The Ins and Outs of Buprenorphine

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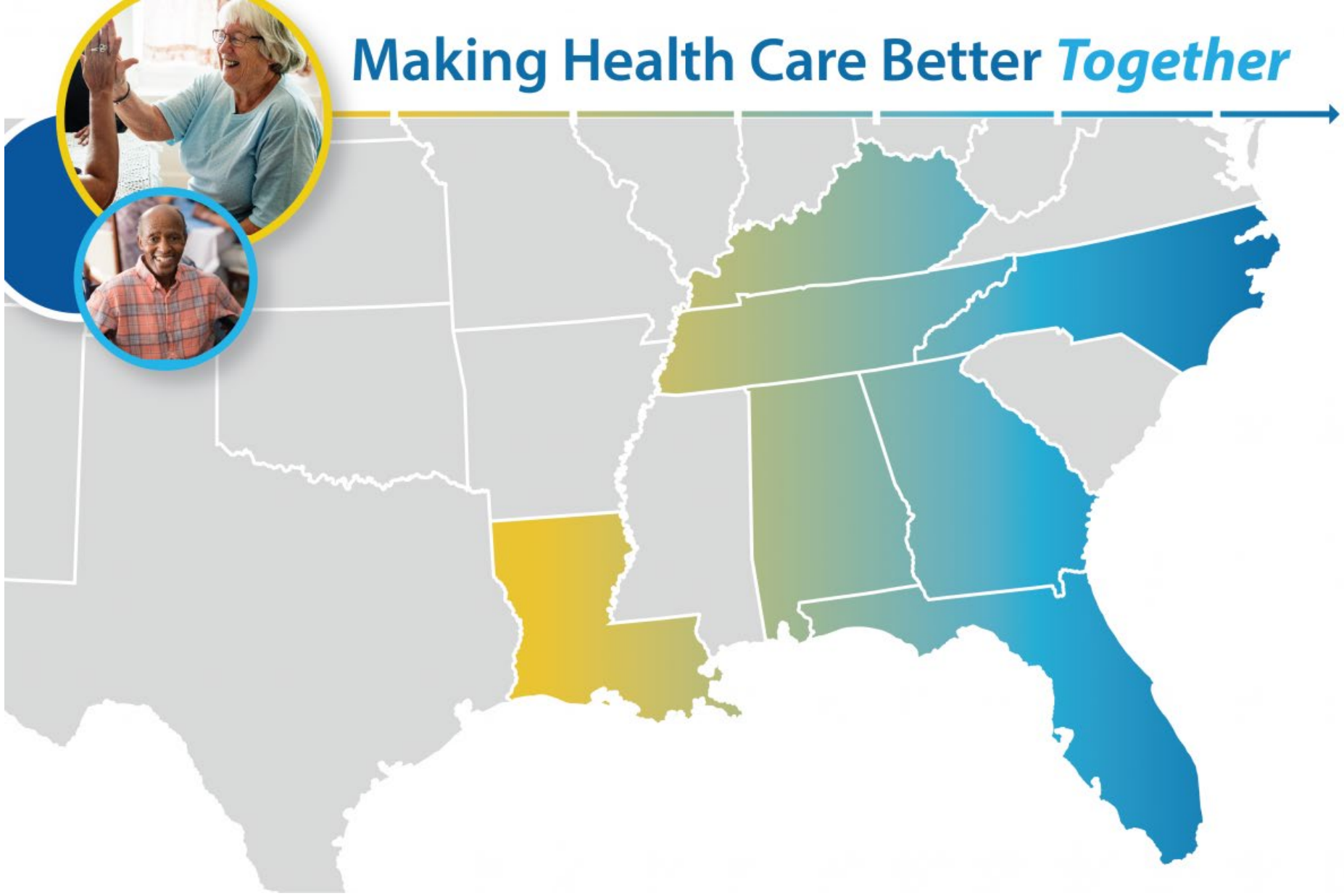

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MEDICATION SAFETY PHARMACIST

Tanya is an IPRO pharmacist with 20 years of clinical pharmacy, community pharmacy, academia, quality improvement and medication safety experience. Prior to joining IPRO, she worked at various community pharmacies and taught at Albany College of Pharmacy and Health Sciences in Albany, NY. She specializes in Medication Therapy Management (MTM), medication reconciliation, opioids, immunizations, and patient self-care. Her formal teaching experience includes courses in pharmacy practice and clinical experiential teaching.

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Disclosure Statement

Scientific Advisory Board: PainScript, LLC

Consultant: Hisamitsu America, Inc.

Objectives

- Delineate between the various pharmacologic mechanisms of buprenorphine that allow its side effects to plateau, but not its analgesic effects.
- Identify the clinical trials that have demonstrated a relative ceiling effect that buprenorphine allows for on various opioid-related adverse effects.
- Recognize the breadth clinical efficacy data that buprenorphine has shown supporting its analgesic potential and place on the analgesic ladder.

Current Landscape of Buprenorphine

Current Landscape of Buprenorphine

- Annual rate per 1,000 population of buprenorphine use has been increasing
  - 1.97 in 2009 → 4.43 in 2018[1]

- Namely driven by policy changes and enhanced awareness of use for opioid use disorder

- Despite this, still drastically underutilized and underrepresented for use in patients with chronic pain[2]

1. Olfson M, et al. JAMA. 2020;323(3):276-277.
2. Rosen K, et al. Clin J Pain. 2014;30(4):295-300

History of Buprenorphine

- First approved 1985 as injectable Buprenex
  - For treatment of moderate to severe pain

- Since that time, eight (8) additional products have come to market
  - Six (6) of these products have approvals for opioid dependence
  - Two (2) of these products have approvals for management of pain

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

Pharmacology of Buprenorphine

Pharmacologic Characteristics

- Considered a 'partial-agonis't 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!!!

- High binding affinity toward MORs compared to all other opioids

- 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;

The Question is…

If it is a *Partial Agonist*, Does that mean it has *Partial Analgesic Effects?*

Why is it Considered a 'Partial Agonist'?

- Buprenorphine has demonstrated to produce less than a 100% effect *in vitro* when binding to and activating G-proteins at MORs

- Specifically, when any opioid binds to and activates MORs…
  - G_a subunits are catalyzed releasing $G_{\beta\gamma}$ along the membrane
  - Leads to inhibition of adenyl cyclase, reduction in calcium currents
  - Deactivation of G-protein gated inward rectifying potassium channel
  - Eventual cellular hyperpolarization and thus cellular hyperpolarization

- However, different isoforms of G_a have been identified…

Bidlack JM, et al. J Pharmacol Exp Ther. 2018;367(2):267-281; Masuho I, et al. Sci Signal. 2015;8(405):ra123-ra123; Al-Hasani R, et al. Anesthesiology. 2011;115(6):1363-1381.

Theory 1: Varying Isoforms of G_α Subunits Allowing for Different Intrinsic Activities

Table 2. Comparison of buprenorphine and morphine activation of MOR via different G-proteins

Comparison of buprenorphine and morphine activation of MOR via different G-proteins[13]

	$G\alpha_{oA}$	$G\alpha_{oB}$	$G\alpha_{z}$	$G\alpha_{i1}$	$G\alpha_{i2}$	$G\alpha_{i3}$
Buprenorphine	87 percent	89 percent	92 percent	42 percent	12 percent	57 percent
Morphine	100 percent	100 percent	100 percent	95 percent	76 percent	93 percent

Bidlack et al. used Bioluminescence Resonance Energy Transfer to measure different Emax values from [^{35}S]GTPγS binding assays depending on the G-protein subunit activated at human MORs expressed on stable Chinese hamster ovary cells by buprenorphine or morphine.

Bettinger JJ, Himayapsill BQ, Cleary J. Journal of Opioid Management. 2021;17(7): 21-31

The Role of β-Arrestin

- β-Arrestin 1 and 2:
  - Proteins that normally bind phosphorylated G-protein-coupled MORs
  - Independent of intracellular cascade mentioned before

- β-Arrestin recruitment is associated with desensitization and sequestration of MORs

- Genetic disruption of β-Arrestin allowed for attenuation of respiratory depression and acute constipation caused by morphine
  - However, did NOT arrest anti-nociception

Raehal KM, et al. J Pharmacol Exp Ther. 2005;314:1195-1201
Bohn LM, et al. Science. 1999;286:2496-2488.

Theory 2: Buprenorphine Associated with Lower β-Arrestin Recruitment

- McPherson et al, Chen et al, Grinnell et al, Bidlack et al…
  - All four studies tested recruitment of β-Arrestin proteins by buprenorphine

- All four studies found little to no recruitment of β-Arrestin by buprenorphine

- Bidlack et al specifically found buprenorphine only mediated 33% β-Arrestin recruitment at MORs
  - Morphine mediated 85% recruitment

McPherson J, et al. Mol Pharmacol. 2010;78:756-766; Chen XT, et al. J Med Chem. 2013;56:8019-8031; Grinnell SG, et al. Synapse. 2016;70(10):395-407; Bidlack JM, et al. J Pharmacol Exp Ther. 2018;367(2):267-281.

Spinal Versus Supraspinal Differences

- Theoretically, analgesic effects of opioids may be mediated within various centers of the brain structure, as well as throughout the descending pain pathway of the spine and peripheral sites as well

- Comparatively, most opioid-related side effects rely on opioid binding and activating MORs within supraspinal (brain) structures
  - MORs within parabrachial nucleus and pre-Bortzinger complex → Respiratory depression
  - MORs within ventral tegmental area and nigrostriatal cortex → Euphoria
  - MORs within chemoreceptor trigger zone → Nausea/vomiting

Theory 3: Buprenorphine has Greater Spinal VS Supraspinal Activity

	Effects of Subcutaneous Buprenorphine	Effects of Subcutaneous Morphine	Effects of Subcutaneous Fentanyl
Pretreatment with Intraperitoneal Naloxone	Effects were antagonized	Effects were antagonized	Effects were antagonized
Pretreatment with Intrathecal Naloxone	Effects were antagonized	Effects were antagonized	Effects were antagonized
Pretreatment with Intracerebroventricular Naloxone	Effects were NOT antagonized	Effects were antagonized	Effects were antagonized

Intraperitoneal and intrathecal administration of naloxone were characterized as "spinal administration", while intracerebroventricular was characterized as "supraspinal administration".
Effects were measure by anti-nociception

Ding Z, Raffa RB. Br J Pharmacol. 2009;157:831-843.

Ok, So What About its Analgesic Efficacy?

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

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 ± 0.45mg PCA Morphine 72 ± 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

What About Dose Titrations????

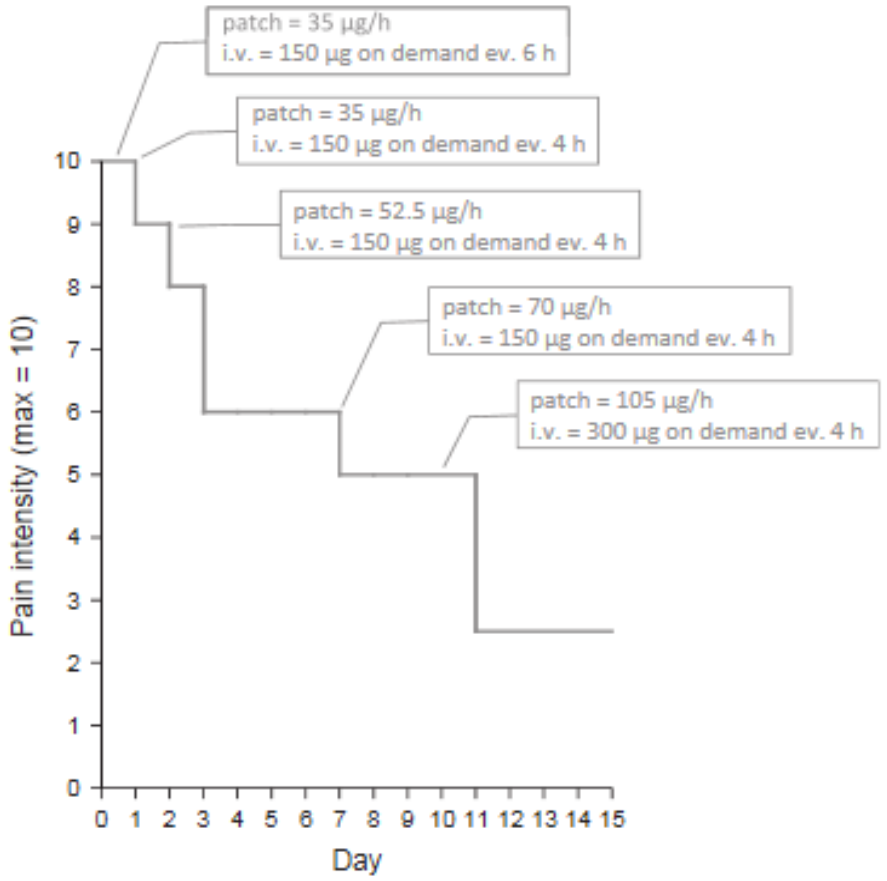


Fig. 5. Progressive increase in pain relief with increasing dose of buprenorphine in a terminally ill cancer patient with liver failure. Drawn based on the narrative in Ciccozzi *et al.*[39]

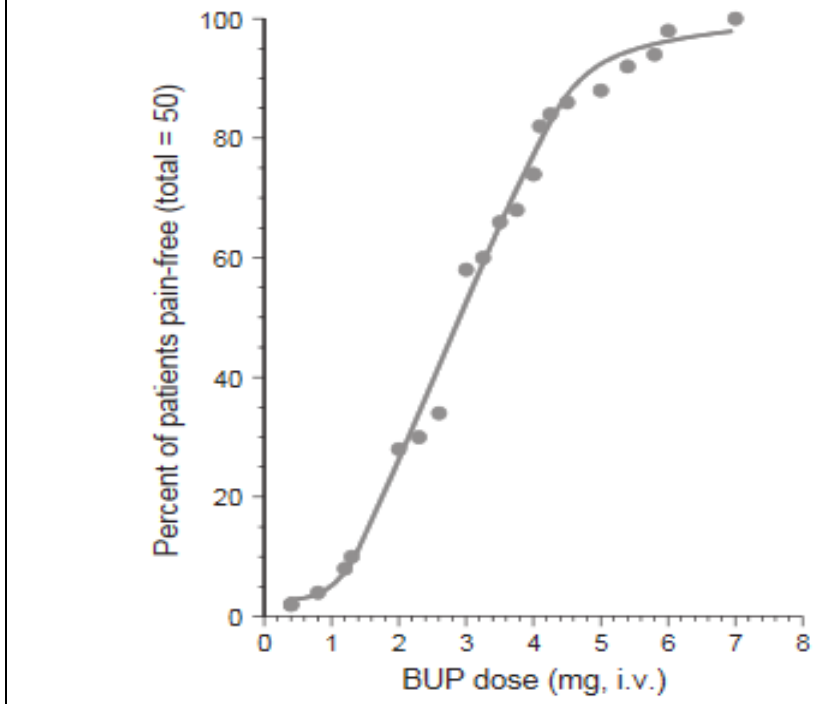


Fig. 6. The analgesic efficacy of i.v. buprenorphine was studied over a 24-h period in post-operative pain relief involving 50 patients (average age = 27·5 years) recovering from elective Caesarean section. Post-operatively, patients received buprenorphine in aliquots of 0·2 mg over 3–15 min, until the 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

What about Butrans and Belbuca?

- As shown in the table, transdermal buprenorphine has shown some direct, head-to-head clinical pain efficacy against full agonist opioids

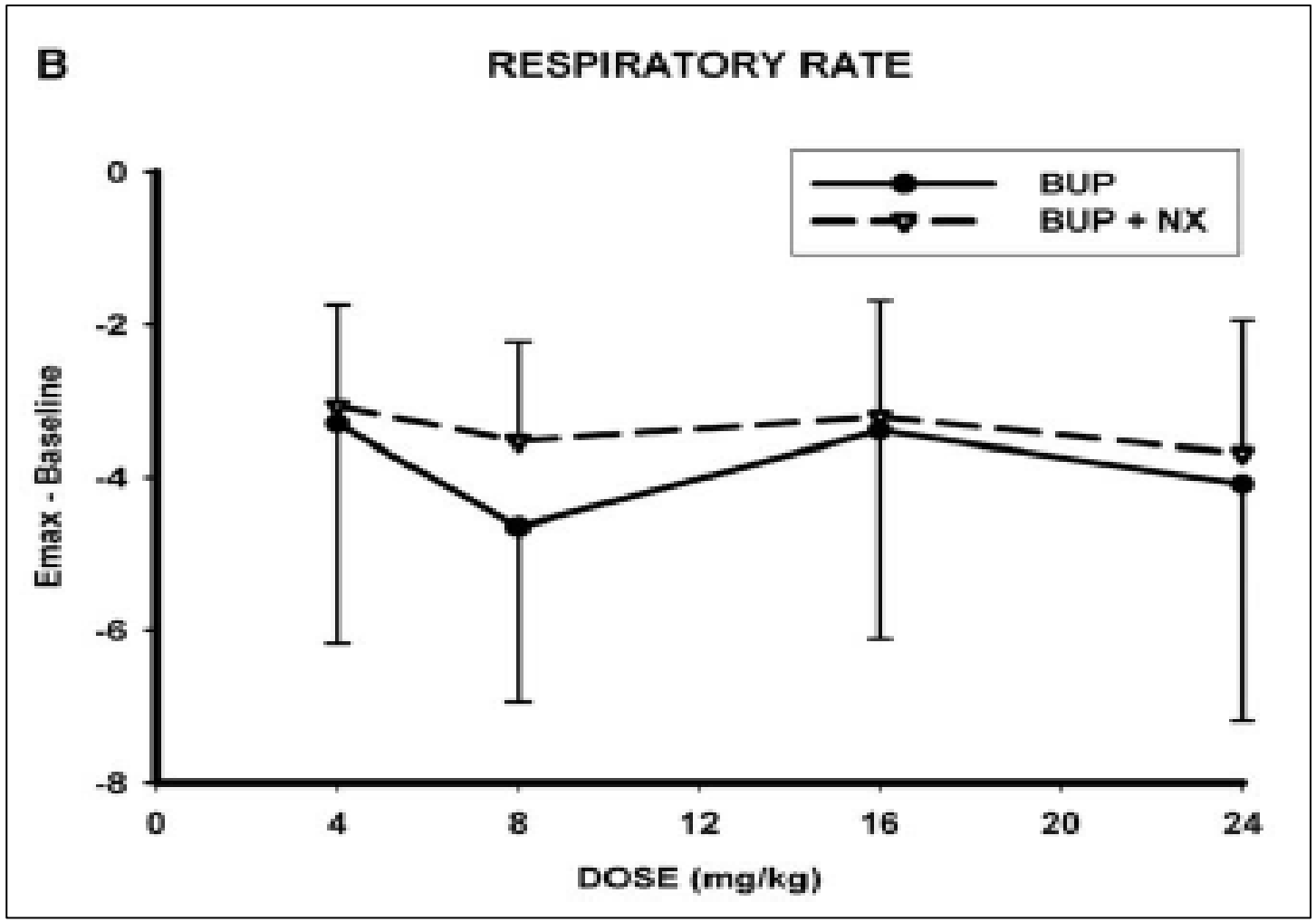
- There is no head-to-head data on Belbuca against full agonist opioids
    - However, evidence in opioid-experienced patients (≤ 160mg MMED) who were switched to and titrated on Belbuca allowed for reduction of pain to mild levels

- Higher allowable doses of Belbuca may allow for better pain effects than Butrans

Gimbel J et al. Pain. 2016;157(11):2517-2526.

What About Side Effects?

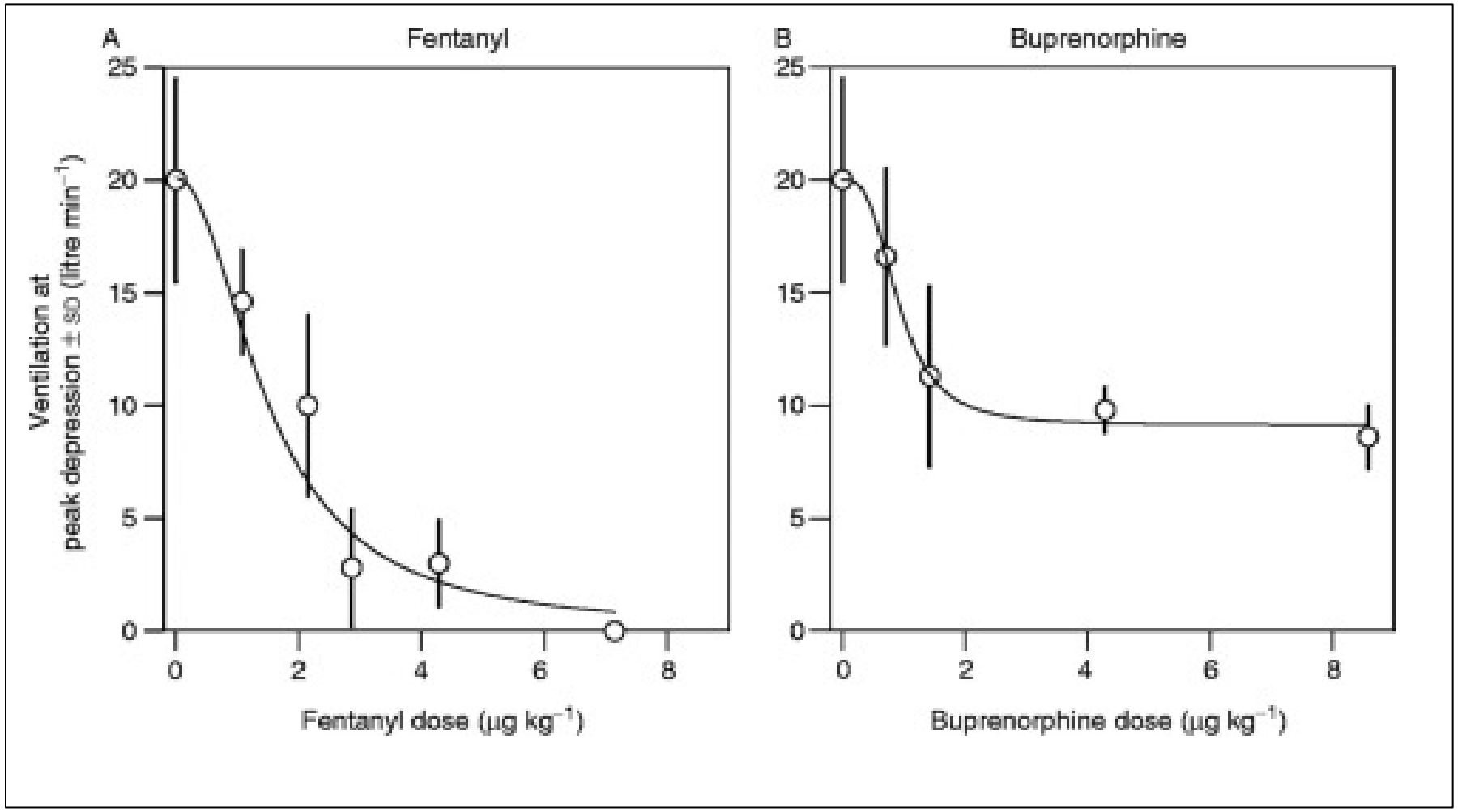
Respiratory Effects



Change in respiratory rate in humans from baseline of titrating doses of Suboxone, up to 24mg doses

Ciraulo DA et al. J Clin Pharmacol. 2006;46:179-192

Respiratory Effects



Minute ventilation at a fixed end-tidal after titrating doses of fentanyl and buprenorphine in humans

Dahan A et al. Br J Anaesth. 2005;94(6):825-834

Abuse Potential?

- Has been shown to elevate feelings of euphoria, well-being, and pleasure
    - Particularly intravenous buprenorphine
- Also has been shown to be self-administered above placebo levels in non-opioid-dependent, recently detoxified individuals
- Comer et al showed that in morphine-maintained heroin abusers, buprenorphine produced increases in positive subjective ratings of likability, HOWEVER:
    - Only opioid to produce statistically significant increases in ratings of **"I feel a bad drug effect"**
    - Only opioid **NOT** self-administered above placebo at any dose tested

Bigelow G et al. Br J Addict. 1991;86(12):1615-1623; Pickworth WB et al. Clin Pharmacol Ther. 1993;53(5):570-576;
Comer SD et al. J Pharmacol Exp Ther. 2002;303(2):695-703; Comer SD et al. Neuropsychopharmacology. 2008;33(5):1179-1191

Gastrointestinal Motility?

- Traditionally lower rates of constipation in trials compared to other opioids (1-5%)
- Tassinari et al showed that TDS buprenorphine was associated with significantly less constipation than equianalgesic doses of SA morphine
- Unlike many opioids, buprenorphine does NOT cause spasm of the sphincter of Oddi

Evans HC et al. Drugs. 2003;63(19):1999-2010; Likar R et al. Clin Ther. 2006;28(6):943-952; Wirz S et al. Eur J Pain. 2009;13(7):737-743; Tassinari D et al. 2008;11(3):492-501

Suppression of Hypogonadal Axis?

- Multiple studies have shown evidence of decreased effect on hypogonadal axis

- Hallinan et al showed that men on maintenance buprenorphine therapy compared to methadone had:
    - Higher testosterone levels
    - Less sexual dysfunction

- Wersocki et al found that transdermal buprenorphine:
    - Was not associated with changes in menstrual cycle in women
    - Was not associated with hormonal changes

Bilsener N et al. J Clin Endocrinol Metab. 2005;90(1):203-206; Hallinan R et al. Int J Androl. 2009;32(2):131-139; Hallinan R et al. J Sex Med. 2008;5(3):684-692; Wersocki E et al. Pain. 2017;158(1):8-16.

QTc Interval?

- Both Butrans and Belbuca have warnings regarding potential for QTc prolongation
    - Other formulations do not

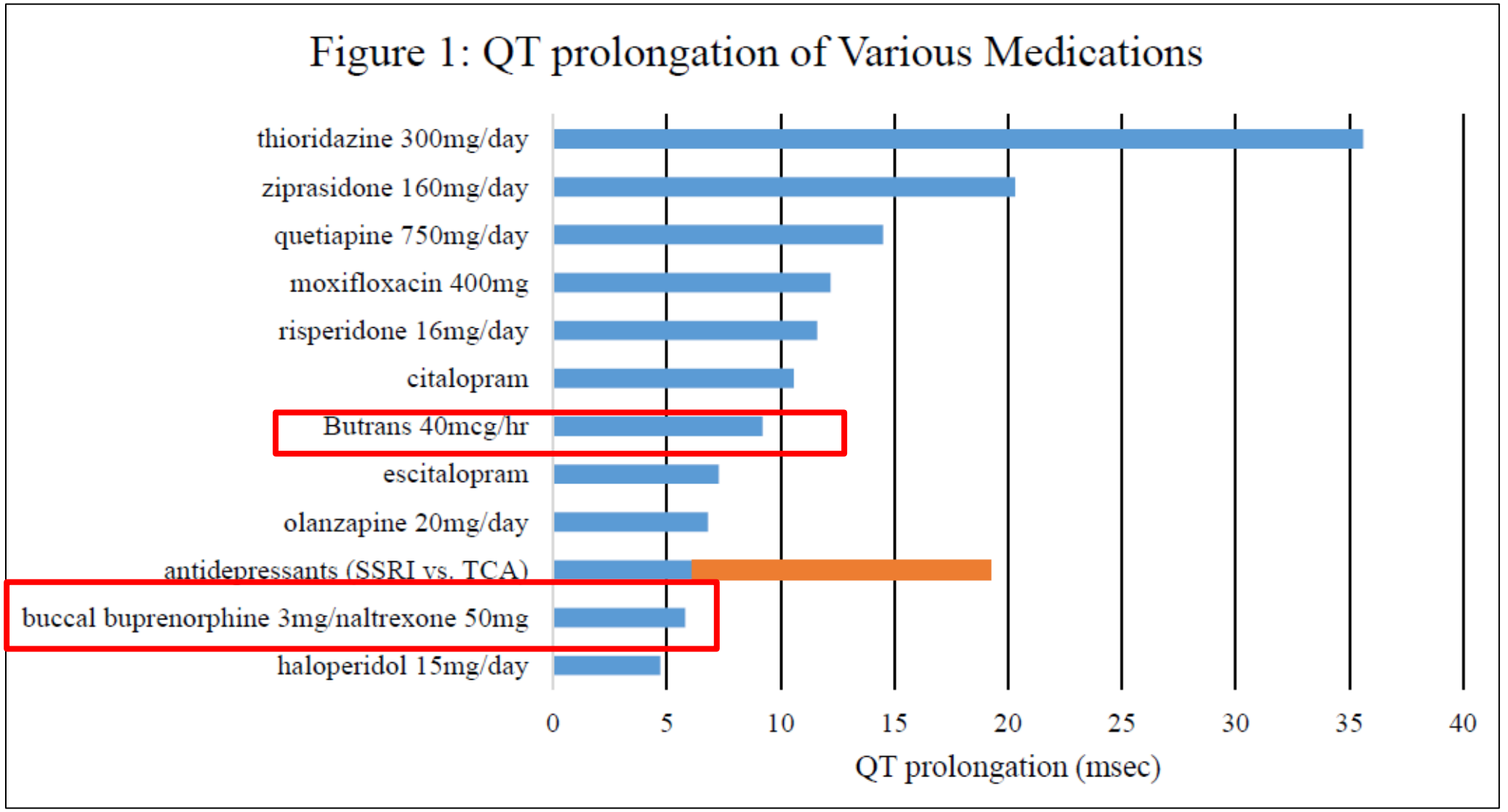
- Harris et al showed:
    - Butrans 10mcg/hr did **NOT** have clinically meaningful effect on mean QTc
    - Butrans 40mcg/hr resulted in a **MAXIMUM** QTc prolongation of 9.2 msec

- Per package insert, in doses of Belbuca up to 900mcg Q12H, 2% demonstrated prolonged QTc of 450-480 msec

- Several other studies have not found buprenorphine to be associated with QTc prolongation when used in opioid use disorder

Harris SC et al. Postgrad Med. 2017;129(1):69-80; Isbister GK et al. Br J Clin Pharmacol. 2017;83:2274-2282; Wedam EF et al. Arch Intern Med. 2007;167:2469-2475; Stallvik M et al. Drug Alcohol Depend. 2013;129:88-93; Fareed A et al. J Addict Dis. 2013;32:244-251

Comparison of QTc Prolongation of Various Medications



Figured obtained with permission from Dr. Jeff Fudin; available from: http://paindr.com/wp-content/uploads/2016/04/buprenorpehine-qtc.pdf

What Could be Buprenorphine's Niche?

Populations that Buprenorphine Could be Safer in than Other Opioids?

- Those at higher risk of respiratory depression?
    - Still a risk, especially with use of other depressant medications
- Those with a history of substance abuse?
    - What about current substance abuse?
- Those at higher risk of endocrine effects?
    - Osteopenia/osteoporosis
    - Hypogonadal disorders
- Prolonged QTc?

Ultimate Place in Therapy

- Would not recommend buprenorphine use over non-opioids for pain management
    - Still significant risks with use

- However, there appears to be evidence to suggest that opioid-related risks may be less than traditional MOR agonists
    - Also evidence that buprenorphine is as clinically effective as an analgesic

- Should it be used prior to consideration of any MOR agonist?
    - Probably

Butrans or Belbuca?

- Overall, Belbuca allows for increased amounts of systemic absorption of buprenorphine than Butrans
    - Therefore, probably better for those on higher doses of MOR agonists

- If considering for those opioid-naïve or those on lower doses of MOR agonists
    - Butrans could be used over Belbuca

- Butrans also may be easier for patients with compliance issues

Summary

- Buprenorphine has different pharmacologic and pharmacokinetic characteristics that allows it to be a unique option for treatment of chronic pain and/or opioid use disorder
- Clinical evidence suggest that although there appears to be a "ceiling effect" on certain opioid-related adverse events (respiratory depression, constipation), there does not appear to be this same effect on analgesia
- Its ultimate place in therapy for chronic pain has yet to be determined, however in the majority of cases, it should probably be considered over most other opioid-agonist medications (if they are appropriate)

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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Nursing Home and Partnership for Community Health:

CMS 12TH SOW GOALS ICONS FOR USE

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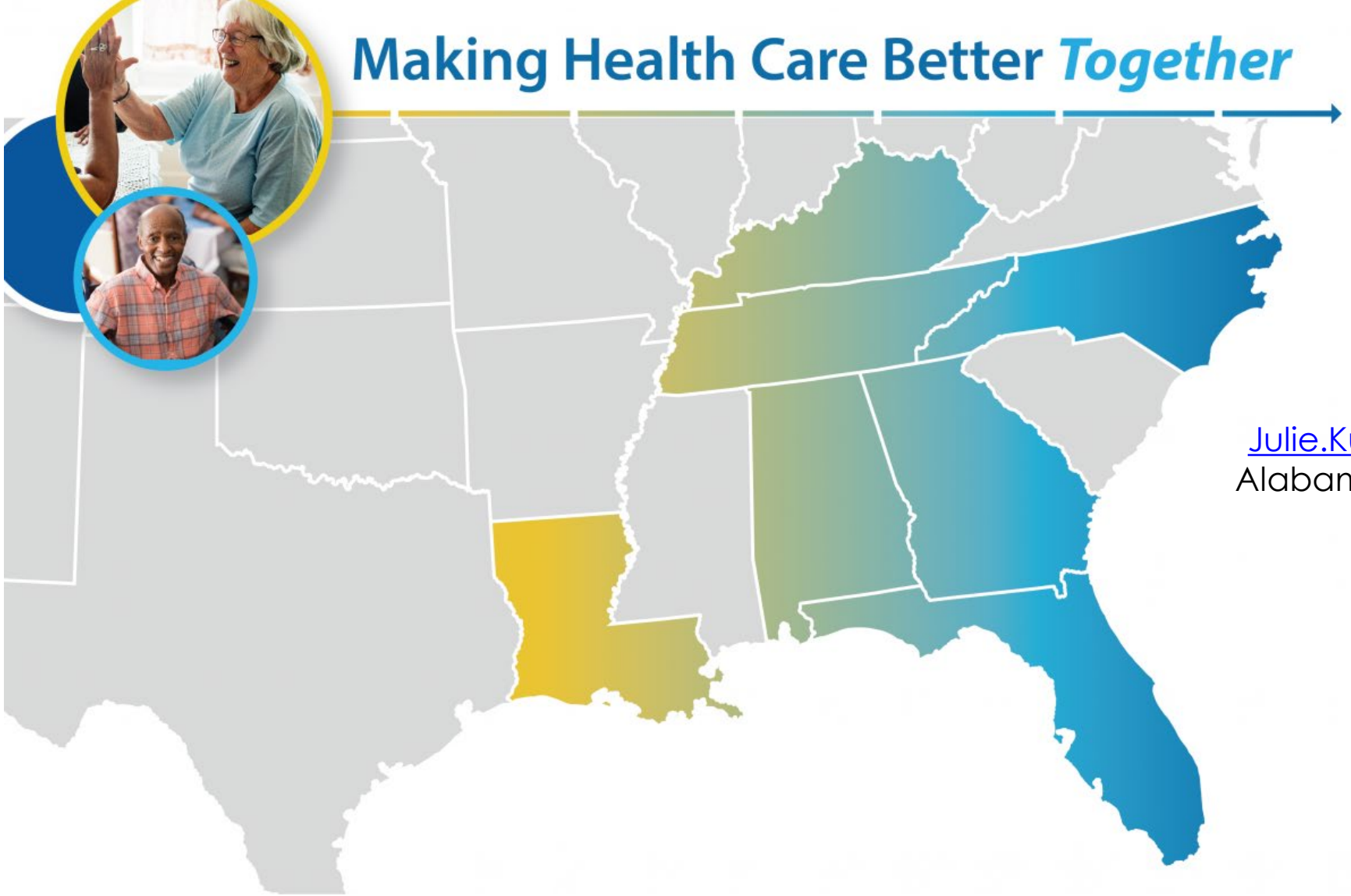

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