Perioperative Pain Management Guidance for Patients on Chronic Buprenorphine Undergoing Elective or Emergent Procedure

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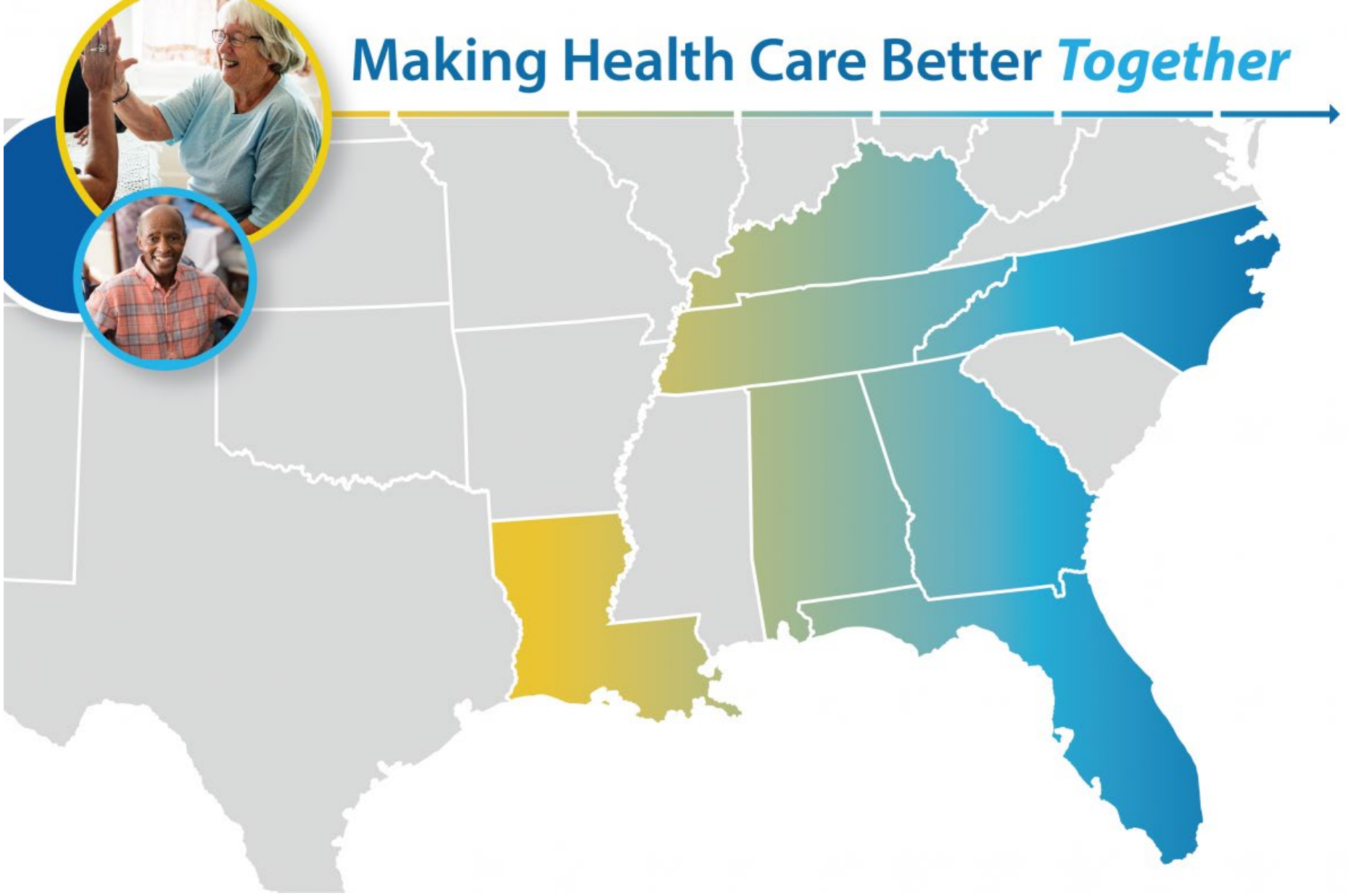

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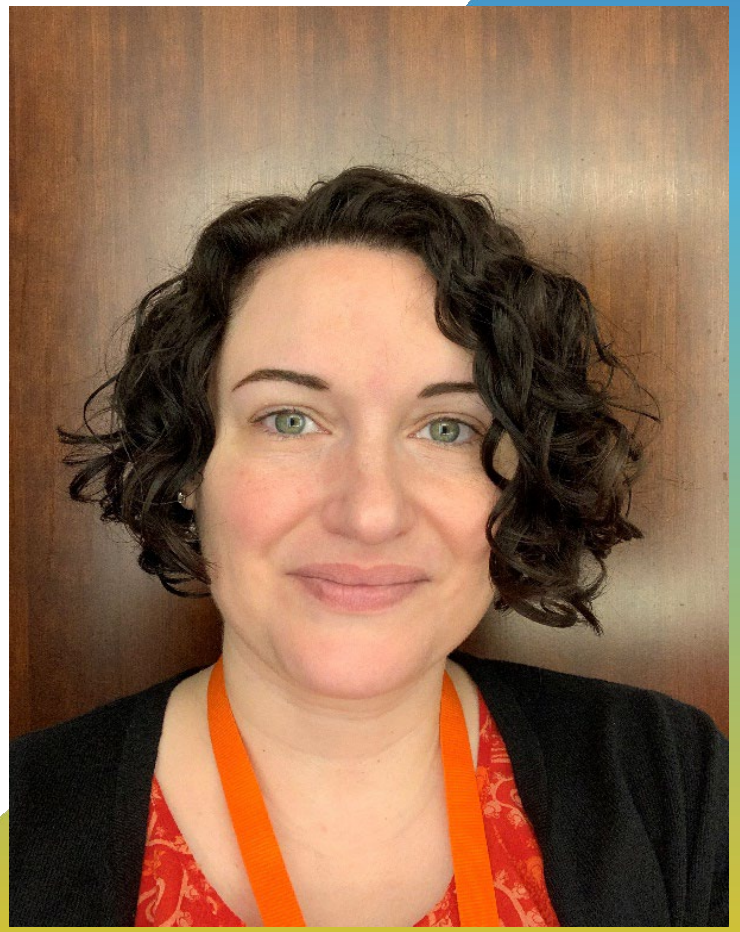

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PAIN MANAGEMENT PHARMACIST

Dr. Jeffrey J. Bettinger, PharmD, is a pain management clinical pharmacist with Saratoga Hospital Medical Group in Saratoga, NY. He also served as an invited expert panel member for the FDA during their public workshop *Morphine Milligram Equivalents: Current Applications and Knowledge Gaps, Research Opportunities, and Future Directions* in 2021. He earned his PharmD from Albany College of Pharmacy and Health Sciences in 2017 with a concentration in nephrology. After his doctoral training, he completed a PGY1 general practice residency at the Stratton VA Medical Center in Albany, NY. Immediately following his general practice residency, he trained with Drs. Jeff Fudin and Erica Wegrzyn and completed a PGY2 pain and palliative care residency at the same institution.

Disclosure Statement

Scientific Advisory Board: PainScript, LLC

Consultant: Hisamitsu America, Inc.

Objectives

- Differentiate between the pharmacologic and pharmacokinetic characteristics that make buprenorphine a unique opioid.
- Review issues that make perioperative pain management difficult in patients on chronic buprenorphine.
- Compare and contrast different recommendations regarding perioperative pain management for patients on chronic buprenorphine therapy for OUD.

Introduction and Background

History of Buprenorphine

- First approved in 1985 as injectable Buprenex.
  - For treatment of moderate to severe pain
- Since then, eight additional products have come to market.
- Six of these products have approvals for opioid dependence.
- Two of these products have approvals for pain management.

Buprenorphine Products Available

Brand Name	Generic Name	Formulation	FDA-Approved Indications	Bioavailability	Elimination Half-Life
Suboxone™	Buprenorphine and naloxone	Sublingual film	Treatment of opioid dependence	~30%	24 to 42 hours
Subutex®	Buprenorphine	Sublingual film	Treatment of opioid dependence and are preferred for induction.	~30%	31 to 35 hours
Zubsolv®	Buprenorphine and naloxone	Sublingual tablet	Treatment of opioid dependence	~30%	24 to 42 hours
Bunavail™	Buprenorphine and naloxone	Buccal film	Treatment of opioid dependence	~30%	16.4 to 27.5 hours
Sublocade®	Buprenorphine	Abdominal subcutaneous injection	Treatment of moderate to severe opioid use disorder	100%	43 to 60 days
Probuphine®	Buprenorphine	Implant for subdermal administration (6 month implant)	Maintenance treatment of opioid dependence in patients who have achieved prolonged clinical stability on low-to-moderate doses of a transmucosal buprenorphine-containing product	31.3%	24 to 48 hours
Buprenex®	Buprenorphine	Intravenous or intramuscular	Management of pain severe enough to require opioid therapy	100%	1.2 to 7.2 hours
Butrans®	Buprenorphine	Transdermal delivery system	Management of pain severe enough to require around-the-clock, long-term opioid treatment	~15%	~26 hours
Belbuca™	Buprenorphine	Buccal film	Management of pain severe enough to require around-the-clock, long-term opioid treatment	46 to 65%	11.2 to 27.6 hours

Introduction and Background

Pharmacologic Characteristics:

- Considered a partial agonist at mu-opioid receptors (MORs) and an antagonist at kappa-opioid receptors (KORs)
- Agonist of opioid receptor-like 1 (low affinity)
- Partial agonist definition primarily due to lower intrinsic activity compared to full MOR agonists in in-vitro binding receptor assay studies
  - SHOULD NOT BE CONFUSED WITH MEASURES OF CLINICAL EFFICACY!
- Extremely high binding affinity toward MORs compared to all other opioids
- Extremely slow dissociation rate from MORs (~90 minutes)

Raffa RB et al. J Clin Pharm Ther. 2014;39(6):577-83; Huang P et al. J Pharmacol Exp Ther. 2001;297:688-695;
Boas RA et al. Br J Anaesth. 195;57(2):192-6; Sadee W et al. J Pharmacol Exp Ther. 1982;223(1):157-62
Volpe DA et al. Regul Toxicol Pharmacol. 2011;59(3):385-390; Bickel WK et al. J Pharmacol Exp Ther. 1988;247(1):47-53

Comparison of Binding Affinities (Ki) of MOR Agonists

Drug	Ki Value (nM)	Drug	Ki Value (nM)
Sufentanil	0.1380	Alfentanil	7.391
Buprenorphine	0.2157	Diphenoxylate	12.37
Hydromorphone	0.3654	Oxycodone	25.87
Oxymorphone	0.4055	Hydrocodone	41.58
Levorphanol	0.4194	Pentazocine	117.8
Butorphanol	0.7622	Propoxyphene	120.2
Morphine	1.168	Meperidine	450.1
Fentanyl	1.346	Codeine	734.2
Nalbuphine	2.118	Tramadol	12,486
Methadone	3.378		

Volpe DA et al. Regul Toxicol Pharmacol. 2011;59(3):385-390;

Issues With Perioperative Management for Patients on Buprenorphine

- The addition of a full MOR agonist may exert some effect; however, it will not effectively displace buprenorphine from MORs:
    - Increased susceptibility for the patient to be in increased pain/agitation

- If higher doses of MOR agonists are used to overcome said effect and buprenorphine is abruptly stopped:
    - Potentially increased risk of opioid-related side effects and opioid-induced respiratory depression (OIRD)

- If buprenorphine is being used for OUD and is stopped before elective surgery:
    - Increased susceptibility for the patient to relapse

- Lack of guidance/evidence in this area

Additional Considerations

Recommendations for Patients on Sublocade or Probuphine

- Increasing prevalence of patients on either formulation.
- For either formulation, it's recommended to refer to options for continuing buprenorphine throughout the perioperative process.
- Due to the half-life of Sublocade and the fact that Probuphine is a physical implant, it would be impractical to attempt to stop, hold or remove either therapy before any type of surgery.

Recommended Additional Opioids To Be Used With Buprenorphine Perioperatively

- In situations where full MOR agonists are needed, we recommend utilizing ones with:
    - **Similar lipophilicity**
    - **Similar binding affinity**

- Fentanyl and Sufentanil are both available IV, highly lipophilic and have high binding affinities toward MORs.

- Hydromorphone is available IV and oral and has a similar binding affinity to buprenorphine.
    - **However, it is relatively hydrophilic.**

Recommendations for Naloxone Education and Counseling

- Opioid mortality prevalence is higher in patients who have a substance abuse history and psychiatric comorbidities.
- Therefore, recommend using RIOSORD for patients discharged post-operatively on opioid medications.
- Those prescribed buprenorphine with little to no risk for OIRD may not need naloxone.
    - **Unless IR opioids are initiated post-operatively**

Recommendations for Screening for Suicidal Ideation Prior to Discharge

- Both chronic pain and SUD represent individual risk factors for increased likelihood of suicide and suicidal behavior.
    - **Only heightened with acute stresses to health and behavioral co-morbidities.**

- It is recommended that clinicians complete screen for suicide prior to discharge to potentially reduce this risk.

REMEMBER: Measures of Clinical Efficacy for Pain

Authors	Year	Interventions	Type of Pain	Number of Patients	Outcome
IV/IM Buprenorphine					
Downing JW et al	1977	IM Buprenorphine 0.6mg IM Morphine 15mg	Post-operative pain following Caesarean section	58	Similar pain relief for first 2-post op hours; greater pain relief after 3h
Hovell BC et al	1977	IM Buprenorphine 0.3mg IM Morphine 10mg	Post-operative pain following abdominal surgery	50	Similar pain relief
Dobkin AB et al	1977	IM Buprenorphine 0.2-0.4mg IM Morphine 5-10mg	Post-operative pain following abdominal surgery	40	Similar or greater pain relief with buprenorphine
Kay B	1978	IV Buprenorphine 0.3mg IV Morphine 10mg	Post-operative following major abdominal surgery	51	Similar pain relief
Tigerstedt I et al	1980	IM Buprenorphine 0.3mg IM Morphine 10mg	Post-operative pain following abdominal surgery	60	Similar pain relief
Ouellette RD et al	1984	IM Buprenorphine 0.15-0.4mg IM Morphine 5-10mg	Post-operative pain following major abdominal, orthopedic, or thoracic surgery	133	Similar pain relief
Cuschieri RJ et al	1984	IM Buprenorphine 0.3mg IM Morphine 10mg	Post-operative pain following abdominal surgery	80	Similar pain relief
Bradley JP	1984	IV Buprenorphine 5mcg/Kg IV Morphine 167mcg/Kg	Post-operative following abdominal hysterectomy or cholecystectomy	80	Similar pain relief
Donadoni R et al	1987	IM Buprenorphine 0.3mg Epidural Sufentanil 50mcg	Post-operative following orthopedic surgery	60	Less pain relief over first 2 hours, but greater pain relief from hours 2 to 8
Rabinov M et al	1987	IV Buprenorphine 0.35mg IV on demand IV Morphine 0.5-6mg/hour IV infusion	Post-operative following coronary bypass surgery	13	Similar pain relief
Maunuksela EL et al	1988	IV Buprenorphine 1.5 or 3mcg/Kg IV Morphine 50 or 100mcg/Kg	Post-operative following lateral thoracotomy in children	57	Similar pain relief
Lehmann KA et al	1991	PCA Buprenorphine PCA Fentanyl	Post-operative following unilateral thoracotomy	60	Similar pain relief
Oifa S et al	2009	Basal and bolus buprenorphine Basal and bolus morphine	Post-operative following abdominal surgery	120	Similar pain relief

REMEMBER: Measures of Clinical Efficacy for Pain

Authors	Year	Interventions	Type of Pain	Number of Patients	Outcome
SL Buprenorphine					
Edge WG et al	1979	SL Buprenorphine 0.4mg IM morphine 10mg	Post-operative following general surgery	N/a	Similar or greater pain relief with buprenorphine
Masson AH et al	1981	SL Buprenorphine 0.4mg Dihydrocodeine 60mg	Post-operative following general surgery	79	Similar or greater pain relief with buprenorphine
Wallenstein SL	1982	SL Buprenorphine 0.8mg IM Morphine 8mg	Chronic cancer pain	8	Similar pain relief
Gaitini L et al	1996	SL Buprenorphine 1.6 $\pm$ 0.45mg PCA Morphine 72 $\pm$ 8mg	Post-operative pain following open prostatectomy	52	Similar pain relief
Brema et al	1996	SL Buprenorphine 0.2mg Q6H Tramadol 100mg Q8H	Chronic neoplastic pain	131	Greater pain relief with tramadol
Neumann et al	2013	SL Buprenorphine/naloxone 14.93mg/3.73mg Methadone 20-60mg/day	Chronic non-cancer pain related to spine or large joint	54	Similar pain relief
Transdermal Buprenorphine					
Aurilio C et al	2009	Transdermal Buprenorphine Transdermal Fentanyl	Chronic cancer pain	32	Similar pain relief
Mitra F	2013	Transdermal Buprenorphine Transdermal Fentanyl	Chronic persistent pain	46	Similar pain improvements in initial 6 months
Buccal Buprenorphine					
Webster et al	2016	Rotation from morphine or oxycodone to buprenorphine	Chronic pain	39	Similar pain relief after transition

Remember: Dose Titrations

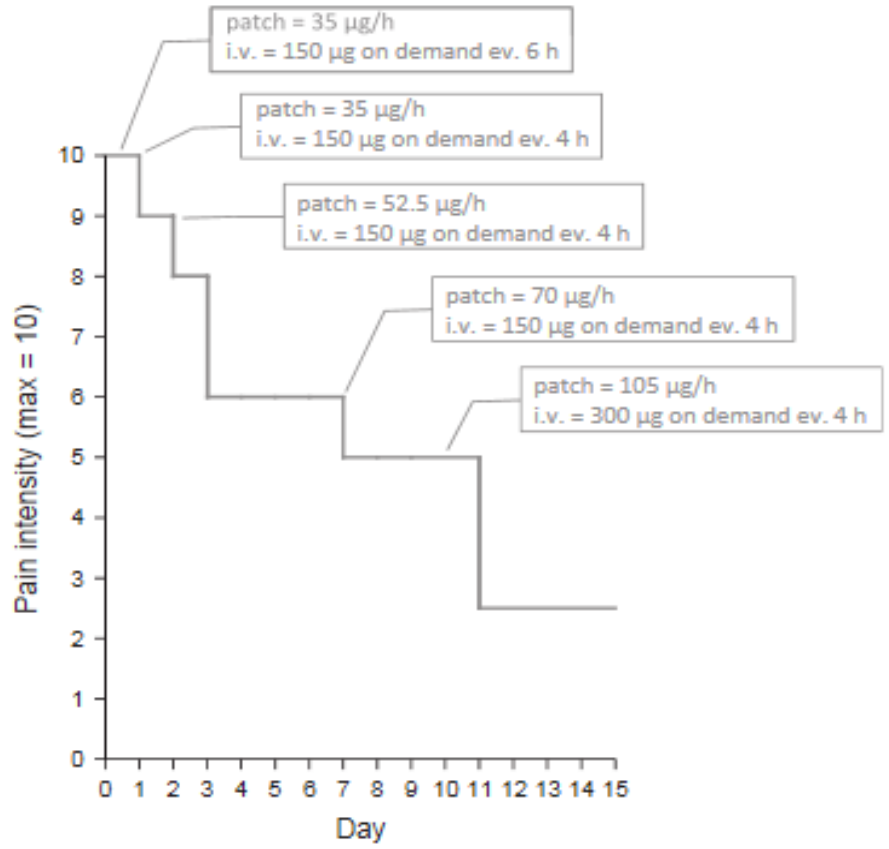

Fig. 5. Progressive increase in pain relief with increasing dose of buprenorphine in a terminally ill cancer patient with liver failure. Drawn based on the narrative in Ciccozzi *et al.*[39]

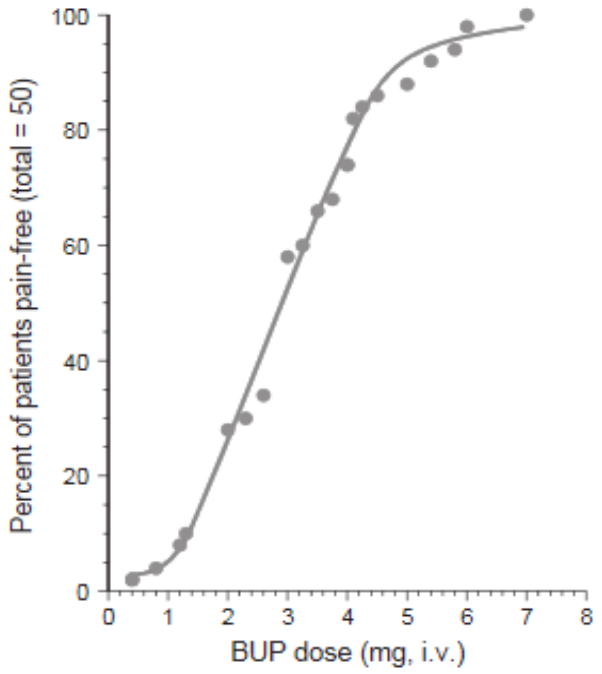

Fig. 6. The analgesic efficacy of i.v. buprenorphine was studied over a 24-h period in post-operative pain relief involving 50 patients (average age = 27·5 years) recovering from elective Caesarean section. Post-operatively, patients received buprenorphine in aliquots of 0·2 mg over 3–15 min, until the pain was relieved. Pain was assessed by its presence or absence at frequent intervals. All of the patients achieved complete analgesic effect with 0·4–7·0 mg of buprenorphine. Drawn based on data reported in Budd.[40]

Raffa RB et al. J Clin Pharm Ther. 2014;39(6):577-83; Ciccozzi A et al. J Opioid Manag. 2012;8:253-259;
Budd K. Anaesthesia. 1981;36:900-903

Considerations

- Given the lack of firm evidence, the following recommendations are mostly based on available evidence and expert opinion.
- It is strongly recommended that, where available, waivered providers or an interdisciplinary team experienced with buprenorphine use be consulted to most effectively and safely help manage these patients.
- It is equally important in every situation to communicate treatment plans with the buprenorphine prescriber, as this will allow for the best transition of care plan back to the community postoperatively.
- **Clinical judgment** is paramount regarding **individual** cases.

Perioperative Buprenorphine Management Goals

Three inter-related goals:

1. Preoperatively, suppression of withdrawal and craving/opioid reinforcement.

2. Intraoperative and post-operatively optimal analgesia.

3. Smooth transition back to maintenance regimen if BUP regimen is altered.

Considerations

- First, determine whether surgery is emergent or elective.

- Second, determine what indication the patient is receiving buprenorphine for:
    - OUD versus chronic pain.

Third, general pre-operative evaluation by the surgical team:
    - This should include urine drug monitoring and querying of prescription drug monitoring program (PDMP) databases.

Regardless of the pain management approach, non-opioid medications, nerve blocks or regional anesthesia, and non-pharmacologic modalities should be utilized and optimized to treat perioperative pain effectively.

Guidance for Perioperative Pain Management: Elective Procedures

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Patients on Chronic Buprenorphine for OUD

There are essentially two options when OUD patients on buprenorphine undergo an elective procedure:

1. For most patients, buprenorphine may be continued throughout the operative period.

2. If the patient is stable enough to be off this medication or patients who will undergo procedures with typically high postoperative pain (e.g., open abdominal/thoracic surgeries and major orthopedic surgeries), buprenorphine can be discontinued to allow for systemic elimination prior to surgery

Recommendation 1: Continue Buprenorphine

Buprenorphine could be continued throughout with maximization of non-opioids for analgesia. In addition, the following two other options may be performed:

1. Divide the current buprenorphine dose and administer it every six to eight hours (three to four times a day) for more optimal pain coverage. The total daily dose of buprenorphine can be titrated up to 32 mg/day in divided doses if needed for pain management.

2. Add an as-needed IR opioid to the baseline SL buprenorphine dose. It is recommended that opioids with similar lipophilicity and binding affinity (fentanyl, hydromorphone) toward MORs be used.
   - It should also be expected that the patient on baseline buprenorphine therapy in the perioperative setting will likely require a higher dose of full MOR agonist and therefore require close monitoring, e.g., in the ICU or step-down type unit.

Recommendation 2: Discontinue Buprenorphine

Providers may prefer to D/C buprenorphine before the procedure if they anticipate moderate to severe postoperative pain or if they anticipate that postoperative pain may be hard to control.

- Buprenorphine may be discontinued 24-72 hours before surgery and restarted after the resolution of acute postoperative pain.
- As needed, short-acting full opioid agonists and/or non-opioid treatment options for withdrawal symptom management, such as an alpha-2 receptor agonist, may be used for pain management and to mitigate withdrawal symptoms that may occur with buprenorphine discontinuation.
- If a short-acting opioid is utilized postoperatively, it is recommended to ensure that the plan includes tapering off the short-acting opioid and conversion back to their previous dose of buprenorphine in consultation with their waivered provider or OUD team.

Recommendation 2: Discontinue Buprenorphine (continued)

Restarting Buprenorphine:

Simple way:

- Discontinue the peri/postoperative full opioid receptor agonist.
- Restart buprenorphine at 2 mg or 4 mg when the initial withdrawal signs are observed by the provider for clinic induction or by the patient (for home induction).
- If and when the withdrawal is alleviated, the remaining prior buprenorphine maintenance dose may be started on Day 1.

Full induction:

- Typically starts with a 2 mg to 4 mg dose of buprenorphine or a 2 mg/0.5 mg to 4 mg/1 mg dose of buprenorphine/naloxone
- A repeat dose may be given after ~ 2 hours if there is continued withdrawal and lack of sedation
- The FDA label recommends a maximum buprenorphine/naloxone dose of 8 mg on Day 1 and 16 mg on Day 2.

Guidance for Perioperative Pain Management: Emergent Procedures

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General Considerations

Potentially more challenging, as emergency procedures leave no time to sufficiently and completely taper off buprenorphine:

- Even if abruptly stopped, it would take up to five days to clear the drug from the body.

Therefore, for these procedures, it is important to consider the anticipated pain level:

- Emergency Procedure with Anticipated Minimal to no Pain
- Emergency Procedure with Anticipated Moderate to Severe Pain

Emergency Procedure: Anticipated Minimal to No Pain

- Buprenorphine would be anticipated to offer enough analgesia to cover the patient during the procedure and post-operatively.
- Buprenorphine doses could be titrated to manage perioperative pain.
- If IR opioids are used in an inpatient and controlled environment, it is recommended to taper the patient off prior to discharge.
- If hospital LOS is short or if outpatient procedures require a brief course of IR opioids, OP post-operative pain care should be offered in consultation with the patient's OUD/Addiction Medicine team.

Examples of procedures with a low risk of postoperative pain: tooth extraction, esophagoduodenoscopy, arthroscopy, colonoscopy, bronchoscopy, etc.

Emergency Procedure: Anticipated Moderate To Severe Pain

There are two recommended options for patients undergoing procedures with moderate to severe pain:

1. Continue the buprenorphine method
2. Discontinue buprenorphine method

Examples of procedures with intermediate or moderate risk of postoperative pain: laparoscopic procedures, video-assisted thoracoscopic procedures, arthroscopic procedures, open neurosurgical procedures, etc.

Examples of procedures with severe postoperative pain or high opioid requirement in the postoperative period: open intra-abdominal surgery, open intra-thoracic surgery and orthopedic procedures.

Emergency Procedure: Anticipated Moderate to Severe Pain

Option 1: Continue Buprenorphine Method

- Buprenorphine could be continued throughout the operation while utilizing non-opioids for anesthesia and postoperative analgesia.
- Postoperatively, buprenorphine doses could be increased (EXCEPT Sublocade or Probuphine) until adequate pain levels are achieved.
- IR full MOR opioids could be used PRN (in addition to buprenorphine); however, it is still recommended to taper the patient off IR opioids prior to discharge or shortly after discharge.

Emergency Procedure: Anticipated Moderate to Severe Pain

Option 2: Discontinue Buprenorphine Method

- Discontinue buprenorphine immediately upon admission in lieu of IR MOR agonists.
- Carefully titrate IR opioids in the short term to overcome buprenorphine's tight binding affinity and overwhelming occupation of MORs.
- Recommend patients remain hospitalized for at least three to five days after discontinuing buprenorphine for close monitoring.
- Patient will most likely require continual adjustments (decreases) of IR opioid dose as buprenorphine is cleared from the patient's system.
- ICU monitoring for respiratory function is recommended for patients that require high doses of full MOR agonists.
- A tapering plan for short-acting opioids should also occur postoperatively.
- Patients should be converted back to buprenorphine if they have a history of OUD and/or pain with substance abuse prior to discharge.

Summary and Conclusions

Summary

- Buprenorphine offers unique pharmacologic and pharmacokinetic characteristics that increase the complexity of perioperative pain management for those maintained on buprenorphine chronically.

- For the majority of patients, it is recommended that buprenorphine treatment be continued throughout the perioperative period while optimizing non-opioids and non-pharmacologic therapies for pain management.

- No matter what method is chosen, appropriate documentation and communication with all health care members (including the OUD team) are essential for safe patient outcomes.

Questions?

Nursing Home and Partnership for Community Health:
CMS 12th SOW GOALS

OPIOID UTILIZATION AND MISUSE

Promote opioid best practices

•

Reduce opioid adverse drug events in all settings

PATIENT SAFETY

Reduce hospitalizations due to c. diff

•

Reduce adverse drug events

•

Reduce facility acquired infections

CHRONIC DISEASE SELF-MANAGEMENT

Increase instances of adequately diagnosed and controlled hypertension

•

Increase use of cardiac rehabilitation programs

•

Reduce instances of uncontrolled diabetes

•

Identify patients at high-risk for kidney disease and improve outcomes

CARE COORDINATION

Convene community coalitions

•

Reduce avoidable readmissions, admissions to hospitals and preventable emergency department visits

•

Identify and promote optimal care for super utilizers

COVID-19

Support nursing homes by establishing a safe visitor policy and cohort plan

•

Provide virtual events to support infection control and prevention

•

Support nursing homes and community coalitions with emergency preparedness plans

IMMUNIZATION

Increase influenza, pneumococcal, and COVID-19 vaccination rates

TRAINING

Encourage completion of infection control and prevention trainings by front line clinical and management staff

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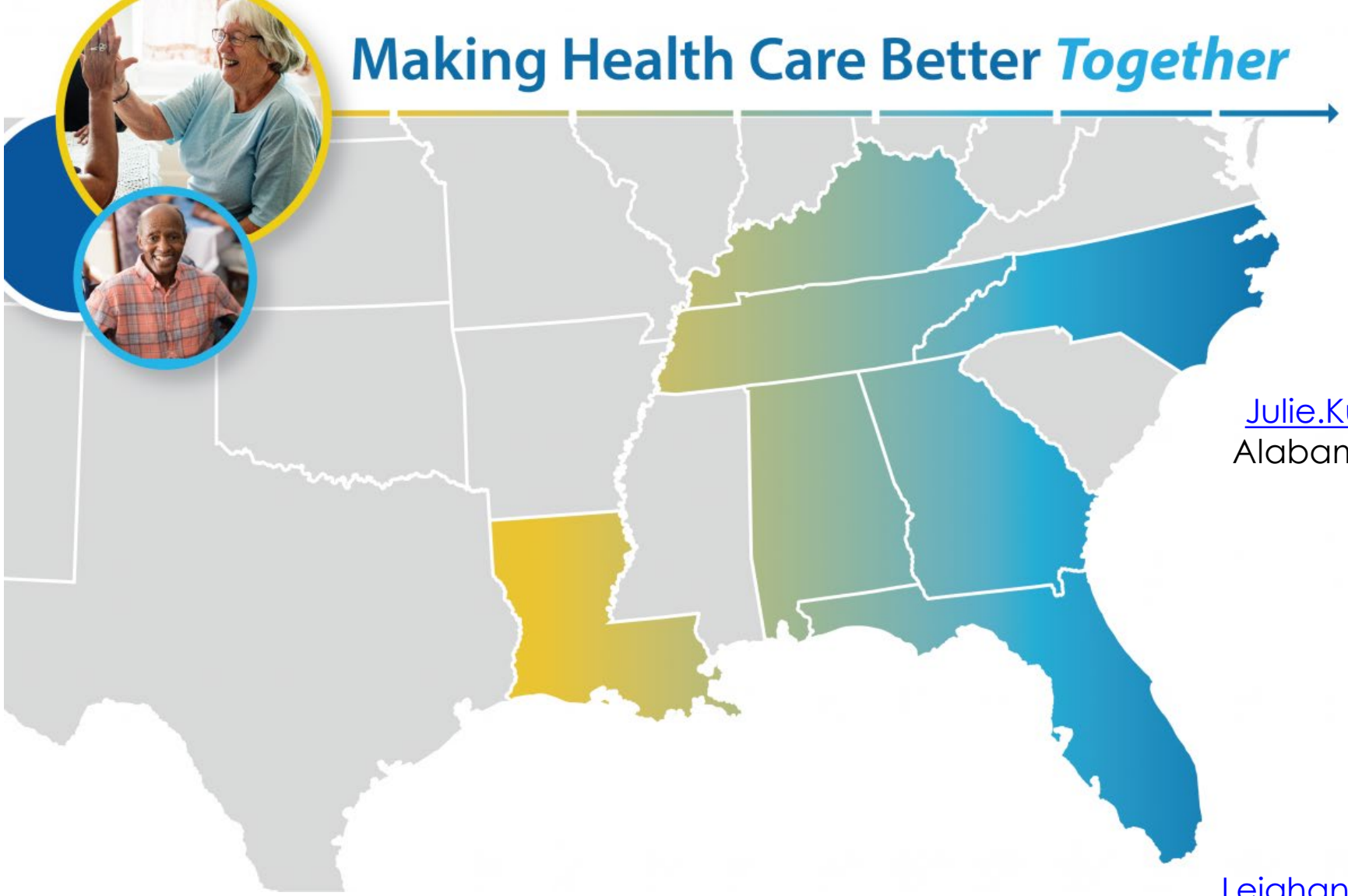

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