Evidence for Continuing Buprenorphine in the Perioperative Period

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Objective: Given there are conflicting recommendations for the perioperative management of buprenorphine, we conducted a retrospective cohort study of our surgery patients on buprenorphine whose baseline dose had been preoperatively continued, tapered, or discontinued.

Materials and Methods: We reviewed charts of patients on buprenorphine who had received elective surgery at Stanford Healthcare from January 1, 2013 to June 30, 2016. Our primary outcome of interest was the change in pain score, defined as mean postoperative pain score—preoperative pain score. We also collected data on patients' tapering procedure and any postoperative nonbuprenorphine opioid requirements.

Results: Out of ~1200 patients on buprenorphine, 121 had surgery of which 50 were admitted and included in the study. Perioperative continuation of transdermal buprenorphine resulted in a significantly lower change in pain score postoperatively (0.606 ± 0.878) than discontinuation (4.83 ± 1.23, $P = 0.012$). Among sublingual patients, there was no statistically significant difference in the change in pain score between those who were tapered to a nonzero dose versus discontinued ($P = 0.55$). Continuation of sublingual buprenorphine resulted in fewer nonbuprenorphine scheduled opioid prescriptions than its taper or discontinuation ($P = 0.028$). Finally, tapers were performed with great variability in the tapering team and rate of taper.

Discussion: On the basis of our findings, we implemented a policy at our institution for the continuation of perioperative buprenorphine whenever possible. Our work reveals crucial targets for the education of perioperative healthcare providers and the importance of coordination among all perioperative services and providers.

Key Words: perioperative, buprenorphine, opioid

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Buprenorphine is a partial agonist with complex pharmacological activity, including not only activity on the kappa, delta, and nociceptin receptors, but also high affinity and partial agonist activity on the μ-opioid receptor. Accordingly, in both animal and human studies it has been shown to have a "ceiling effect" on factors such as euphoria, respiratory depression, and sedation.[1,2] Since these characteristics grant buprenorphine a lower abuse potential and higher safety profile, the perioperative management of patients on buprenorphine who require surgery has traditionally required discontinuing or at least tapering patients' baseline buprenorphine dose within 48 to 72 hours before surgery.[3,4]

However, there is no evidence of a ceiling effect on analgesia in humans, not only according to the original 1995 pharmacologic studies on buprenorphine but also recent reviews.[3,5] For instance, one review concluded that maintaining buprenorphine perioperative does not lead to worse clinical outcomes, and deemed there was enough available evidence to continue buprenorphine at a reduced dose when indicated.[6] Another review included 4 observational studies that independently demonstrated equivalent perioperative and postoperative pain control among patients whose buprenorphine had been continued.[7] However, like most literature on perioperative buprenorphine, this review was limited to C-section incisions, a procedure unique not only in its nociceptive input, but also in its "positive" indication of childbirth, as opposed to the "negative" indication of most surgeries like joint repair or tumor excision.[8–11]

Hypothesizing that continuing buprenorphine perioperatively may provide better pain control than its taper or discontinuation, we conducted a retrospective cohort study on our elective surgery patients. Our primary outcome was the change in pain score, or mean postoperative—preoperative pain score. Secondary outcomes included intraoperative opioid and postoperative nonbuprenorphine opioid requirements.

MATERIALS AND METHODS

Study Population

With Institutional Review Board approval, we reviewed patient charts from January 1, 2013 to June 30, 2016 who had been prescribed buprenorphine for at least 1 month before receiving elective surgery at Stanford Hospital. We collected data on their course of buprenorphine management, pain scores, any intraoperative or postoperative opioid administration, and other factors of perioperative pain management. Demographic data was collected from electronic health records of patients who had provided written informed consent for this access and included patient sex, age, ethnicity, body mass index, weight, and type of surgery.

Patients were included if they were on a transdermal or sublingual buprenorphine formulation, undergoing an elective surgery, and not on buprenorphine for cancer-related pain. Patients were excluded if they were requiring emergent surgery, discharged from the hospital in <24 hours after surgery, intubated in the immediate postoperative period, or cared for by the private practice medical service at Stanford Hospital since this service does not use the same modalities for pain management as the academic pain service. Cardiac surgery patients were also excluded because postoperatively they were directly transferred under sedated and intubated conditions to the cardiovascular

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intensive care unit, where pain management was performed by the cardiac critical care team.

Outcomes

As pain is a subjective experience, our primary outcome measure was the change in pain score per patient via the self-reported numerical pain rating scale of 0/10 to 10/10 pain. The preoperative score was collected on the day of the procedure in the preoperative area whereas postoperative scores were collected every 4 to 6 hours up to 24 hours after the procedure as a part of the vital sign checks for medication administration. Each patient's change in pain score was calculated as the difference between their mean postoperative pain score—single preoperative pain score, recorded as a negative value if the preoperative pain score was higher than the average of the postoperative pain scores.

Secondary outcome measures included each patient's lowest postoperative pain score and their postoperative opioid requirements, which included nonbuprenorphine opioids given within the first 24 hours after surgery, new scheduled (ie, non Pro re nata [PRN]) nonbuprenorphine opioid prescriptions, and new PRN nonbuprenorphine opioid prescriptions. Additional data included intraoperative opioid requirements that were each converted into their morphine milligram equivalents (MME) (calculations shown in Table 1).[12–16] Finally, for tapered and discontinued patients, we collected data on their tapering procedure, which included the team who managed the taper and the patients' baseline buprenorphine dose, day-of-surgery buprenorphine dose, duration of taper, and what we termed the "adjustment period," which was the number of days during which a patient took their day-of-surgery dose before their actual day of surgery. The rate of taper was calculated for each patient as follows:

$$\text{Rate of taper } (\text{mg}/\text{d}) = \frac{\text{Baseline dose} - \text{Day-of-surgery dose}}{\#\text{ of days taper was achieved}}.$$

Statistical Analyses

Given a limited sample size that precluded the assumption of a normal Gaussian distribution, we used an unpaired, 1-tailed Mann-Whitney test for comparisons between 2 groups and a Kruskal-Wallis test for comparisons among 3 or more groups. All differences in proportion were calculated using a χ^2 analysis. All analyses were conducted in PRISM 7.0a (GraphPad Software, San Diego, CA). Our threshold for significance was defined at an α level of 0.05.

TABLE 1. Calculation for Intraoperative Morphine Milligram Equivalents

Opioid Name	Conversion
IV fentanyl/remifentanil	10 mcg = 1 mg IV morphine[12–14]
IV hydromorphone	0.2 mg = 1 mg IV morphine[12]
IV sufentanil	1 mcg = 1 mg IV morphine[15]
IV methadone	1 mg = 1 mg IV morphine*[16]
IV meperidine	0.4 mg = 3 mg IV morphine[12]

*For single dosing, not continuous or long term use.

RESULTS

Demographics

Out of ~1200 patients on buprenorphine during our study period, 121 patients had surgery, of which 61 patients were admitted and 60 patients were discharged within 24 hours. We included 50 of the 61 admitted patients, with the 11 exclusions for: intubation in the immediate postoperative period, cardiac surgery, and care provided by the private medical service at Stanford Hospital and thus not consulted by the academic medical center pain service.

Demographics are outlined in Table 2. Of the 50 patients included in the study, 21 (42%) were on a transdermal formulation, of which 13 patients were continued on their baseline buprenorphine dose, 7 patients were discontinued, and 1 patient was tapered. Of the remaining 29 patients (58%) on a sublingual formulation, 15 patients had their dose continued, 6 patients had their dose tapered, and 8 patients had their dose discontinued. Regarding other demographics, there was no difference in the proportion between the continued and tapered or discontinued groups for transdermal versus sublingual buprenorphine formulation ($P = 0.47$), average age ($P = 0.16$), sex distribution ($P = 0.28$), ethnicity ($P = 0.58$), average body mass index ($P = 0.98$), receipt of regional anesthesia ($P = 0.077$), or receipt of the following intraoperative opioids: fentanyl ($P = 0.91$), sufentanil ($P = 0.69$), remifentanil ($P = 0.13$), hydromorphone ($P = 0.47$), meperidine ($P = 0.37$), or methadone ($P = 0.25$). None of the 50 patients required intraoperative morphine. There was also no difference in the proportion between the continued and tapered or discontinued groups for postoperative ketamine infusion ($P = 0.28$) or postoperative lidocaine infusion ($P = 0.38$).

According to a χ^2 analysis, more continued patients received intraoperative ketamine than tapered or discontinued patients ($P = 0.016$), but there was no difference in the change in pain scores between patients who received versus did not receive ketamine ($P = 0.46$). Similarly, more continued patients also received intraoperative lidocaine than tapered or discontinued patients ($P = 0.012$), but like ketamine there were no differences in the change in pain score for recipients versus non- recipients ($P = 0.42$). Finally, more continued patients received postoperative buprenorphine than tapered or discontinued patients ($P = 0.036$), but again there was no difference in the change in pain score between recipients versus nonrecipients ($P = 0.29$).

The surgery types represented by our patient population were orthopedic (36%), spinal (26%), general (22%), or other (16%), which included thoracic, ENT, neurological, and urological surgery. We used a χ^2 analysis to compare the proportion of surgery types in continued versus tapered/discontinued groups and found no difference across surgical types ($P = 0.94$).

Transdermal Formulation

Of the 21 transdermal patients, 13 patients (61.9%) had their dose continued, 7 patients (33.3%) had their dose discontinued, and 1 patient (4.76%) had their dose tapered from 0.96 to 0.48 mg over the course of 1 day, reaching their 0.48 mg dose 1 week before their date of surgery. The patients who had their transdermal buprenorphine dose discontinued before surgery had on average a higher change in pain score (4.83 ± 1.23) than those whose dose was continued (0.606 ± 0.878; Fig. 1A, $P = 0.012$).

As mean postoperative pain score may not be the only reliable measure of postoperative pain, we also assessed the median, highest, and lowest postoperative pain scores. Of these, the discontinued patients had a lowest postoperative to

TABLE 2. Demographics and Characteristics for Admitted Patients (n = 50)

	Continued	Tapered or Discontinued	*P*
Preoperative considerations			
No. patients, n (%)	28 (56)	22 (44)	
Age, mean (SD)	57 (13)	52 (14)	0.155
Female, n (%)	17 (60.7)	10 (45.5)	0.283
Ethnicity, n (%)			
Caucasian	25 (89.3)	20 (90.9)	0.579
Asian	0	1 (4.54)	
Hispanic	1 (3.57)	1 (4.54)	
Native American	1 (3.57)	0	
Other	1 (3.57)	0	
Smoking status, n (%)			
Former	12 (42.9)	7 (31.8)	0.350
Current	2 (7.14)	3 (13.6)	
Average BMI, mean (SD) (kg/m^2)	28.7 (5.64)	28.7 (8.27)	0.978
Average weight, mean (SD) (kg)	81.3 (16.6)	83.2 (20.8)	0.715
ASA classification, n (%)*			
ASA 1	0	0	0.070
ASA 2	4 (14.3)	8 (36.4)	
ASA 3	24 (85.7)	14 (63.6)	
ASA 4	0	0	
Buprenorphine formulation, n (%)			
Transdermal	13 (46.4)	8 (57.1)	0.474
Sublingual	15 (53.6)	14 (63.6)	
Reason for buprenorphine treatment, n (%)			
Chronic pain	18 (81.8)	13 (59.1)	0.777
History of opioid use disorder	3 (10.7)	3 (13.6)	
Both	6 (21.4)	6 (27.3)	
Other (off label)	1 (3.57)	0	
Co-prescription with CNS depressant, n (%)			
Benzodiazepine	13 (46.4)	4 (18.2)	0.365
Sleep agent	6 (21.4)	4 (18.2)	
Type of surgery, n (%)			
General	7 (25.0)	4 (18.2)	0.94
Orthopedic	10 (35.7)	8 (36.4)	
Spine	7 (25.0)	6 (27.3)	
Other	4 (14.3)	4 (18.2)	
ENT	0	2 (9.09)	
Plastics	1 (3.57)	0	
Neurosurgery	0	1 (4.54)	
Thoracic	2 (7.14)	0	
Urology	0	1 (4.54)	
Interventional radiology	1 (3.57)	0	
Intraoperative considerations, n (%)			
Regional anesthesia given	10 (35.7)	3 (13.6)	0.077
Intraoperative opioid infusion given, n (%)			
Fentanyl	22 (78.6)	17 (77.3)	0.91
Sufentanil	5 (17.9)	3 (13.6)	0.69
Remifentanil	3 (10.7)	6 (27.3)	0.13
Hydromorphone	13 (46.4)	8 (36.4)	0.47
Meperidine	1 (3.57)	0	0.37
Methadone	0	1 (4.55)	0.25
Ketamine	18 (64.3)	9 (32.1)	0.016*
Lidocaine	18 (81.8)	10 (45.5)	0.012*
Morphine	0	0	
Postoperative considerations, n (%)			
Ketamine	3 (10.7)	6 (21.4)	0.28
Lidocaine	2 (9.09)	4 (18.2)	0.38
Buprenorphine	13 (46.4)	4 (18.2)	0.036*

*ASA classification = American Society of Anesthesiologists physical status classification.

BMI indicates body mass index; CNS, central nervous system.

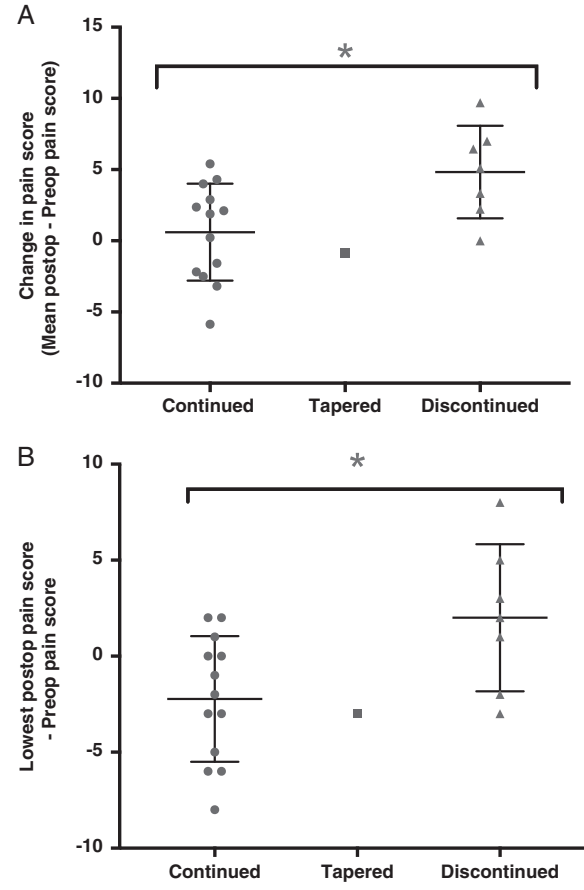

FIGURE 1. Postoperative Pain Scores for Patients on the Transdermal Formulation. A, The change in pain score (ie, the difference between the mean postoperative—preoperative pain scores) among continued, tapered, and discontinued groups. B, The difference between the lowest postoperative—preoperative pain scores among continued, tapered, and discontinued groups. We were unable to perform statistical analyses on the transdermal tapered group given the n of 1, which is only shown graphically. *$P < 0.05$; **$P < 0.01$.

preoperative pain score difference of 2.00 ± 1.45, which was higher than the continued group's lowest postoperative to preoperative pain score difference of -2.23 ± 0.907 (Fig. 1B, $P = 0.014$).

Sublingual Formulation—Preoperative Considerations

Given that our patients' average dose of sublingual buprenorphine was 12.97 ± 8.46 mg, about 36 times higher than the average transdermal buprenorphine dose of 0.36 ± 0.21 mg, and that the field is most lacking in data on the perioperative management of sublingual buprenorphine, we focused the majority of our analyses on the sublingual buprenorphine population.

Of our 29 sublingual patients, 15 patients (51.7%) had their dose continued, 6 patients (20.1%) had their dose tapered, and 8 patients had their dose discontinued (27.6%). There was no association between the change in pain score and continuation, taper, or discontinuation of sublingual buprenorphine (Fig. 2A, $P = 0.55$). There was also no difference between the lowest postoperative pain score and the preoperative pain score for

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continued, tapered, and discontinued groups (Fig. 2B, $P=0.55$). Given this finding, since discontinued patients had been tapered off of their original dose to 0.0 mg as their day-of-surgery dose, for our further analyses we combined the tapered or discontinued patients into 1 group (labeled as tapered/discontinued).

Despite a wide range of sublingual patients' baseline dose, from as low as 1.5 mg/d to as high as 32 mg/d, a higher baseline dose was not a confounding factor in the change in pain score (Fig. 2C, $P=0.44$). We also did not observe a dose-dependent effect on the change in pain score when we stratified sublingual groups according to baseline doses of ≤ 10 mg/d (Fig. 2D, $P=0.18$) or >10 mg/d (Fig. 2E, $P=0.13$).

Finally, continued patients were discharged on fewer non-buprenorphine scheduled (non-PRN) opioid prescriptions (MME/d) than the tapered/discontinued group (Fig. 3A, $P=0.028$). There was no difference in the maximum PRN opioid dose (MME/d) between continued versus tapered/discontinued groups (Fig. 3B, $P=0.49$) and no difference between these two groups in their nonbuprenorphine opioid requirements in the first 24 hours postoperatively (Fig. 3C, $P=0.28$).

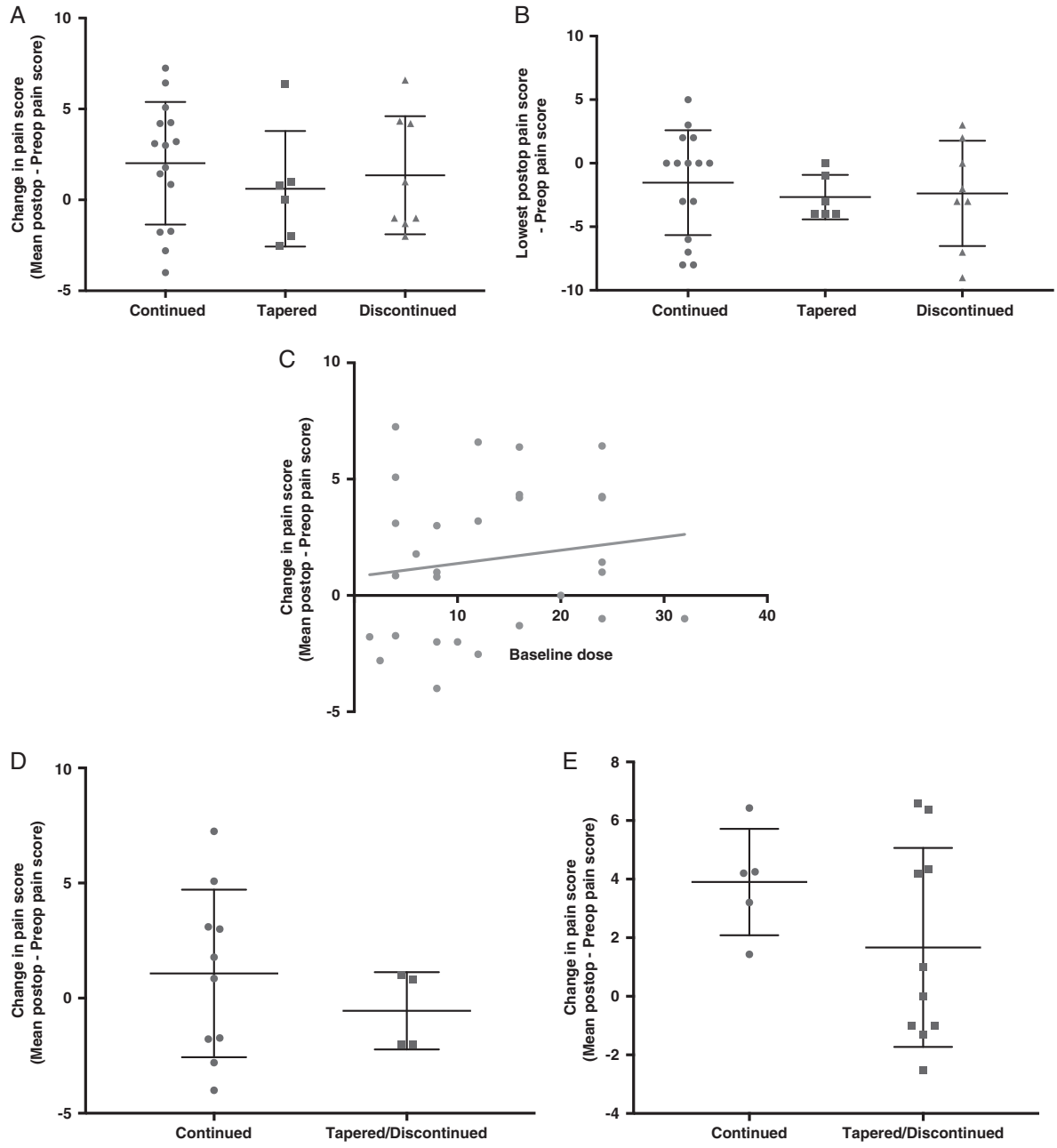

FIGURE 2. Postoperative Pain Scores for Patients on the Sublingual Formulation. A, The change in pain score (ie, the difference between the mean postoperative—preoperative pain scores) among continued, tapered, and discontinued groups. B, The difference between the lowest postoperative—preoperative pain scores among continued, tapered, and discontinued groups. C, Change in pain score by baseline dose. D, Change in pain score by baseline doses of ≤10 mg. E, Change in pain score by baseline doses of >10 mg. *$P<0.05$; **$P<0.01$.

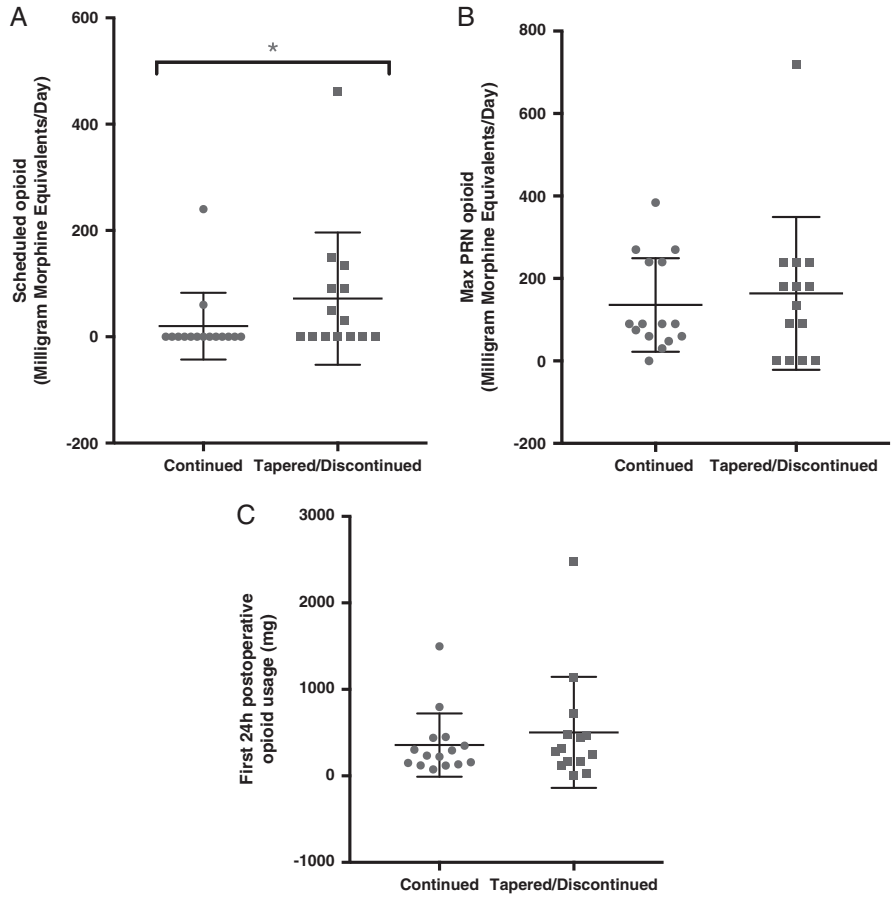

FIGURE 3. Nonbuprenorphine postoperative opioid requirements for patients on the sublingual formulation. A, Nonbuprenorphine scheduled opioid prescriptions (MME/d) in continued versus tapered/discontinued group (calculations for MME shown in Table 1). B, Maximum PRN nonbuprenorphine opioid dose (MME/d) between continued versus tapered/discontinued groups. C, Nonbuprenorphine opioid requirements in the first postoperative 24 hours between continued versus tapered/discontinued groups. MME indicates morphine milligram equivalent; PRN, Pro re nata. *$P < 0.05$; **$P < 0.01$.

Variability in Tapers

The process of tapering sublingual buprenorphine varied widely, from the treatment team who managed the taper to the duration of taper and day-of-surgery dose. 100% of tapers were performed by a non-Stanford pain physician, whereas 37.50% of discontinuations were managed by a non-Stanford pain physician, 25% were managed by the Stanford Preoperative Clinic, 12.50% were managed by the Stanford Pain Clinic, 12.50% were managed by the surgical team, and 12.50% were managed by the patient themself (Fig. 4A). There was no difference in the change in pain score regardless of whether a patient's dose was discontinued by an entity not affiliated with Stanford, that is, a non-Stanford pain physician or the patient themself, versus a Stanford-affiliated entity, that is, the Stanford pain clinic, preoperative clinic, or surgical team (Fig. 4B, $P = 0.49$).

We also collected tapering data on patients' baseline dose, day-of-surgery dose, and duration of taper. For 20.7% of sublingual patients, their original dose was tapered to a mean day-of-surgery dose of 3.39 ± 1.08 mg/d, with a range from 0.36 to 8 mg/d. To best reflect the variables above in a single equation, in this paper we calculated the rate of taper as the difference in the baseline dose—day-of-surgery dose over the duration of taper in days (see the Materials and Methods section). The rate of taper was significantly higher in discontinued patients (13.71 ± 3.67) compared with tapered patients (2.39 ± 1.13; Fig. 4C, $P = 0.0023$). A higher rate of taper was not necessarily associated with a higher change in pain score (Fig. 4D, $P = 0.53$), nor was a higher baseline dose associated with a longer duration of taper (Fig. 4E, $P = 0.38$). Furthermore, tapers were achieved anywhere from 1 to 28 days, with a higher average number of days in the tapered group (9.83 ± 4.05 d) than the discontinued group (2.13 ± 0.789 d; Fig. 4F, $P = 0.019$). Finally, for cases in which a taper had already been completed days or weeks before the scheduled date of surgery, the tapered sublingual patients had an average of 11.3 ± 4.33 days for their adjustment period, which was significantly longer than the average of 4.00 ± 1.39 days for discontinued patients (Fig. 4G, $P = 0.049$).

DISCUSSION

In this study, we sought to determine if continuing, tapering, or discontinuing buprenorphine perioperatively resulted in different pain outcomes. For the transdermal

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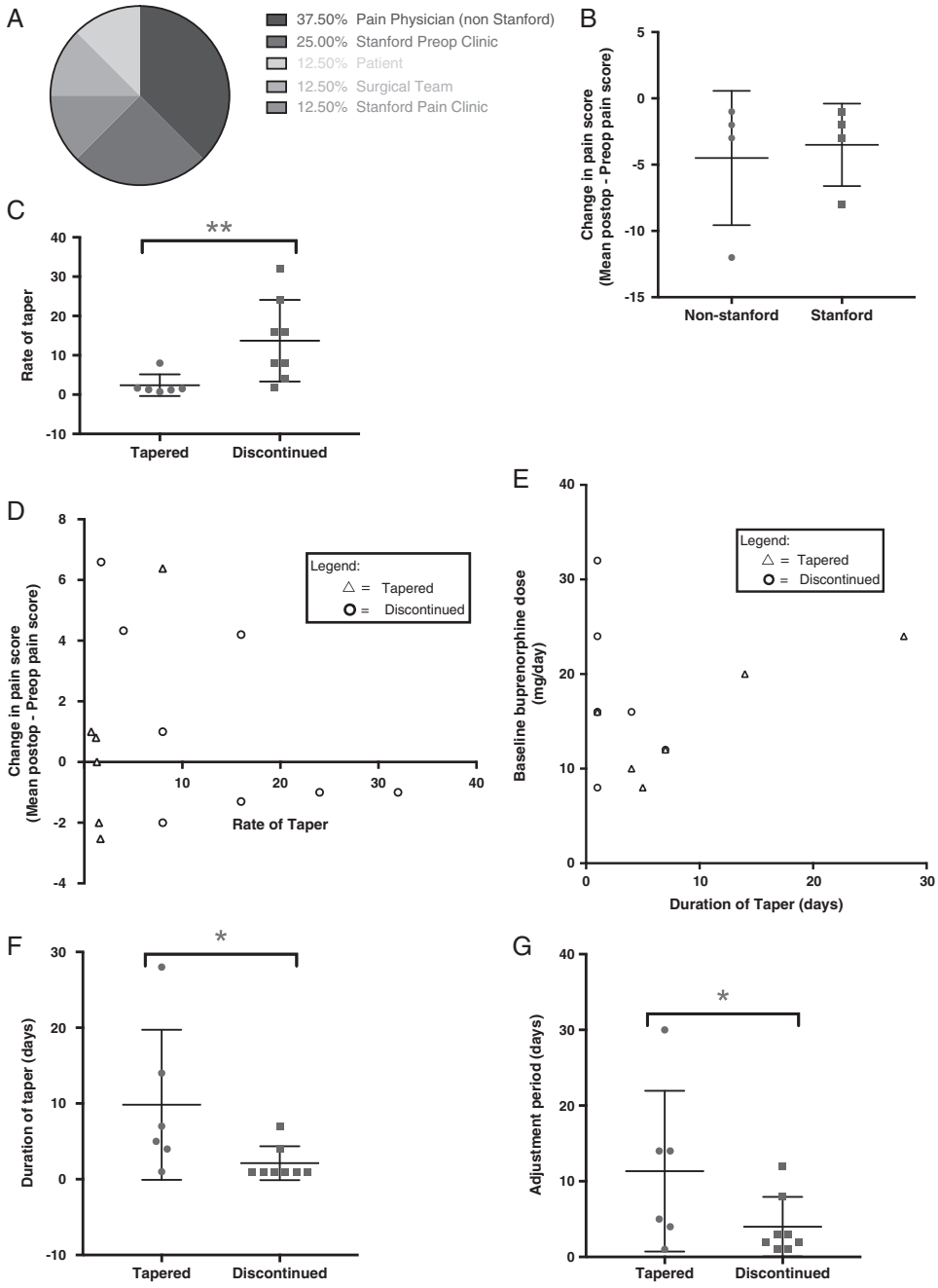

FIGURE 4. Variability in tapers. A, Proportion of tapers conducted by each responsible entity. B, Change in pain score for non-Stanford versus Stanford-affiliated entities. C, The rate of taper (ie, the difference in baseline dose and day-of-surgery dose divided by the duration of taper in days) for tapered versus discontinued patients. D, Change in pain score versus rate of taper. E, Baseline buprenorphine dose versus duration of taper. F, Duration of taper for tapered versus discontinued patients. G, Adjustment period (in days) between tapered and discontinued patients. *$P < 0.05$; **$P < 0.01$.

formulation, we observed a lower change in pain score in patients who had been continued versus discontinued. For the sublingual formulation, we observed fewer MMEs of scheduled (non-PRN) postoperative opioid prescriptions in patients who had been continued versus tapered or discontinued. Given our findings, we implemented a policy for buprenorphine perioperative management at our institution that advocated for continuation whenever possible.

Our study focused on the sublingual population, not only because data is most lacking in this area, but also because the average sublingual dose was 12.97 ± 8.46 mg/d, 36 times higher than the average transdermal dose of 0.36 ± 0.21 mg/d. More importantly, low-dose transdermal buprenorphine has been approved by the Food and Drug Administration for chronic pain since 2010, even when patients are concurrently prescribed PRN opioids.[17] Given its low dose,

transdermal buprenorphine is not at a high enough dose to block other agonists, supporting its continuation.[17] Indeed, in our study we found that transdermal discontinuation led to poorer pain control than its continuation in both the difference between mean postoperative—preoperative score (Fig. 1A) and lowest postoperative—preoperative score (Fig. 1B). If discontinued patients reported higher scores in the lowest postoperative pain score they were able to achieve, this suggests that even the lowest level of pain they were able to obtain was higher than patients who had been continued on their baseline transdermal buprenorphine dose. In this light, it was unfortunate that the transdermal patients in this study were not continued in the first place. We can only surmise this was due to the fact our data was sampled from 2013 to 2016, a time when even less was known about perioperative buprenorphine management, which overall highlights an area for educational intervention in perioperative management.[18] Furthermore, recent work by Martin et al[19] demonstrated that among patients on a transdermal formulation, those with greater preoperative doses were associated with greater postoperative opioid requirements. In this light, future research on perioperative buprenorphine management should separate comparisons of pain scores according to transdermal or sublingual formulation. Since our data suggested the discontinuation of transdermal buprenorphine is inferior to its continuation, the remainder of our analyses were focused on sublingual buprenorphine.

As we found no difference in the change in pain score in both mean postoperative—preoperative score (Fig. 2A) and lowest postoperative—preoperative score (Fig. 2B) between tapered and discontinued sublingual patients, we combined the tapered and discontinued groups into 1 group, labeled as "tapered/discontinued." To account for the possibility that a higher baseline dose could confound patients' pain scores, we plotted all 29 sublingual patients' change in pain score by their baseline dose and found no association (Fig. 2C). Finally, to assess for a dose-dependent effect of patients' baseline dose, we compared the change in pain score between continued and tapered/discontinued patients, stratified by baseline doses of ≤ 10 mg/d (Fig. 2D) or > 10 mg/d (Fig. 2E) and saw no difference. However, we did see higher MME in scheduled (non-PRN) opioid prescriptions for the tapered/discontinued group compared with the continued group, suggesting the tapered/discontinued group had poorer pain control and thus needed higher MME scheduled opioids at discharge (Fig. 3A). Our findings were consistent with a recent March 2020 study by Quaye et al, conducted on 55 patients, which compared discontinued versus continued patients and found significantly higher opioid prescriptions in the discontinued group as well as more MME dispensed and significantly higher post-anesthesia care unit pain scores.[20] Furthermore, prior studies have studied perioperative buprenorphine in comparison with other opioids such as methadone. For instance, a 2013 study compared patients on buprenorphine versus methadone and found that among surgical patients who were maintained on buprenorphine preoperatively, withholding buprenorphine the day after surgery significantly increased their requirement for patient-controlled analgesia opioids compared with those who had received their daily dose.[21] However, our study is novel in that the prior 2013 study did not specifically address if buprenorphine should be continued or tapered/discontinued before surgery.

An alarming finding in our study was the high variability in the tapering process. Groups ranging from the preoperative clinic to the patients themselves were responsible for managing the taper (Fig. 4A). To standardize comparisons of the tapering process within the literature, we calculated the rate of taper as the difference between a patient's baseline dose and day-of-surgery dose divided by the duration of taper in days. There was a significantly higher rate of taper in discontinued patients compared with tapered patients, suggesting discontinued patients quickly dropped to their day-of-surgery dose of 0 mg (Fig. 4C). In this vein, discontinued patients not only underwent a significantly shorter duration of taper than tapered patients (Fig. 4F), but also had a shorter adjustment period than tapered patients (Fig. 4G). Although having a longer adjustment period was not necessarily associated with a better change in pain score (Fig. 2A), future work needs to consider if a longer adjustment period can confound tapering data by allowing patients more time to adapt their pain tolerance to this lower buprenorphine dose compared with other patients whose taper was achieved the day before surgery.

Issues surrounding the discontinuation of buprenorphine therapy have been well documented separately from issues around pain control.[3,4] For instance, the National Drug Abuse Treatment Clinical Trials Network Prescription Opioid Addiction Treatment Study, presented at the 2010 American Psychiatric Association annual meeting, showed that tapering buprenorphine over 9 months led to almost universal relapse in people dependent on prescription opioids.[22] Relapse prevention theories suggest that stress associated with unrelieved pain is more likely to trigger a relapse compared with new opioid prescriptions in the acute care setting.[22,23] Indeed, prior studies have demonstrated how chronic pain is a predictor for postoperative pain.[24,25] Hence, the perioperative period can be a very challenging time for some patients and has been associated with relapse to opioid abuse/overdose, heroin use, and death.[26] Despite limited evidence, the practice of discontinuing or at least tapering a patient's baseline buprenorphine dose 48 to 72 hours before surgery[3,4] has been driven primarily by 3 theoretical concerns over the properties of buprenorphine. The first is that because buprenorphine has a ceiling effect on opioid effects like respiratory depression, it must also have a ceiling effect on analgesia.[18,27] However, the original human pharmacologic studies conducted by Walsh et al[3] did not actually examine any analgesic effects, but rather long-acting opioid agonist effects such as respiratory depression, pupillary constriction, sedation, and euphoria. In fact, a study tested 2 incremental doses of buprenorphine in 20 healthy young volunteers and, while it confirmed a ceiling effect for respiratory depression, did not find one for analgesia.[28] A second concern has been that the high affinity of buprenorphine for μ-opioid receptors must block the analgesic effects of any co-administered opiates.[18,29] However, buprenorphine has been shown to not only increase μ-receptor expression but also occupy fewer receptors for analgesia, leading to a receptor reserve for additive μ-agonists.[30,31] Furthermore, for therapeutic doses in humans, neither an analgesic ceiling effect nor antagonism on a combination of buprenorphine with pure μ-receptor agonists has been observed.[32] Finally, a third concern has been that because buprenorphine is only a partial μ-agonist, it must have low analgesic potency.[18,27,33,34] However, there is literature that conflicts with this theoretical concern; for instance, a case report found that when the same chronic pain patient underwent the same surgery twice, the patient had more easily-achieved pain control and greater functional recovery when buprenorphine was maintained throughout the perioperative period versus when a full μ-agonist opioid was given preoperatively for chronic pain.[18]

Reasons to continue buprenorphine before surgery include preventing the need for reinduction after surgery and respecting patient preference for remaining on buprenorphine out of a fear of relapse.[35] Buprenorphine has additional benefits compared with other opioids, including increased antihyperalgesic effects for chronic pain patients undergoing surgery in the postoperative period, safer use in elderly patients via the transdermal route and in patients with renal failure, and lower rates of constipation and its complications.[36–39] Furthermore, discharging patients with increased requirements for prescription opioids is dangerous not only because it increases the likelihood of relapse in an individual with a history of opioid use disorder, but also introduces well-studied issues such as diversion, the improper disposal of leftover medication that leads to excess and possibly inappropriately-shared opioids.[40] In addition, continuing buprenorphine simplifies planning at discharge; very few of the patients in our study were noted to have plans regarding their buprenorphine dosage at discharge. In a meta-analysis, at 1 month of discontinuation, the rates of relapse to illicit opioid use were $>50\%$ in every study.[41] Another concern of continuing patients on buprenorphine has been that it will cause subsequent opioids to be ineffective.[29] However, the majority of patients, including all patients on a transdermal formulation of buprenorphine, can be managed by supplemental opioids and multimodal analgesic management. Prior studies have also used high-dose buprenorphine to manage postoperative pain by changing a dosing regimen in real-time; for instance, in a study of 50 elective C-section cases performed under general anesthesia, a range of buprenorphine doses from 0.4 mg to as high as 7.0 mg was shown to produce total, long-lasting analgesia with minimal side effects, including serial blood gas samples that demonstrated a lack of respiratory depression.[42] In fact, the administration of postoperative buprenorphine was a practice observed in our own study, carried out in 13 (46%) of our 29 patients on a sublingual formulation. For these patients, the total dose of postoperative buprenorphine given in the first 24 hours was an average of 7.60 ± 2.34 mg in the continued group, which was not statistically different from the 2.29 ± 1.31 mg average for the tapered group ($P = 0.062$). Furthermore, there was no difference in the average length of time from entry into the postoperative area to delivery of the first dose of postoperative buprenorphine between the continued group (10.6 ± 1.96 h) and tapered group (8.00 ± 3.05 h, $P = 0.53$).

Together, our results informed our policy to continue buprenorphine in the perioperative period whenever possible. Our institution's policy is outlined in Figure 5. Preoperatively, the perioperative buprenorphine policy is dose-dependent for patients taking ≤ 10 mg versus >10 mg of buprenorphine/d. Patients on a baseline dose of ≤ 10 mg/d (or on the patch or implant) are required to meet the following 3 guidelines: (1) buprenorphine should be continued, (2) the buprenorphine prescriber should be made aware of upcoming surgery, and (3) a consult to the Pain Service should be placed via the preoperative order set. The above guidelines also apply to patients on a baseline dose of >10 mg/d; however, for scheduled procedures with an anticipated high degree of postsurgical pain, our guideline is to consider tapering to an 8 mg/d dose in conjunction with the buprenorphine prescriber at least 72 hours before surgery, or delaying the surgery if it is elective. Our 8 mg threshold was in keeping with an algorithm suggested by Quaye and Zhang.[6]

Regarding intraoperative considerations, for the day of surgery all patients are instructed to take their buprenorphine or arrive to the day of surgery with their patch on with plans to have their patch reapplied immediately postoperatively. Preoperatively, patients also receive nonopioid pain medications, specifically acetaminophen, gabapentin/pregabalin, and an nonsteroidal anti-inflammatory drug. Furthermore, regional or neuraxial anesthesia is employed if possible; otherwise, patients should receive an infusion of ketamine ± lidocaine. Finally, at the anesthesiologist's discretion, patients should be induced with an opioid of their choice before intubation; meanwhile, the dose of opioid required to achieve a decrease in the respiratory rate is reported to the acute pain service.

Postoperatively, patients are followed by the acute pain service in the immediate postoperative period for multimodal management (patient-controlled analgesia at higher doses with IV hydromorphone ± ketamine infusion ± lidocaine infusion in addition to other nonopioid analgesics). Patients are also continued on their home dose of buprenorphine; however, for higher home dosages, this is divided into q6h or q8h dosing with consideration of a supplemental PRN dose of buprenorphine.[43] Finally, discharge plans require providing the patient with a follow up plan with their buprenorphine provider and a 1-week supply of PO opioid for acute pain needs.

Limitations of this study included the small sample size that may have precluded the achievement of statistical significance in our comparisons among continued, tapered, and discontinued perioperative buprenorphine. Similarly, given the limited sample size of our study on surgical subspecialties such as ENT and plastics, which had to be grouped into a shared category, it would be of interest to compare the changes in pain scores by procedure within surgical subspecialties. Although our data showed sublingual patients required more opioid prescriptions at discharge if their dose had been tapered or discontinued, this may have been confounded by a practice pattern in which clinicians prescribe standing opioid for patients who have been on long-acting opioid agents recently but are not currently receiving such agents. Another limitation was our ability to collect detailed data on the indication for why each patient had been prescribed sublingual versus transdermal buprenorphine; as shown in Table 2, we were only able to assess if each patient's indication was for chronic pain, a history of opioid use disorder, both, or for off-label use. Future studies should recognize the importance of differentiating between the designation of a history of opioid use disorder from current opioid use disorder. As with any retrospective analysis, our study had poor control over the exposure factor in terms of each patient's buprenorphine regimen. Our analyses also did not include long-term follow-up, relapse rates, or mortality. Further work includes performing a comprehensive retrospective cohort study on the buprenorphine patients who were managed after the implementation of our policy and extending this into a longitudinal study to monitor for long-term rates of addiction relapse, including long-term morbidity and mortality whenever possible.

Finally, our study revealed several practices in buprenorphine management concerning for patient safety that require future investigation, including how to avoid rapid tapers that were uncoordinated with discharge plans and how to prevent potential postoperative respiratory depression and sedation from the high rates of co-prescribed central nervous system depressants with buprenorphine. Our attempt at designing an evidence-based institutional policy for perioperative buprenorphine management highlighted crucial areas of

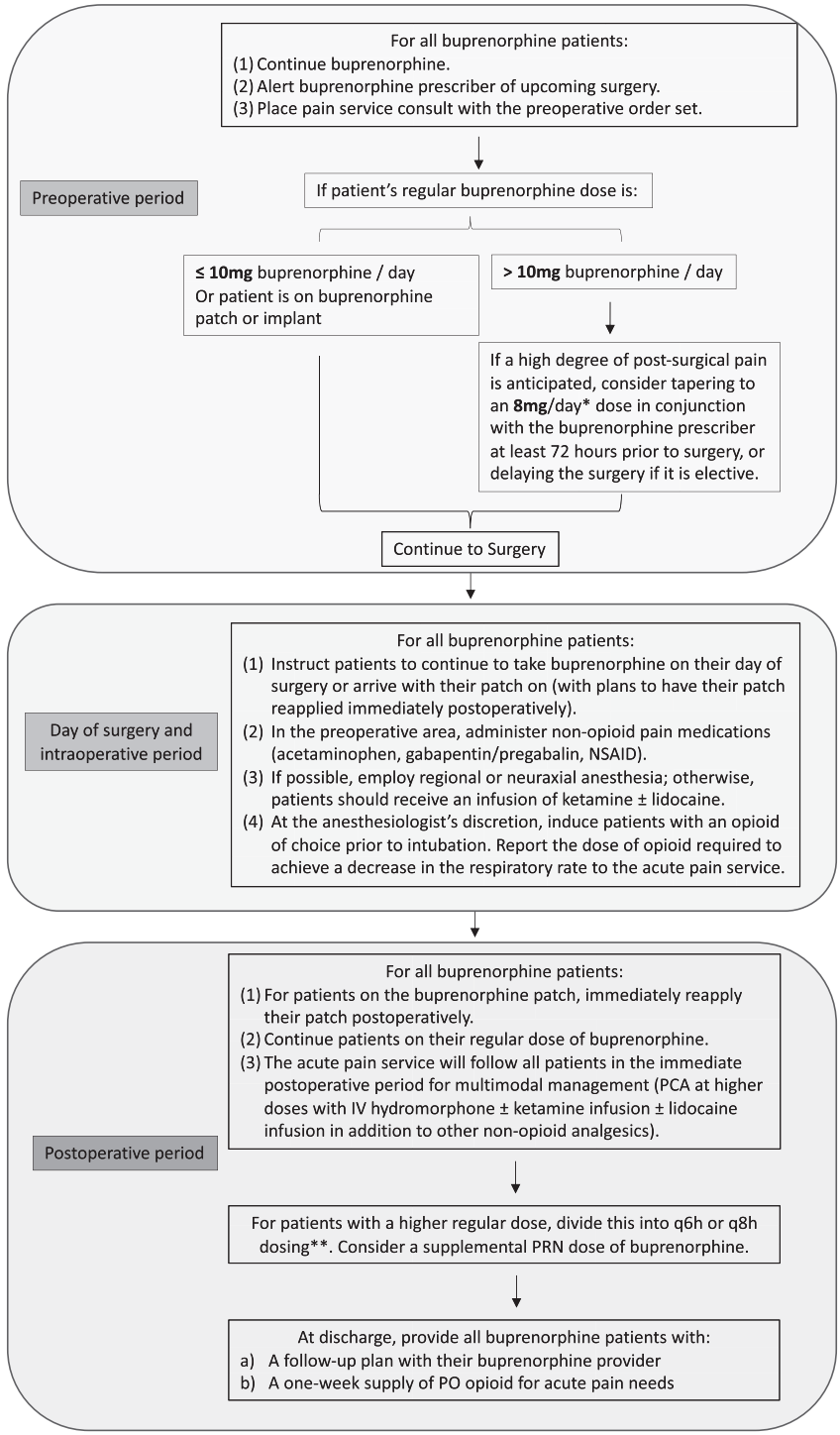

FIGURE 5. Stanford Policy for Perioperative Buprenorphine Management. *Quaye and Zhang.[6] **Lembke et al.[43]

improvement in safety, prevention of perioperative adverse events, and pain management.

CONCLUSIONS

We found improved postoperative pain scores in patients whose transdermal buprenorphine had been continued perioperatively and lower MME in scheduled opioid prescriptions for patients whose sublingual buprenorphine had been continued perioperatively. We also found a wide array of practices and opportunities for pain physicians and anesthesiologists to study and implement data-driven institutional policies to improve perioperative pain control, decrease potential adverse events in the perioperative period, and offer guidance to

aid the management of complex patients who are increasingly presenting for surgical and anesthetic management.

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