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RESEARCH ARTICLE

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Converting adults with sickle cell disease from full agonist opioids to buprenorphine: A reliable method with safety and early evidence of reduced acute care utilization

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Abstract

Buprenorphine, a novel opioid with complex pharmacology, is effective for treating pain and is qualitatively safer than high-dose full agonist opioid therapy; but transitioning to buprenorphine can be technically complex and carries some risk of precipitated withdrawal. We report our clinic's experience converting 36 patients with sickle cell disease (SCD) from full agonist opioids to buprenorphine using a method developed in the past 10 years. Thirty of these patients were induced using a standard outpatient protocol and six were induced during medical admissions. Typically, patients were on high-dose chronic opioid therapy (COT) with inadequate response, and often with very high acute care utilization. Unlike prior case series, the method of induction, dosing, and management of withdrawal are detailed, as are post-induction adverse events. There were seven adverse events in the first 3 days following standard induction, and two of which were judged to be definitely related to the induction but none with any lasting sequelae. At 6 months follow-up, five participants had discontinued buprenorphine (16.67%), and overall acute care visits dropped from a mean of 10.50 (SD 11.35) in the 6 months pre-induction to 2.89 (SD 3.40) in the 6 months post-induction. In an appropriately interdisciplinary care setting, buprenorphine shows promise as a safe alternative to COT with early evidence of benefit for high-utilizing patients with SCD.

1 | INTRODUCTION

Sickle cell disease (SCD) is a genetic hematologic disorder that affects between 80 000 and 100 000 individuals in the United States and leads to severe morbidity and early mortality.[1–6] Acute painful crises are the most common complications of SCD and drive a large number of acute care visits and hospitalizations.[7–10] In addition, SCD pain can evolve into a chronic pain condition with poorly understood physiology.[11–16] Half or more of adult SCD patients in the United States likely meet criteria for chronic pain.[11,17] People living with SCD consistently describe pain as the greatest detriment to their quality of life, and an optimal pain management strategy remains unclear.[18] Numerous studies show that patients and healthcare providers are dissatisfied with the quality of SCD pain management.[18–20]

Disease-modifying therapies that prevent acute crises have little effect on chronic SCD pain.[16,21] The evidence base for management of chronic pain in SCD is sparse,[22] but chronic opioid therapy (COT) is one major modality. Clinical trials of opioids for chronic non-cancer pain (CNCP) support efficacy relative to placebo, but also frequently fail to produce clinically significant improvements. Risks emerge with

longer term and higher dose COT, including increased risk of death.[23–25] Additionally, opioids can have pro-nociceptive effects that can be clinically relevant, but for which there is no definitive diagnostic test.[26,27] There is some evidence that pain processing differs in patients with SCD who are taking COT versus those who are not,[28] but the causality and clinical implications of the difference are unclear. When COT carries excessive risk or produces inadequate benefit for CNCP, there is evidence that multidisciplinary interventions that involve dose reduction can lead to improvement, or at least cause no worsening.[29–31]

Buprenorphine is a possible alternative to full agonist opioids for the treatment of chronic SCD-related pain. Because of its high receptor affinity, long duration of action, and partial mu opioid receptor agonism, buprenorphine provides pain relief at a lower risk for accelerating tolerance, withdrawal, and overdose.[11] Buprenorphine was first approved for clinical use for acute pain,[32] then for treatment of opioid use disorder, and more recently with newer preparations marketed for chronic pain. Small case series have suggested buprenorphine can be useful in SCD.[33,34] Our group previously reported preliminary results of transitioning 21 patients to buprenorphine, followed by Osunkwo et al. reports of a similar sized group with similar results.[35,36] Both preliminary reports showed a significant decrease in acute care utilization following buprenorphine induction.

Clinically, transition to buprenorphine is not straightforward. Due to its complex receptor pharmacology, it can precipitate opioid withdrawal when co-administered with higher doses of opioid agonists. No prior report has detailed a reproducible transition method, and concerns for precipitated withdrawal are often a barrier to attempting transition to buprenorphine in patients who may benefit. Similarly, details on final maintenance doses of buprenorphine and acceptability/tolerability over the intermediate term have not been reported.

In this report, we describe the experience of 36 patients with SCD who consented to have data reported and were transitioned to buprenorphine using a standard outpatient protocol or during medical admissions between the years 2015 and 2020. The aims of this study were:

1. To describe a reproducible outpatient process that has been developed through years of iterative experience for transitioning patients from full agonist opioids to buprenorphine and report the interrelationships of opioid dose, pain, and opioid withdrawal symptoms in that process. Included within this aim was a description of the relationship between outpatient opioid dose and final maintenance buprenorphine dose as a preliminary guide for outpatient dosing.
2. To describe the experience of participants who were transitioned from full agonists to buprenorphine during inpatient admissions, and to determine if outcomes differed.
3. To describe initial adverse events, longer-term discontinuations, and changes in acute care utilization before and after buprenorphine inductions.

2 | METHODS

2.1 | Participant selection and description

The study was conducted at the Johns Hopkins Sickle Cell Center for Adults (SCCA), an adult SCD treatment center based in an urban academic medical center in Baltimore, Maryland, USA. The study was reviewed and approved by the Johns Hopkins Institutional Review Board. Of 55 patients who had transitioned to buprenorphine at our center, 43 patients consented to have their outcomes reported as part of this study. Of those patients, 30 were transitioned using our standard outpatient protocol, 6 were transitioned as inpatients during medical admissions, and the remaining 6 were transitioned prior to the development of the protocol or under other nonstandard conditions. These nonstandard inductions included one immediately after an inpatient hospitalization, one on an inpatient psychiatric interdisciplinary pain treatment unit, and four induced as outpatients outside the standard protocol, most prior to the development of the protocol. These nonstandard inductions were too heterogeneous to summarize and are not included in this report. All patients were over the age of 18 years, and had sufficient medical insurance to pay for medication and visits to the SCCA. Patient characteristics were assessed as of the time of induction and outcomes collected from records pre- and post-inductions. Patients were not induced if they had evidence of current illicit drug use other than cannabinoids, were pregnant, or had known hypersensitivity to buprenorphine.

Transition to buprenorphine was recommended for patients when the interdisciplinary team has reached consensus that full agonist opioid therapy has failed. This includes continued frequent acute pain visits despite attempts at maximal disease modifying therapy (38.89% of the present group); inadequate pain control despite use of COT for a long period or at high doses (94.44%); or being unable to complete a planned wean of full agonist opioids without intolerable withdrawal symptoms (16.67%). Exactly, half of the patients had two indications. Participants' genders and SCD genotypes were extracted from the medical record. For analyses, hemoglobin (Hgb) SS and $S\beta^0$ thalassemia were combined, and compared to all other genotypes. Age was defined as age on the date of the buprenorphine induction. Race and ethnicity were derived from the participants' self-report in the medical record.

2.1.1 | Pre-induction management

Participants decided to convert to buprenorphine therapy after discussion of the clinical reasoning for the recommendation and discussion of the possible risks and benefits and the process of induction, including addressing any concerns the patients had about stigma. Most participants underwent an opioid dose reduction with a target pre-induction dose of 90 milligrams oral morphine equivalents (OME) or less to prevent precipitated withdrawal and reduce severity of spontaneous withdrawal during induction. The process of weaning was highly variable depending on individual patient comfort and

ongoing discussion between the provider and patient. Patients typically were maintained on one long-acting opioid and one short-acting opioid as needed for exacerbations, and the long-acting opioid was tapered first with the short-acting opioid then reduced further if needed to achieve the target dose for induction.

All management occurred in the setting of a comprehensive interdisciplinary care system. This included the most aggressive practical disease modifying therapies and frequent outpatient visits. Patients were typically seen weekly during this process for medical management, support, and education by an advanced practice provider with extensive experience in the management of SCD. Goals were agreed upon between the patient and the provider, which helped to build an interpersonal relationship. Care plans were coordinated for outpatient visits, emergency department (ED) visits, and inpatient admissions ensuring that opioid dose management was uniform. It is standard practice for clinic staff to check the state prescription drug monitoring program frequently for patients prescribed opioids, and in the process to have information regarding visits to other institutions. A psychiatrist with long experience in SCD and pain treatment (author CPC) was available for direct consultation and advice, but relatively few patients were under his direct care. In the center generally, core team members meet weekly to discuss the management of all patients.

2.1.2 | Induction process and outcomes

Standard inductions

For standard inductions ($n = 30$), patients held all opioids 12–24 h prior to the day of induction. On arrival to the Sickle Cell Infusion Center (SCIC) on induction Day 1, patients underwent a history and physical examination including vital signs, urine toxicology screen, complete blood count, comprehensive metabolic panel, and reticulocyte count. Patients were assessed for opioid withdrawal severity using the Clinical Opioid Withdrawal Scale[37] (COWS) and had their pain intensity recorded using a standard 11-point verbal numeric rating scale. Induction began when the COWS score was 5 or higher, indicating at least mild opioid withdrawal. If the COWS score was lower than 5 on presentation, the patients were asked to continue holding their opioids and return the next day. The patients received the first dose of buprenorphine sublingually, typically in the range of 2–4 mg of Subutex® or an equivalent preparation. Pain ratings and COWS score were obtained at least hourly, and additional doses of buprenorphine were administered hourly if the COWS score remained elevated. This process was continued until the COWS score was stably below 5. The total buprenorphine administered on the induction day was considered the starting daily dose. A visit was scheduled the following day to give the starting daily dose, assess any pain, adverse events, or any withdrawal symptoms, as well as to assist with any insurance issues which may prevent the buprenorphine being filled for home use. If necessary, doses were adjusted on Day 2.

Inpatient inductions

In addition to patients induced using the standard protocol, the results of six other patients induced during inpatient medical stays are reported. These patients typically were on higher maintenance doses of outpatient opioids and were in the process of protracted or difficult outpatient tapers in preparation for induction. In the course of a medical hospitalization finishing the transition to buprenorphine while inpatient was offered. The principles involved in induction were the same, however. Opioid doses were held, typically overnight, and buprenorphine induction was started when COWS assessment exceeded 5. Because of lack of uniform experience and training with COWS withdrawal assessments on inpatient teams, withdrawal assessments and the decision to initiate induction were made on recommendation of the SCD consultation service and with shared decision making with the patient.

Buprenorphine dosing

For analysis, sublingual buprenorphine doses were standardized to equivalents of the Subutex®/Suboxone® preparations assuming 5.7 mg of Zubsolv® was equivalent to 8 mg as Subutex®. Baseline (6 months prior to induction) and pre-induction opioid doses were calculated as the average daily OME abstracted from the medical record.[38] Average daily dose of as-needed opioids prescribed was calculated by dividing the total OME per prescription by the duration of the prescription.

2.1.3 | Adverse events and causal attribution

For standard inductions, adverse events were defined as unexpected events that led to clinical contact or an unplanned visit within 3 days of induction. As inpatient inductions occurred during hospitalizations and clinical contact was not a meaningful trigger, events noted in the chart which led to clinical intervention or a change in management were coded as adverse events. Each adverse event was coded by clinical consensus between two authors (MD and CPC) as definitely related, probably related, possibly related, unlikely related, or unrelated; and further coded as to whether it resolved and whether there were medical sequelae. If causal category was unclear, coders erred on rating the event to be more likely related. As withdrawal symptoms were expected, these were not coded as adverse events, but are reported using quantification of COWS scores. The exceptions were when patients had increased or clinically significant withdrawal after the induction day during standard inductions, which was coded as an adverse event.

2.1.4 | Post-induction outcomes

Patients' acute care utilization was quantified as the count of ED visits, SCIC visits, and hospital admissions at Johns Hopkins Hospital related to pain or SCD complications in the electronic medical record in the 6 months prior to induction (baseline) and post induction. Visits to other institutions were not available. If patients discontinued buprenorphine by self-report or by not receiving prescriptions, the date of discontinuation was recorded and the total time treated was calculated.

2.2 | Analysis

Authors MD, SL, CPC, and MPM were responsible for analyzing the data and all authors had access to the data.

2.2.1 | Initial data exploration

All statistical analyses were performed in the R statistical computing environment.[39] Descriptive statistics and exploratory figures were examined to confirm the appropriate methods of analysis. Neither utilization nor opioid doses were highly skewed in the study patients so standard parametric methods were appropriate.

2.2.2 | Planned comparisons

Change in acute care utilization after buprenorphine induction was tested using a paired sample *t* test. The relationship of opioid dose to withdrawal severity during induction was modeled using a linear model predicting initial and final COWS scores by baseline opioid dose; then entering pre-induction (post-taper) dose to test its role in mediating any relationship. This was done to ascertain whether baseline dose might be a predictor of severity of withdrawal independent of pre-induction dose and, therefore, a baseline predictor of risk for difficulties during induction.

3 | RESULTS

3.1 | Screening for confounders

A screening linear model was fit predicting pre-induction utilization by age, gender, SCD genotype (Hgb SS/Sβ^0 vs. other genotypes), and baseline opioid dose to screen for confounding relationships. Neither the overall model nor any individual predictor were statistically significant (full model adjusted $R^2 = -0.005$; $p = .444$). Because no confounds were found, these were not entered into analyses predicting changes in utilization. Patient characteristics, induction process measures, and outcomes were compared between those with standard and inpatient inductions. No significant differences were found, though due to the small number of inpatient inductions statistical power to detect differences was limited.

3.2 | Baseline characteristics

Patients were predominantly female (66.67%) and had a mean age of 37.31 years (SD 10.31) (see Table 1). All patients identified as African American. Patients' genotypes were predominantly SS and Sβ^0 thalassemia ($n = 27$ and 2, respectively; total 80.56% of the sample). Others included SC (8.33%) and Sβ^+ thalassemia (11.11%). Baseline utilization among the sample was high, with a mean 6-month acute care visit rate of 10.50 (SD 11.35). The mean baseline opioid dose was 158.15 OME per day (SD 109.89).

3.3 | Induction process and results

For all patients induced, mean opioid dose after weaning and prior to induction was 79.48 OME (SD 62.60), and the mean buprenorphine dose at induction was 12.12 mg (SD 5.41). There were no statistically distinguishable differences between patients or outcomes in conventional versus inpatient inductions, though due to the small number of inpatient inductions statistical power to detect differences was probably limited (see Table 1).

Standard inductions: For standard inductions, mean pain at the beginning of induction was 6.87 (SD 2.11) and after induction was 4.03 (SD 2.54). Mean COWS rating pre-induction was 9.00 (SD 3.57) and 3.17 (SD 2.29) after induction. The mean buprenorphine dose was 11.21 mg (SD 5.03).

Inpatient inductions: Among patients induced inpatient ($n = 6$), pain prior to buprenorphine induction was 7.33 (SD 0.82) and after induction was 6.17 (SD 2.48). Mean COWS ratings pre-induction were 8.33 (SD 5.47) and 4.33 (SD 3.39) after induction. The mean buprenorphine dose was 16.67 mg (SD 5.32).

3.3.1 | Withdrawal experience

Two patients induced inpatient had a documented increase in COWS scores on the day of induction: one from 2 to 9, the other from 2 to 7. The low starting scores likely reflect withdrawal scales being checked relatively quickly after opioids being held in the inpatient setting, and induction starting based on clinical assessment of SCCA staff without a later COWS score documented.

3.3.2 | Adverse events

There were seven adverse events, all among standard inductions (23.33% of standard inductions), with two judged definitely related to induction though only one of these was medical. Those definitely related included one instance of protracted/recurrent withdrawal for which the patient's buprenorphine dose was increased. Interestingly, this patient's outpatient dose was on the lower end of the distribution (42.67 OME prior to induction). One patient had unforeseen insurance barriers to buprenorphine which resulted in temporary inability to fill the prescription, which though not a medical event was clearly related to the induction. This patient visited the infusion center daily for buprenorphine treatment until this could be resolved. Of the adverse events categorized as less likely to be related to the induction, one patient presented to the ED seeking treatment after an uneventful induction. The patient did not return to clinic thereafter. One patient had a series of severe medical events, including pneumonia, acute kidney injury, and suspicion of a transfusion reaction from a

TABLE 1 Participant characteristics, induction process, and outcomes

	All Inductions ($n = 36$)	Outpatient ($n = 30$)	Inpatient ($n = 6$)	p (Out versus in)
Demographics				
Age	37.31 (10.31)	36.07 (9.85)	43.5 (11.18)	.176
Female	66.67%	60.00%	100%	.155
Sickle cell anemia	80.56%	80.00%	83.33%	1.000
Baseline opioid dose	158.15 (109.89)	143.3 (93.88)	232.38 (159.61)	.237
Acute visits pre-induction	10.5 (11.35)	11.03 (12.18)	7.83 (5.56)	.329
Induction process				
Induction opioid dose	79.48 (62.6)	69.27 (49.12)	130.52 (98.39)	.192
Pain pre-induction	6.94 (1.96)	6.87 (2.11)	7.33 (0.82)	.370
Pain post-induction	4.39 (2.62)	4.03 (2.54)	6.17 (2.48)	.096
COWS pre-induction	8.89 (3.86)	9 (3.57)	8.33 (5.47)	.784
COWS post-induction	3.36 (2.49)	3.17 (2.29)	4.33 (3.39)	.450
Buprenorphine dose	12.12 (5.41)	11.21 (5.03)	16.67 (5.32)	.054
Outcomes				
Adverse events at 3 days	19.44%	23.33%	0.00%	.451
Discontinued at 6 months	13.89%	16.67%	0.00%	.666
Acute visits post-induction	2.89 (3.4)	2.7 (3.59)	3.83 (2.23)	.334

Note: Continuous data are reported as mean (SD), proportions as percent. Superscripts of the form -*n* represent *n* missing observations for that cell. Unconventional inductions included inpatient inductions and inductions prior to the development of the conventional protocol, as described in Section 2. Visits are for 6 months pre- and post-induction. Opioid doses are in mg oral morphine equivalents. All univariate comparisons between conventional and unconventional inductions were not statistically significant at the $\alpha = .05$ level.

TABLE 2 Adverse events within 3 days of induction, causal attribution, and clinical response

Adverse event	Relatedness	Response
Recurrent/protracted withdrawal	Definitely	Dose increased
Insurance barrier to outpatient buprenorphine; worsened pain	Definitely	Daily dosing in infusion center until insurance managed
Tongue numbness and headache	Possibly	Discontinued
ED visit for treatment	Possibly	Patient discontinued
Pneumonia, transaminase elevations, and possible transfusion reaction	Unlikely	Held, then discontinued
Central retinal artery occlusion	Unlikely	No change
Neck swelling	Unlikely	No change

Abbreviation: ED, emergency department.

prior transfusion. Though there was an unclear relationship to buprenorphine, the therapy was discontinued out of an abundance of caution. One patient reported tongue numbness and headaches with multiple buprenorphine formulations. Of all patients with an adverse event, three discontinued the medication; two due to possible relationship between the adverse event and buprenorphine; and one who did not return for treatment. Details of adverse events are provided in Table 2. All medical adverse events were judged to have resolved without sequelae.

The relationship of final buprenorphine dose to prior opioid dose was expected to be nonlinear due to the known "ceiling effect" in agonist activity for buprenorphine. Instead of a formal analysis, the relationship was plotted and presented as a figure (see Figure 1) to provide guidance on probable maintenance doses based on both baseline opioid dose and pre-induction dose.

3.4 | Post-induction outcomes

Five patients discontinued buprenorphine within 6 months of induction, all from the standard induction group (16.67%). In addition to the three mentioned above, one stopped 14 days after induction during an asthma exacerbation, and the second stopped at Day 12 in the setting of repeated evidence of illicit drug use. Participants' mean 6-month acute care visits reduced from 10.50 (SD 11.35) pre-induction to 3.35 (SD 3.79) post-induction (paired $t = 4.25$, $p < .001$, see Figure 2). When limited to those who continued buprenorphine, the change was 9.26 (SD 11.18) to 2.42 (SD 2.63, paired $t = 3.566$, df $= 30$, $p = .001$).

3.5 | Relationship of opioid dose to withdrawal

Baseline opioid dose alone predicted post-induction withdrawal ($\beta = .009$ change in COWS per OME, SE $= 0.004$, $p = .021$), but the

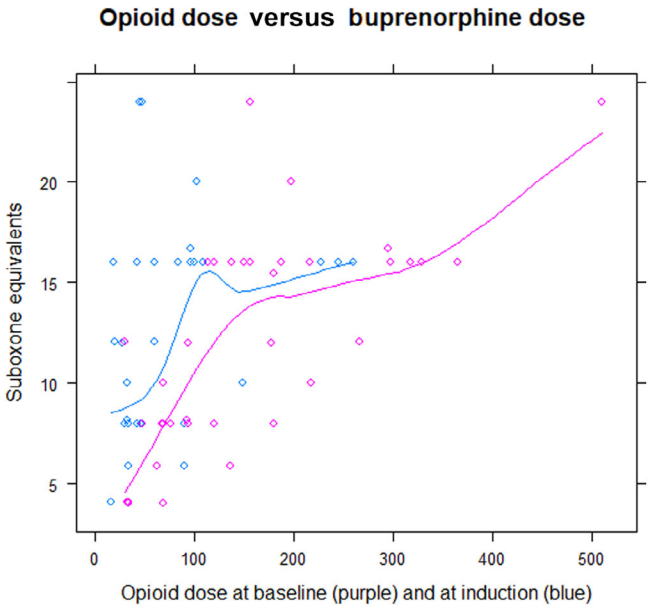

FIGURE 1 Opioid dose in oral morphine equivalents versus induction buprenorphine dose in equivalents of sublingual buprenorphine. Blue points and lines represent opioid dose at induction, and purple points and lines represent opioid dose at baseline 6 months prior to induction. Estimated curves generated by LOESS smoothing function. [Color figure can be viewed at wileyonlinelibrary.com]

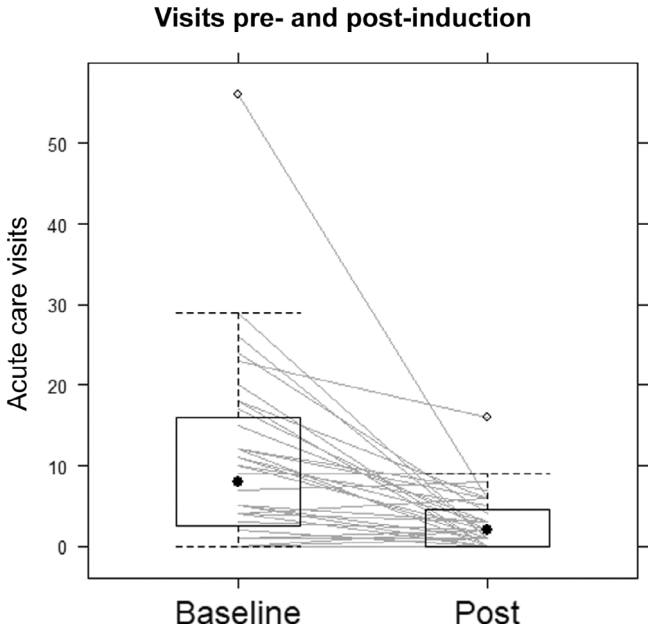

FIGURE 2 Box and whisker plots of counts of acute care visits in the 6 months prior to induction and the 6 months after

relationship reduced to trend level when pre-induction (post-taper) dose was entered (baseline $\beta = .006$ change in COWS per OME, SE = 0.004, $p = .091$; pre-induction $\beta = .014$ change in COWS per OME, SE = 0.006, $p = .028$), suggesting that the dose to which the patient is tapered is more important than the baseline dose in predicting withdrawal during induction. However, the relationship is very modest and overall withdrawal symptoms after induction were quite low (mean 3.36, SD 2.49).

4 | DISCUSSION

Our results demonstrate the safety and tolerability of buprenorphine in patients with SCD when the transition is handled according to the strategy described above. Previously reported findings of reduced acute care utilization among a generally high-utilizing group of patients were replicated in this larger sample.

Regarding opioid withdrawal during induction, 80.56% scored in the mild range or below at the beginning of induction and all scored mild or below by the end of induction; 69.44% had no clinically significant withdrawal symptoms post-induction (COWS < 5). Post-taper opioid dose did predict greater end-induction withdrawal symptoms, but the statistical relationship was modest (1.43 point increase in COWS per 100 OME, 95% CI 0.165 to 2.70). It should be noted that in patients with SCD and chronic pain, baseline COWS scores might be nonzero as the COWS includes "bone or joint aches," which can account for up to four points. Two participants who were induced inpatient (2.33%) had an increase in withdrawal on the day of induction which might be an artifact of having buprenorphine started relatively early at lower levels of withdrawal symptoms than the standard protocol (both COWS initially two, one increased to eight and the other nine). These were easily managed with dose increases as needed.

There was one instance of prolonged or recurrent withdrawal symptoms in the standard induction group that necessitated a dose increase (3.33% of standard inductions). The results support the dose target of 90 OME or less prior to induction to be a reasonable benchmark, though this was developed by clinical consensus and has not been empirically tested as optimal. Buprenorphine discontinuation due to patient preference in the first 6 months was also unusual with only 8.33% of participants discontinuing treatment on their own, all within the first month and most within the first 2 weeks. Two patients had their buprenorphine discontinued in response to an adverse event, though in both cases, the relationship to buprenorphine was tenuous.

Strikingly, overall acute care utilization reduced by 72.5% on average. It should be noted that induction on buprenorphine in the SCIC is a part of a coordinated, interdisciplinary system that includes aggressive disease modifying therapy, individualized acute care plans, and high frequency of outpatient contact besides induction on buprenorphine. By the same token, the participants were in the same care system throughout, and the decline in utilization was striking after buprenorphine induction. One of the most consistent risk factors for early mortality in SCD is frequency of acute care visits.[6] Undoubtedly, this has much to do with the severity of the patient's SCD and simply reducing utilization may be insufficient to reduce mortality. Simultaneously, hospital-associated adverse events and the disrupted outpatient care due to frequent acute care episodes may also contribute to adverse outcomes. In the setting of aggressive disease-modifying therapy and close outpatient follow-up, reduced acute care utilization like does suggest an improved illness course.

4.1 | Limitations and strengths

The study was not prospective, randomized, nor controlled. The participant pool was limited to those patients who consented to have their data reported. In addition, while all inductions followed the same fundamental strategy—opioid dose reduction to a target of less than 90 OME, holding opioids until mild withdrawal emerges, and repeated buprenorphine doses until withdrawal is controlled—not all inductions followed the same protocol. In particular, those that were performed inpatient tended to be patients who were on higher opioid doses as an outpatient and the patients were induced at a higher post-taper dose on average; this often being intentional to take the opportunity to induce them safely in an inpatient setting after a prolonged taper. These differences might have created a number of biases in patient selection and capacity to detect adverse events in the inpatient group. Granted these limitations, this is the largest number of patients with SCD treated with buprenorphine reported so far.

5 | CONCLUSION

The buprenorphine induction strategy reported here produced few medical adverse events and all resolved without further complication. Participants experienced minimal withdrawal, and little if any precipitated withdrawal. Final maintenance doses of buprenorphine were moderate and no participants had protracted withdrawal that was not quickly manageable with dose adjustment. Induction was associated with a marked reduction in acute care utilization.

AUTHOR CONTRIBUTIONS

Mandy S. David: Authored manuscript; assisted in design of study; supervised conduct of data collection and clinical management. **Sophie M. Lanzkron**: Assisted in design of study and supervision of study conduct; edited manuscript. **Ashley Lauriello**: Assisted with data collection and clinical management. **Ijeoma Nnake**: Assisted with data collection and clinical management. **Jennifer Jones**: Edited manuscript; assisted with data collection. **Manuela Plaza Montana**: Responsible for data management and chart abstractions. **Benjamin Salzberg**: Assisted with data collection. **Carlos Buri-Nagua**: Assisted with data collection and chart abstractions. **Kyra Lasko**: Assisted with data collection and chart abstractions. **C. Patrick Carroll**: Primary statistical analysis and data presentation; co-wrote and edited manuscript.

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CONFLICT OF INTEREST

Sophie M. Lanzkron was involved in consulting—Novartis, Bluebird Bio, Pfizer; received research grant funding from Global Blood Therapeutics Shire, Novartis, Imara, Patient-Centered Outcomes Research Institute, and Health Resources and Services Administration.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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