Escalation of Opioid Withdrawal Frequency and Subsequent AMA Rates in Hospitalized Patients From 2017 to 2020

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**Objective:** To measure trends for the emergence of opioid withdrawal (OW) and leaving against medical advice (AMA) among hospitalized patients.

**Method:** Retrospective time-series of hospitalized patients with OW, defined by a Clinical Opioid Withdrawal score ≥8, using electronic health record data at a tertiary health system and of patients with a discharge status of AMA from January 1, 2017 to December 31, 2020.

**Results:** The average number of monthly hospitalizations with OW showed a year-to-year increment of 15% in 2018, 21% in 2019, and 34% from 2019 to 2020, whereas the total monthly hospitalizations remained stable. The segmented regression analysis showed that the upward trend in hospitalizations with OW became significant after January 2019 (slope: 1.14, 95% confidence interval [CI]: 0.70, 1.57). After August 2019, Fentanyl was added to the hospital urine drug testing panel and was identified in most OW patients. The monthly proportion of patients who left AMA was significantly higher among the OW patients than among all other admitted patients. There was a significant increase of 0.39 (95% CI: 0.29–0.49, P < 0.001) per month in %AMA among patients with OW. The estimated difference in %AMA among OW patients versus all other patients was 7.25 (95% CI: 5.12–9.38) in January 2017, and 16.92 (95% CI: 14.60–19.24) in December 2020.

**Conclusions:** The number of hospitalized patients either presenting with or developing OW increased between 2017 and 2020 with a significant rise occurring after January 2019. The percentage of patients who left AMA among those who developed OW steadily worsened during the entire study period.

**Key Words:** fentanyl, hospitalized patients, leaving against medical advice (AMA), opioid withdrawal

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Opioid-related overdose death rates continue to escalate. The emergence of fentanyl into the illicit drug supply has been implicated. The impact of the evolving opioid epidemic on health systems during the pandemic is less well described. Though Emergency room visits for nonfatal opioid-related overdoses increased despite decreases in overall admissions, rates of hospitalizations of patients with opioid use disorders (OUD) and their outcome has not been reported. It is well known that patients who leave against medical advice (AMA) are at increased risk of adverse outcomes and readmissions. Moreover, patients with OUD are at high risk of leaving AMA because of the fear and under treatment of opioid withdrawal (OW). We hypothesized that the number of hospital admissions with OW and AMA increased during the last 4 years because of both the emerging fentanyl epidemic and COVID 19 pandemic. We conducted a retrospective study at a tertiary care health system in which Electronic Health Records-embedded screening and monitoring using the Clinical Opioid Withdrawal Scale (COWS), urine drug screening (UDS), and treatment of OW using buprenorphine or methadone are standardized practices.

**METHODS**

**Study Setting**

We studied trends in OW and AMA among patients hospitalized within the ChristianaCare Health System between January 2017 and December 2020. ChristianaCare is one of the largest health care providers in the mid-Atlantic region, serving all of Delaware and parts of Pennsylvania, Maryland, and New Jersey. Since 2016, all hospital admissions with illicit opioid
use identified during nursing onboarding or clinician assessment undergo COWS monitoring and UDS testing. Fentanyl was added to all UDS results after August 2019. OW is treated with buprenorphine, methadone, or other opioids based on patient preference and clinical context. Those electing to continue medications to treat OUD are transitioned to community-based providers upon discharge.

The study was approved by ChristianaCare’s Institutional Review Board.

Data Source and Variables

The data were obtained from the Electronic Health Records data warehouse of ChristianaCare. We extracted demographic information including age, sex, race and ethnicity, discharge status, clinical information such as comorbid-ities according to the Elixhauser algorithm, severe infections (endocarditis, sepsis, empyema, discitis/osteomyelitis) using ICD10 discharge diagnoses, UDS results, and COWS scores for all hospitalizations from January, 1, 2017 to December, 31, 2020. The highest COWS score was selected for each hospitalization. We used a COWS score threshold of 8 or above to define OW in our analyses. Total number of hospitalizations, of hospitalizations with OW, of hospitalizations that ended with leaving AMA, and number of AMA among hospitalizations with OW for each month during the study period were calculated.

Statistical Analysis

Demographic and clinical characteristics of unique patients admitted with COWS 8 in each year were summarized using mean and standard deviations for age, and count and percent for gender, race, ethnicity, comorbidities and UDS results. Temporal trends were visualized using time series plot of number of monthly hospitalizations with OW versus total number of hospitalizations, and percent of AMA among patients admitted with OW versus percent of AMA among all admitted patients. The trend in number of hospitalizations with OW was analyzed using a segmented regression model with the R package “segmented.” An ordinary least square model of AMA with time, diagnosis of OW versus all other, and interaction of OW diagnosis and time was fitted to evaluate the trends of AMA in hospitalizations with OW and all other admissions. Further, the previous models were extended by introducing an additional variable related to pandemic – coded as 0 if before March 2020 (onset of COVID-19-related state-wide stay at home order in Delaware), and incremented integer values starting from 1 for each month after March 2020, to estimate the effect of pandemic on the trends. Statistical significance was set at 0.05. All analyses were performed in R.

RESULTS

Patients Characteristics

There were 286, 321, 400, and 499 patients who developed OW in 2017, 2018, 2019, and 2020, respectively (Table 1). The race and gender distribution were similar across years. The frequency of depression, psychosis, alcohol abuse, and severe infections was high in this population but did not show

| Variable | 2017 (n = 286)* | 2018 (n = 321)* | 2019 (n = 400)* | 2020 (n = 499)* |
|----------|----------------|----------------|----------------|----------------|
| Age, mean (SD), years | 41.63 (13.37) | 43.08 (13.24) | 44.00 (13.30) | 44.20 (13.40) |
| Male, No. (%) | 149 (52.10) | 162 (50.47) | 209 (52.25) | 264 (52.91) |
| Race, No.† | | | | |
| White | 203 (70.98) | 246 (76.64) | 306 (76.50) | 368 (73.75) |
| Black or African American | 73 (25.52) | 68 (21.18) | 74 (18.50) | 106 (21.24) |
| Other Race‡ | 9 (3.15) | 7 (2.18) | 20 (5.00) | 25 (5.00) |
| Ethnicity, No.(%)§ | | | | |
| Hispanic or Latino | 19 (6.64) | 11 (3.43) | 26 (6.50) | 28 (5.61) |
| Non-Hispanic or Latino | 262 (91.61) | 309 (96.26) | 368 (92.00) | 465 (93.19) |
| Diabetes, No. (%) | 58 (20.28) | 66 (20.56) | 88 (22.00) | 112 (22.44) |
| Hypertension, No. (%) | 119 (41.61) | 143 (44.55) | 194 (48.50) | 251 (50.30) |
| Depression, No. (%) | 190 (66.43) | 226 (70.40) | 278 (69.50) | 320 (64.13) |
| Psychoses, No. (%) | 43 (15.03) | 55 (17.13) | 59 (14.75) | 74 (14.83) |
| Alcohol abuse, No. (%) | 115 (40.21) | 148 (46.11) | 167 (41.75) | 226 (45.29) |
| Liver disease, No. (%) | 94 (32.87) | 127 (39.56) | 142 (35.50) | 197 (39.48) |
| Bacteriemia/Sepsis, No. (%) | 33 (11.54) | 41 (12.77) | 42 (10.50) | 55 (11.02) |
| Emphyema, No. (%) | 6 (2.10) | 5 (1.56) | 8 (2.00) | 7 (1.40) |
| Endocarditis, No. (%) | 20 (6.99) | 18 (5.61) | 16 (4.00) | 31 (6.21) |
| Osteomyelitis/Discitis, No. (%) | 13 (4.55) | 24 (7.48) | 25 (6.25) | 38 (7.62) |
| UDS Opioid, No. (%)§ | 181 (63.29) | 194 (60.44) | 215 (53.75) | 235 (47.09) |
| UDS Fentanyl, No. (%)§ | Not measured | Not measured | 143 (35.75) | 334 (66.93) |
| UDS Benzodiazepines, No. (%)§ | 59 (20.63) | 81 (25.23) | 82 (20.50) | 114 (22.85) |
| UDS Cocaine, No. (%)§ | 106 (37.06) | 117 (36.45) | 141 (35.25) | 167 (33.47) |

*The patient population consists of unique patients in each year from 2017 to 2020.
†Numbers do not sum to group totals because of a few missing values.
‡The category “Other race” includes American Indian, Alaska Native, Asian, Other not defined.
§The results are not mutually exclusive.
||Fentanyl was measured in the UDS beginning August 2019.

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a clear increasing pattern. The OW patients who left AMA were younger than the overall OW patients (Table 2). Opioid, Fentanyl, and cocaine were found more frequently in the UDS of those who left AMA (Tables 1 and 2).

**Trends in Hospitalizations**

The average number of monthly hospitalizations with OW was 26 ± 7 in 2017, 30 ± 8 in 2018, 38 ± 10 in 2019, and 51 ± 7 in 2020. This corresponds to a year-to-year increment of 15% in 2018, 21% in 2019, and 34% from 2019 to 2020, whereas the total monthly hospitalizations remained stable with mean ± standard deviations of 4143 ± 142, 4163 ± 132, 4274 ± 192 in 2017, 2018, 2019 but decreased sharply in the first quarter of 2020 (3902 ± 347) because of the pandemic lockdown (Fig. 1). The segmented regression analysis showed that the trends in number of hospitalizations with OW before and after January 2019 were significantly different (Fig. 1). The upward trend in hospitalizations with OW was not significant before January 2019 (slope = 0.33, 95% confidence interval [CI]: —0.05, 0.70) but became significant after January 2019 (slope = 1.14, 95% CI: 0.70, 1.57). This corresponds to an increase in average number of hospitalizations with OW by 1.14 each month. The pandemic-related variable was not significant in the model indicating that it did not modify the trends.

**Trends in Leaving AMA**

The monthly proportion of patients who left AMA was significantly higher among the OW patients than among all other admitted patients during the study period (Fig. 1). The trend of monthly %AMA among all hospitalizations was not significant. However, there was a significant increase of 0.39 (95% CI: 0.29–0.49, P < 0.001) per month in %AMA among patients with OW between January 2017 and December 2020. Compared to the %AMA in all hospitalizations, the %AMA in patients with COWS >8 increased by an additional 0.36 (95% CI: 0.22–0.50) per month (P < 0.001). The estimated difference in %AMA among OW patients versus all other patients was 7.25 (95% CI: 5.12–9.38) in January 2017, and 16.92 (95% CI: 14.60–19.24) in December 2020.

**DISCUSSION**

We found a significant increase in the number of patients admitted to the hospital developing OW after January 2019 compared to 2017–2018, a change that preceded the pandemic. Concomitantly, we show a sustained increased rate of AMA among patients with OW despite well-established OW screening and treatment protocols. Historically, hospitals served as a reachable moment to engage opioid-dependent patients into life sustaining treatments such as methadone or buprenorphine in part by addressing OW.11–14 Our results suggest that the evolving opioid epidemic is negatively
impacting this critical role. There is an acute need to investigate causality including the role of fentanyl and determine if established practices such as buprenorphine induction should be modified.\textsuperscript{13}

Limitations to the study include the use of COWS monitoring to estimate incidence of OW, a method that is yet to be validated. UDS for fentanyl began in August 2019 and comparisons to early periods are not possible. Among patients with COWS $\geq 8$, only approximately 60\% had opioid-positive UDS in 2017–2018, suggesting that many might also have been positive for fentanyl had this been measured. Lastly, the opioid epidemic has evolved with regional differences\textsuperscript{15} and results from a single health system may not be generalizable.

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