interventions. Future studies should also analyze the impact of COVID-19 on naloxone prescribing.

Author contributions

Christine Ramdin, PhD conceived the idea, performed the analysis, and drafted and revised the manuscript.

Kira Chandran, BS conducted the literature review and helped to draft and critically revise the manuscript.

Lewis Nelson, MD contributed to the study oversight, helped to conceptualize the study design, and critically reviewed and provided feedback to the manuscript.

Maryann Mazer-Amirshahi, MD oversaw the study, helped to conceive the study idea, helped to conceptualize the study design, and critically reviewed the manuscript and provided feedback.

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CRediT authorship contribution statement

Christine Ramdin: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Kira Chandran:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Conceptualization. **Lewis Nelson:** Writing – review & editing, Supervision, Software, Resources, Investigation, Conceptualization. **Maryann Mazer-Amirshahi:** Writing – review & editing, Supervision, Resources, Investigation, Conceptualization.

Declaration of Competing Interest

The authors report no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ajem.2023.01.006>.

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