Scott M. Fishman, MD
University of California, Davis

Dr. Scott M. Fishman is the Fullerton Endowed Chair in Pain Medicine, Professor of Anesthesiology (primary) and Psychiatry (secondary), Executive Vice Chair for the Department of Anesthesiology at the University of California, Davis, and Director of the Center for Advancing Pain Relief at UC Davis. He is the founding Chief of the Division of Pain Medicine, a position he held for 20 years. His medical degree is from the University of Massachusetts Medical School. Formal clinical training is in Internal Medicine (Greenwich/Yale University School of Medicine) and Psychiatry (Massachusetts General/Harvard Medical School). He completed Pain Medicine fellowship training through the Department of Anesthesia and Critical Care at Massachusetts General Hospital. Dr. Fishman has received board certification in Internal Medicine (American Board of Internal Medicine 1995-2005), Psychiatry (American Board of Neurology and Psychiatry), Pain Medicine (American Board of Pain Medicine) and Palliative Medicine (American Board of Hospice and Palliative Medicine.)

Dr. Fishman is past president of the American Academy of Pain Medicine, past chairman of the board of directors of the American Pain Foundation, and previously served on the board of directors for the American Pain Society. He is the immediate past Chair and a current member of the Pain Care Coalition (American Society of Anesthesiologists, American Pain Society, & Academy of Pain Medicine). He has authored “The War on Pain” (Harper Collins Publishers), “Listening to Pain” (Oxford Univ. Press), Responsible Opioid Prescribing (Federation of State Medical Boards), and coauthored Spinal Cord Stimulation: Implantation Techniques (Oxford Univ. Press). He has also coedited Bonica’s Management of Pain 4th and 5th eds. (Lippincott), “The Massachusetts General Hospital Handbook of Pain Management 2nd edition” (Lippincott), and Essentials of Pain Medicine and Regional Anesthesia (Elsevir). Dr. Fishman has authored many peer-reviewed articles in medical journals, book chapters, and other scholarly reviews. He is senior editor of the journal Pain Medicine, and editor for Acute and Chronic Pain for UpToDate. He advocates for safe and effective use of pain treatments with physicians, consumers and lawmakers. He has led a national and international effort to transform pain education through developing and enacting core competencies for pain education.

Dr. Fishman has been honored with the University of California, Davis Dean’s Award for Excellence in Mentoring, the American Pain Society John and Emma Bonica Award for Public Service, the American Academy of Pain Medicine Award for Outstanding Contributions to the Social and Political Aspect of Pain Medicine, the National Pain Foundation Ambassador of the Year, The Head & Heart Award from the American Academy of Pain Management, the Washington, DC Capitol Hospice Josephina Magno Award for Excellence in Education and Leadership, the American Academy of Pain Medicine Public Service Award, the Federation of State Medical Boards Distinguished Service Award, the UC Davis Faculty Senate Public Service Award, and the American Pain Society Elizabeth Narcessian Award for Outstanding Educational Achievements in the Field of Pain. In 2015, the American Pain Society named the UC Davis Center for Pain Medicine a Center of Excellence and the American Academy of Pain Medicine named the UC Davis Center for Pain Medicine the recipient of their 2016 Award for Excellence in Fellowship Education. He was most recently honored with a 2017 Presidential Commendation from the American Academy of Pain Medicine.

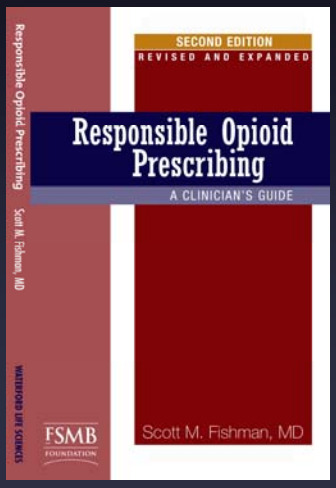
Stephen G. Henry, M.D.
University of California, Davis

Dr. Stephen Henry is a general internist and associate professor at University of California, Davis. He earned his medical degree from Vanderbilt University and completed residency and research training at the University of Michigan before joining UC Davis in 2012.

His research and teaching interests focus on developing strategies to improve patient-clinician communication, particularly around opioids and pain management. He currently leads NIH-funded research projects to encourage patient opioid tapering and to train primary care physicians to more effectively communicate about chronic pain and opioids.

Dr. Henry also leads several research projects involving the CURES database, including projects involving collaborations with the California Departments of Justice and Public Health to evaluate opioid prevention efforts in California.

Buprenorphine



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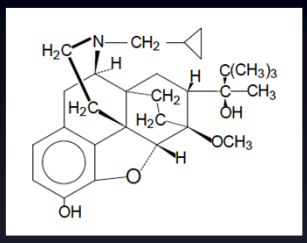
Disclosures

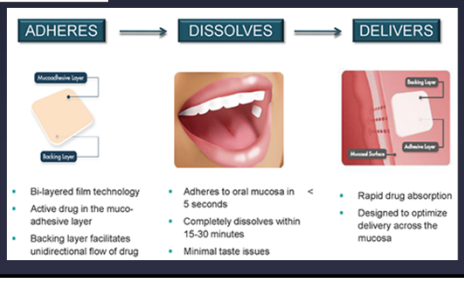
- I have NO Direct Financial Relationships with drug companies
- I receive NO compensation from industry speakers or consultation programs
- I participate in official CME programs (and receive honorarium and travel reimbursement)
- I receive payment from publishers of books and journals I have authored /edited
- I authored *Responsible Opioid Prescribing* by The Federation of State Medical Boards
- I am…
  - Past President of The American Academy of Pain Medicine
  - Past Chair of Board for The American Pain Foundation
  - Past Chair and current member of the Pain Care Coalition
    - [ASA, APS, AAPM]
- I am not a lawyer and do not offer legal advice

Buprenorphine

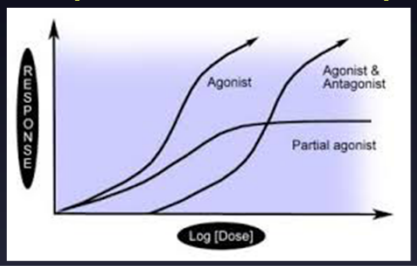


- Partial Mu Receptor Agonist –
  - High **affinity** but low intrinsic activity for the mu opiate receptors
  - Binds strongly but does not produce a full effect
- Weak Kappa Receptor Antagonist
- Misconceptions have limited its clinical use
  - Stigma – Indicated for Addiction Treatment
  - Analgesic ceiling effect?

Buprenorphine Preparations



Buprenorphine and Respiratory



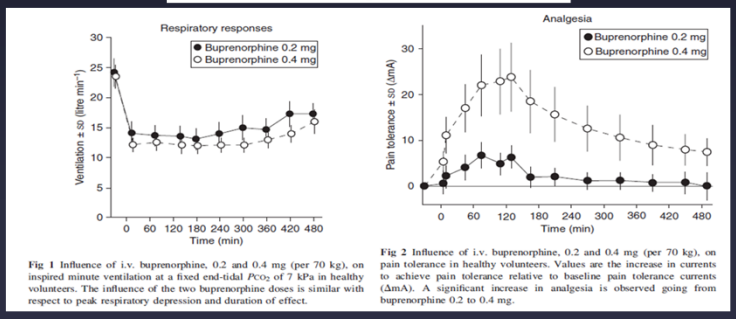


Fig 1 Influence of i.v. buprenorphine, 0.2 and 0.4 mg (per 70 kg), on inspired minute ventilation at a fixed end-tidal P_{CO_2} of 7 kPa in healthy volunteers. The influence of the two buprenorphine doses is similar with respect to peak respiratory depression and duration of effect.

Fig 2 Influence of i.v. buprenorphine, 0.2 and 0.4 mg (per 70 kg), on pain tolerance in healthy volunteers. Values are the increase in currents to achieve pain tolerance relative to baseline pain tolerance currents (ΔmA). A significant increase in analgesia is observed going from buprenorphine 0.2 to 0.4 mg.

Oxford Journals Medicine & Health BJA Volume 96, Issue 5Pp. 627-

Buprenorphine Advantages

1. Effective in Pain
2. Effective in Treating Neuropathic Pain
3. Treats a Broader Array of Pain Phenotypes Than other Certain Potent Mu Agonists
4. Associated With Less Analgesic Tolerance / hyperalgesia
5. Can Be Combined With Other Mu Agonists
6. Produces Less Constipation Than Other Potent Mu Agonists
7. Does Not Adversely Affect the Sphincter of Oddi
8. Ceiling Effect on Respiratory Depression

Buprenorphine Advantages

9. Less Cognitive Dysfunction Than Certain Other Opioids
10. Not Immunosuppressive
11. Does Not Adversely Affect the Hypothalamic-Pituitary-Adrenal Pathway or Cause Hypogonadism
12. Does Not Significantly Prolong the QTc Interval, and Is Associated With Less Sudden Death Than Methadone
13. Safest Opioid in Patients With Renal Failure and on Dialysis
14. Milder Withdrawal Symptoms and Less Drug Dependence


The New York Times

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When Children's Scribbles Hide a Prison Drug

Officer Paul Cabral at the Maine Correctional Center in Windham handing screened mail to an inmate. Subo... has changed how mail is handled.

By ABBY GOODNOUGH and KATIE ZEZIMA

Published: May 26, 2011


The New York Times

May 27, 2011

Subscribe (hint: the fish) was hidden in this coloring book.


The New York Times

HEALTH

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THE DOUBLE-EDGED DRUG

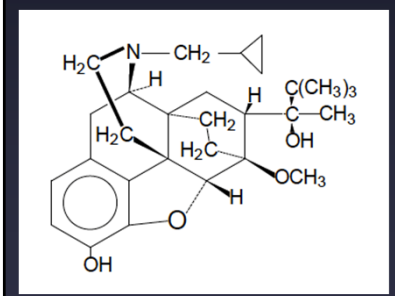
Addiction Treatment With a Dark Side

Is Demand in Clinics and on the Street, 'Bupe' Can Be a Savior or a Menace

THANK YOU

For a PDF File of these slides,
smfishman@ucdavis.edu

Buprenorphine



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Disclosures

- I have NO Direct Financial Relationships with drug companies
- I receive NO compensation from industry speakers or consultation programs
- I am principal investigator of research studies supported by the NIH, US Bureau of Justice Assistance, and the CDC.

Use of buprenorphine for opioid addiction treatment clearly prevents overdose deaths

Why Buprenorphine Is So Successful in Treating Opiate Addiction in France

In France, all registered medical doctors have been allowed to prescribe buprenorphine without any special education or licensing since 1995. This has led to a rapidly increasing number of opiate-dependent users under buprenorphine treatment in primary care.

Management of opioid addiction with buprenorphine: French history and current management

This policy has had a direct, positive impact on the number of deaths caused by heroin overdose, which was reduced by four-fifths between 1994 and 2002. In addition, certain associated

In order to treat with MAT in an outpatient office setting, a physician needs a DATA-waiver.

The most common way to obtain a waiver ("X-license") is to take an additional 8-hour training

- **This is a major barrier to MAT**

California does not have enough DATA-waivered physicians to meet demand for MAT

As of 2016, approximately 200,000 Californians with opioid use disorder lack access to local treatment via buprenorphine or methadone.

https://www.urban.org/policy-centers/health-policy-center/projects/california-county-fact-sheets-treatment-gaps-opioid-agonist-medication-assisted-therapy-oa-mat-and-estimates-how-many-additional-prescribers-are-needed

Federal code provides 8 pathways to obtain a DATA 2000 waiver

I. Board certification in addiction psychiatry or addiction medicine from ABMS

II. Addiction certification or board certification from ASAM or American Board of Addiction Medicine

III. Board certification in addiction medicine from American Osteopathic Association

21CFR §823(g) 2G(iii)

Federal code provides 8 pathways to obtain a DATA-waiver

IV. Complete an 8-hour training provided by ASAM, AAAP, AMA, AOA, APA, or other organizations that the Secretary determines is appropriate. Standard 8-hour waiver training

V. Participated as an investigator in clinical trial(s) leading to the approval of a narcotic drug in schedule III, IV, or V for maintenance or detoxification treatment.

21CFR §823(g) 2G(iii)

Federal code provides 8 pathways to obtain a DATA-waiver

VI. Has other such training or experience as the state medical licensing board (of the state in which the physician will provide treatment) considers to demonstrate the ability of the physician to treat and manage opiate-dependent patients

This Pathway Would Include the MBC

21CFR §823(g) 2G(iii)

Federal code provides 8 pathways to obtain a DATA-waiver

VII. Has other training or experience as the Secretary considers to demonstrate the ability of the physician to treat and manage opiate-dependent patients.

VIII. Graduated in good standing during 5-year period immediately preceding date on which physician submits to the Secretary a written notification and successfully completed a comprehensive curriculum.... [*new pathway-SUPPORT Bill 2018*]

21CFR §823(g) 2G(iii)

Rhode Island has used pathway VI to increase number of DATA-waivered physicians in that state

Brief Report: Access to Treatment for Opioid Use Disorders: Medical Student Preparation

Elinore F. McCance-Katz, MD, PhD,[1,2] Paul George, MD, MHPE,[1] Nicole Alexander Scott, MD, MPH,[1,3] Richard Dollase, EdD,[1] Allan R. Tunkel, MD, PhD,[1] James McDonald, MD, MPH[3]

[1]The Warren Alpert Medical School of Brown University, Providence, Rhode Island
[2]Rhode Island Department of Behavioral Healthcare, Developmental Disabilities and Hospitals, Cranston, Rhode Island
[3]Rhode Island Department of Health, Providence, Rhode Island

Arizona is also pursing pathway VI to increase state capacity for MAT

- Arizona schools (MD, DO, NP, PA, ND, DMD) wrote a voluntary statewide curriculum on pain and addiction that covered all required elements of pathway VI
- Currently developing a SOP whereby AZ medical and osteopathic boards will certify graduates of schools that have implemented the statewide curriculum

Graduating students as automatically eligible for the waiver is a game changer

Eliminates the barrier to the DATA-waiver

- It could increase the number of persons prescribing and interested in MAT
- It destigmatizes the diagnosis and treatment of chronic pain and opioid use disorder
- It entices medical schools to use curricula that meet the UC pain and addiction competences

Limitations

- Pathway VI would only work for trainees that stay in California.
- If someone left California, they would technically need to get a new DATA-waiver

University of California Opioid Curriculum Workgroup

- Formed in 2018 by UCOP
  - Includes representatives from all UC medical schools
- Tasked with formulating a shared UC curriculum around opioids, pain, and substance abuse
- Multiple phone and in person meetings throughout 2018 and 2019

University of California Opioid Curriculum Workgroup

- *Recommend that all graduates of UC medical schools and residency programs receive training that meets federal requirements for obtaining a DATA-waiver*
- Adding an opioid-related case into 4th year student OSCEs required for medical school graduation

University of California Opioid Curriculum Workgroup

- Created a set of competencies now endorsed by Deans of UC medical schools.
- Competencies will guide undergraduate and graduate training
  - Builds on existing competency frameworks
  - Includes sections on *pain*, *substance use disorder*, and *public health*

MBC should consider using pathway VI to expand MAT access and increase consumer safety

- *Training that addresses the new UC competencies would easily meet federal requirements for DATA-waver training.*
- If MBC certifies that a school's curriculum meets requirements for pathway VI
  - Students would automatically be eligible for a DATA-waiver if they pursue residency in California (once they have a license)

MBC should consider using pathway VI to expand MAT access and increase consumer safety

- Rhode Island created an educational license category and developed a standardized procedure whereby graduating students were licensed with a DATA-waiver (and thus eligible to provide MAT) on day 1 of residency.
- New CA educational license process may allow for a similar process in California

Thank you

Questions:

sghenry@ucdavis.edu

REVIEW

Twelve Reasons for Considering Buprenorphine as a Frontline Analgesic in the Management of Pain

Mellar P. Davis, MD, FCCP, FAAHPM

ABSTRACT Buprenorphine is an opioid that has a complex and unique pharmacology which provides some advantages over other potent mu agonists. We review 12 reasons for considering buprenorphine as a frontline analgesic for moderate to severe pain: (1) Buprenorphine is effective in cancer pain; (2) buprenorphine is effective in treating neuropathic pain; (3) buprenorphine treats a broader array of pain phenotypes than do certain potent mu agonists, is associated with less analgesic tolerance, and can be combined with other mu agonists; (4) buprenorphine produces less constipation than do certain other potent mu agonists, and does not adversely affect the sphincter of Oddi; (5) buprenorphine has a ceiling effect on respiratory depression but not analgesia; (6) buprenorphine causes less cognitive impairment than do certain other opioids; (7) buprenorphine is not immunosuppressive like morphine and fentanyl; (8) buprenorphine does not adversely affect the hypothalamic-pituitary-adrenal axis or cause hypogonadism; (9) buprenorphine does not significantly prolong the QTc interval, and is associated with less sudden death than is methadone; (10) buprenorphine is a safe and effective analgesic for the elderly; (11) buprenorphine is one of the safest opioids to use in patients in renal failure and those on dialysis; and (12) withdrawal symptoms are milder and drug dependence is less with buprenorphine. In light of evidence for efficacy, safety, versatility, and cost, buprenorphine should be considered as a first-line analgesic.

Buprenorphine was originally developed as an analgesic, and is a semisynthetic thebaine derivative that has a unique cyclopropylmethyl group also classified as an oriparvine derivative of morphine.[1,2] It has been available in a parenteral formulation since 1981 in the United States. Sublingual tablets are now available in certain countries and are licensed for analgesia. However, in the United States, sublingual buprenorphine is licensed only for addiction maintenance therapy.[3] Buprenorphine in a transdermal delivery system preparation (TDS buprenorphine) is available in the United States and Europe for moderate pain; it is available only in Europe for severe pain. The transdermal formulation has buprenorphine embedded in an acylated benzyl acetate polymer matrix that prevents dose dumping.[4,5]

Buprenorphine has a unique and complex pharmacology. It is classified as a partial agonist in vitro by activation of the pertussis toxin–sensitive G protein, and as a full analgesic agonist clinically. The published conversion ratio between oral morphine and TDS buprenorphine ranges from 75:1 to 115:1.[6,7] Buprenorphine is nearly as potent as fentanyl.[7–10]

Buprenorphine activates a distinct subset of the G protein, different from what is activated by morphine, fentanyl, and methadone.[11–14] Downstream from receptor activation, buprenorphine interacts with adenyl cyclase in a timeframe that differs from methadone. (Activation of the adenyl cyclase is associated with analgesic tolerance and withdrawal.)[15] Buprenorphine is a kappa receptor antagonist; unlike morphine and fentanyl, it acts as a "chaperone" ligand, which means that buprenorphine increases mu receptor expression on membrane surfaces.[10,16,17] Buprenorphine is also an opioid receptor–like 1 (ORL1) agonist that has a unique interaction with pain processing. Activation of the ORL1 receptor in the dorsal horn is analgesic, but cerebral ORL1 activation blunts antinociception as seen in animal models. Paradoxically, ORL1 also blocks analgesic tolerance.[1,18] ORL1 blunts the rewarding effects of potent opioids as seen in morphine-tolerant animals; ORL1 agonists block conditioned place preference.[19–21]

Dr Davis is at the Cleveland Clinic Lerner School of Medicine at Case Western University, and the Palliative Medicine and Supportive Oncology Services in the Division of Solid Tumor Oncology at the Taussig Cancer Institute of the Cleveland Clinic, Cleveland, Ohio.

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The availability of sublingual buprenorphine is 30%–50% and the availability of buccal buprenorphine is 28%, relative to parenteral buprenorphine. Terminal half-life of sublingual buprenorphine is long, relative to parenteral administration, because of the sequestration of the drug in oral mucosa and buccal fat.[22–24] Sublingual buprenorphine blood levels peak at 2 hours, then rapidly decline for 6 hours, and finally slowly decline over 24 hours.[25] The prolonged terminal half-life is in part due to enterohepatic recirculation. Buprenorphine is largely excreted in the stool.[26,27] The main metabolite of buprenorphine, norbuprenorphine, is generated through the cytochrome CYP3A4. Buprenorphine and its metabolites do not inhibit cytochromes at therapeutic doses, and as a result have few drug interactions.[28,29] Buprenorphine and norbuprenorphine are rapidly conjugated by UGT2B7 and UGT1A1 in the liver. Although both conjugations are rate limiting to buprenorphine metabolism, they are relatively spared in liver disease; as a result, buprenorphine is relatively safe in mild to moderate liver failure.[30–34] Buprenorphine-3-glucuronide and norbuprenorphine-3-glucuronide blood levels can exceed the parent drug levels. Buprenorphine-3-glucuronide in vitro is a mu, delta, and ORL1 agonist, whereas norbuprenorphine-3-glucuronide is a kappa and ORL1 ligand. Neither buprenorphine nor the glucuronide metabolites reduce respiratory rates, although norbuprenorphine-3-glucuronide has been demonstrated to reduce tidal volume in animal models.[35,36]

Norbuprenorphine is a weak mu agonist. Pharmacokinetic/pharmacodynamic studies performed in rats have found norbuprenorphine to be responsible for respiratory depression. However, norbuprenorphine rarely exceeds 10% of buprenorphine blood concentrations, well below levels associated with respiratory depression in normal human volunteers.[37] Norbuprenorphine activation of mu receptors appears to be responsible for respiratory depression.[38]

The usual parenteral/TDS buprenorphine dosage for cancer pain ranges from 35 mcg/hour to 70 mcg/hour, but dosages greater than 210 mcg/hour have been used without a ceiling effect on analgesia. Equivalent sublingual doses are 1.6 mg to 3.2 mg daily if a 50% bioavailability is assumed.[39]

There are limitations to the present opioids commonly used for pain (fentanyl, oxycodone, morphine, hydromorphone, and methadone). Opioid-related side effects limit titration; common titration-limiting side effects include nausea, vomiting, and cognitive dysfunction. Physicians greatly fear respiratory depression and often fail to titrate doses for that reason.[40] Individuals often do not respond to the first opioid, and require a second opioid that is non–cross-analgesic tolerant.[41] Potent opioids can have unusual adverse effects, such as hypogonadism, which can lead to loss of libido; long-term effects include osteoporosis and loss of muscle mass.[42] Opioids that are metabolized through cytochromes will have altered pharmacokinetics resulting in liver failure.[43] Accumulation will lead to delayed toxicity; certain opioids that are conjugated will accumulate in renal failure.[44] When swallowing is no longer possible, having transdermal and sublingual routes of administration improves patient compliance and facilitates continued analgesia.[45] Having both routes as options will reduce the need for computerized activated delivery devices (CADD pumps) and syringe drivers for parenteral opioid delivery, as well as their associated technical problems.[46–48] Buprenorphine has the potential to address many of these problems.

REASONS FOR CONSIDERING BUPRENORPHINE AS A FRONTLINE ANALGESIC FOR CANCER PAIN

1. Buprenorphine Is Effective in Pain

Large numbers of cancer and noncancer patients with pain have been treated with buprenorphine.[49–55] Starting doses for severe pain have ranged from 35 mcg/hour (74%) to 52.5 mcg/hour (21%) to 70 mcg/hour (5%). Pain severity on average decreases from 62 mm on the visual analogue scale to 16 mm (range, 0 = no pain, 100 mm = severe pain) over a 2-week period. On average, 85% of patients experience pain relief in the range of good to very good. Sleep quality improves in 48% of individuals, and only 3% discontinue buprenorphine.[50,51] The great majority of patients like the convenience of a transdermal patch. Sublingual and parenteral formulations have also been effectively used for chronic cancer pain with the same benefits as transdermal buprenorphine.[49,52–59] Based upon the number of studies and individuals treated with buprenorphine, the evidence of benefit is equivalent to that of morphine, hydromorphone, oxycodone, fentanyl, and methadone.[46–51]

A low dose of buprenorphine has been used in the opioid-naive individual who has moderate pain. The starting dose was 17.5 mcg/hour (that is, one-half of a 35-mcg/hour patch) or 0.8 mg of sublingual buprenorphine. Pain intensity was reduced by 1 week. Dose adjustments occurred over 4 weeks, with dose increases up to 41%, on average. Pain control could be achieved as early as 1.5 days after starting a low dose of TDS buprenorphine. In addition, improvement in patients' quality of life has been reported.[60] An expert consensus panel concluded that buprenorphine is a valuable treatment for chronic cancer pain and its neuropathic component.[39] In a systematic review of the efficacy and safety of buprenorphine, fentanyl, and morphine in pain management, transdermal fentanyl was associated with greater nausea (odds ratio [OR], 4.66), a significant higher rate of discontinuation because of adverse events (OR, 5.94), and a nonsignificant difference in analgesia. In comparison with morphine, transdermal buprenorphine reduced pain intensity to a greater degree (mean difference, −16.20 by visual analogue scale) whereas morphine caused more constipation (OR, 5.63), nausea (OR, 4.23), vomiting (OR, 15.85), and increased treatment discontinuation because of adverse effects (OR, 4.26).[61]

2. Buprenorphine Is Effective in Treating Neuropathic Pain

Both central sensitization and peripheral neuropathy activate rostral ventromedial medulla "on" cells, which facilitates pain through the dorsal lamina funiculus.[62] There is a close

association between peripheral neuropathy and loss of conditioned pain modulation known as diffuse noxious inhibitory control (DNIC).[63] When ORL1 receptors are activated, "on" cells and pain-facilitation pathways are blocked.[64,65] In animal models, buprenorphine is fully effective in producing antinociception for neuropathic pain.[9,66,67]

In human experimental pain, buprenorphine – unlike other potent mu agonists – blocks secondary hyperalgesia from central sensitization.[65–68] There is some evidence that certain potent mu agonists actually increase secondary hyperalgesia.[69] Morphine has been known to inhibit diffuse noxious inhibitory control (DNIC) as has buprenorphine. Interference with DNIC may contribute to the analgesia in neuropathic pain or be a mechanism of hyperalgesia.The issue is controversial.[70–74] Neuropathic pain is associated with loss of pertussis toxin–sensitive G-protein activity.[75] Morphine analgesia is highly dependent on pertussis toxin–sensitive G protein, whereas buprenorphine analgesia is not highly dependent on pertussis toxin–sensitive G proteins.[11,76,77] Buprenorphine has successfully treated neuropathic pain.[52,66,67,78–80] In 2 case series, buprenorphine has produced responses where transdermal fentanyl failed to do so.[52,81] In this small group of patients, buprenorphine potency was greater than anticipated, with an oral morphine–to–transdermal equianalgesia of 110:1 to 115:1. In addition, 40% of individuals with various central neuropathic syndromes (usually considered refractory to opioid analgesia) responded to buprenorphine. Starting doses were low (8.75 mcg/hour) and were titrated.[82] In a double-blind, randomized study involving patients with post-thoracotomy pain, intravenous (IV) buprenorphine was effective in reducing pain.[83] Response rates are as high as 69% with doses from 35 mcg/hour to 70 mcg/hour. A consensus panel stated that although there are no randomized control trials comparing buprenorphine with other opioids, there is significant evidence that buprenorphine effectively relieves neuropathic pain.[16,67] More studies are needed to identify neuropathic syndromes that are responsive to buprenorphine, and randomized studies are needed to compare those responses to buprenorphine vs responses to other opioids.[67]

3. Buprenorphine Treats a Broader Array of Pain Phenotypes Than Do Certain Potent Mu Agonists, Is Associated With Less Analgesic Tolerance, and Can Be Combined With Other Mu Agonists

Animal models have demonstrated that buprenorphine reduces pain from a variety of mechanisms, including formalin injection, cold temperature tail flick, and DNIC tests.[67] A comparison of buprenorphine vs. fentanyl with human volunteers and different pain phenotypes found that buprenorphine was effective in a larger number of pain phenotypes than was fentanyl. Buprenorphine attenuated experimental bone pain, heat pain, pain related to nerve growth–factor injections, and cold pressor pain, whereas fentanyl at equal analgesic doses was effective only in attenuating cold pressor pain.[84] A similar but less dramatic finding has also been reported by another researcher but with less differences between fentanyl and buprenorphine.[85] The differences between the studies may be related to design and outcome measures. However, there is evidence of a distinctively different tissue-differentiating effect and pain-phenotype response between buprenorphine and fentanyl.

Analgesic tolerance to opioids seems to be related to a number of mechanisms. Dynorphin, an endogenous kappa agonist, is upregulated by morphine, and paradoxically promotes central sensitization.[86] Buprenorphine reduces opioid tolerance by blocking kappa receptors. Morphine impairs DNIC in a naloxone-reversible manner and thus facilitates pain via bulbospinal pathways.[70,71,74,87] Buprenorphine blocks secondary hyperalgesia and central sensitization to a greater extent than do other mu agonists, possibly through ORL1 receptors.[65] Chronic opioids (morphine and methadone) cause a selective increased sensitivity to cold pressor pain, which is less so with buprenorphine.[88]

Buprenorphine produces less analgesic tolerance than does fentanyl, as measured by an opioid escalation index in a retrospective study involving nearly 900 cancer and noncancer patients.[7] Non–cross-tolerance between opioids is seen with rotations between fentanyl and buprenorphine.[89] Buprenorphine has been successfully combined with morphine and tramadol without loss of analgesia.[90–93] Supra-additive analgesia is reported with the combination of buprenorphine plus oxycodone or hydromorphone; additive analgesia has been reported with morphine.[10,94–96] Despite its high affinity for the mu receptor, buprenorphine occupies fewer receptors for analgesia, which leads to a significant receptor reserve for other mu agonists.[97] Buprenorphine increases mu receptor expression, which allows other mu agonists to interact with receptors.[97] Future studies will need to confirm combination therapy and the role of buprenorphine in opioid rotation.

4. Buprenorphine Produces Less Constipation Than Do Certain Other Potent Mu Agonists, and Does Not Adversely Affect the Sphincter of Oddi

Buprenorphine-related constipation in large longitudinal or pooled randomized trials has ranged from 1% to 5%.[98–100] Other studies have not verified the relatively low rate of constipation associated with buprenorphine, but conversion ratios were different from what are usually reported in the literature.[101] Cancer patients often have a variety of causes for constipation other than opioids, which may falsely increase the reported frequency of constipation with buprenorphine. In a meta-analysis of randomized, controlled trials, TDS buprenorphine and fentanyl were each associated with significantly less constipation than were equianalgesic doses of sustained-release morphine (OR, 0.38).[102]

Spasm of the sphincter of Oddi may be one of the causes of colic associated with opioids. Unlike other opioids, buprenorphine does not cause spasm of the sphincter of Oddi.[103,104] Therefore, in addition to NSAIDs (nonsteroidal anti-inflammatory drugs), buprenorphine should be considered in the management of biliary colic and/or pancreatitis.

5. Buprenorphine Has a Ceiling Effect on Respiratory Depression

Respiratory depression occurs in approximately 1% to 11% of individuals receiving systemic or spinal opioids. The frequency is dependent upon the definition of respiratory depression (which varies, depending on whether it is defined in terms of respiratory rate, carbon dioxide levels, or hypoxia).[105] For most opioids, the risk is greater for patients who receive a background infusion with demand patient-controlled analgesia and in those receiving high doses of opioids except for buprenorphine. Populations who are at risk for respiratory depression include the morbidly obese, those with sleep apnea (central rather than obstructive), those with neuromuscular diseases, the very old, the very young, and the very ill.[105]

Buprenorphine is unique in that it has a dose-ceiling effect on respiratory depression, but not on analgesia. The relative safety increases with dose titration.[106–109] In an animal model that used 80% of the LD_{50} dose (that is, the dose that would be lethal to half of the subjects); buprenorphine only slightly reduced arterial oxygen pressure (PaO_2), whereas fentanyl, morphine, and methadone caused significant carbon dioxide (CO_2) retention. Methadone, fentanyl, and morphine reduced the time in expiration, whereas buprenorphine did not.[110] Respiratory depression associated with buprenorphine is related to its metabolite, norbuprenorphine, and not to the parent drug; paradoxically, buprenorphine prevents and reverses respiratory depression in rats that are given lethal injections of norbuprenorphine.[111] In a study that compared the safety index of buprenorphine with fentanyl using pharmacokinetic/pharmacodynamic data, the OR of analgesia to respiratory depression was narrower (1.2) with fentanyl than with buprenorphine, which was 10-fold greater (14).[112] Buprenorphine's mild to minimal respiratory depression is adversely influenced by the addition of benzodiazepines or alcohol.[36,113–115] This interaction is both pharmacodynamic and pharmacokinetic.[116,117] However, the combination of buprenorphine plus benzodiazepine is safer than is the methadone-benzodiazepine combination.[118] Those with liver disease are at a particular risk for a respiratory depression with the combination of buprenorphine plus a benzodiazepine.[119–121]

Case reports found no respiratory depression in patients who had attempted suicide and were being treated with buprenorphine doses as high as 88 mg.[122] In human volunteers, fentanyl had a linear dose-related analgesia and respiratory depression without a ceiling effect on either outcome; buprenorphine had a linear analgesic effect and improved cutaneous pain 3-fold when doses were increased from 3 mcg/kg to 6 mcg/kg, but had no additional effect on respiration.[108] Similar results have been observed in other pharmacokinetic/pharmacodynamic studies of fentanyl and buprenorphine in normal human volunteers.[37] Doubling buprenorphine doses from 0.2 mg/70 kg to 0.4 mg/70 kg in healthy volunteers remarkably improved tolerance to transcutaneous electrical stimulation pain (from 29% to 160% above baseline) without changing minute ventilation.[107] Doses as high as 1,600 mcg/hour or 32 mg of sublingual buprenorphine daily have not produced respiratory depression.[123,124]

Buprenorphine is one of the safest analgesics to use in individuals who are at risk for respiratory depression; however, it should not be combined with benzodiazepines, particularly in individuals with liver disease. In the rare circumstances in which respiratory depression does occur, 2 mg of naloxone should be given as a bolus, followed by 2 mg to 4 mg of naloxone infused over 90 minutes because of the high receptor affinity and the long half-life of buprenorphine.[105] Most of the data have been derived from the perioperative setting and from normal volunteers. Further studies are needed in cancer patients and in those with severe illness.

6. Buprenorphine Causes Less Cognitive Dysfunction Than Do Certain Other Opioids

Opioids can impair cognition and driving ability. Increased motor vehicle accidents have been reported in individuals on methadone or buprenorphine maintenance therapy (OR, 2). Other factors common to addiction (such as impaired reliability and risk-taking behaviors) can contribute to cognitive dysfunction and impair driving ability.[125] Patients on chronic opioids demonstrate an increased impulsiveness and reduced ability to comprehend instructions.[126] Several studies have demonstrated that opioids in stable doses do not necessarily impair complex activities such as driving ability; however, because of intraindividual variability in opioid responses and other confounding factors (eg, pain intensity, comorbidity), a judgment regarding driving ability must be made on an individual basis.[127] The addition of alcohol or a sedative to opioid maintenance therapy will impair driving ability.[128,129] Various tests have been performed to gauge driving ability. Individuals on buprenorphine (8 mg daily) have been compared with those on morphine (average dosage, 348 mg daily). Those on buprenorphine had better visual pursuit test results.[130] There was less impairment on certain portions of the driving-related psychomotor battery in individuals who were on buprenorphine, compared with those on methadone maintenance.[131,132] In 2 studies, it was shown that a group of patients who had chronic pain and received sustained treatment with transdermal fentanyl or buprenorphine performed significantly better in tests than did healthy persons with a legally relevant 0.05% concentration of blood alcohol.[133] Patients receiving a stable dosage of sublingual buprenorphine (7.3 mg +/− 3.9 mg daily) showed no significant impairment of complex psychomotor or cognitive performance, compared with healthy controls.[134] Compared with healthy opioid-naive controls, individuals on TDS buprenorphine were noninferior when they were tested for attention, reaction time, visual orientation, motor coordination, and vigilance.[135] Buprenorphine has been reported to have lower psychomotor side effects than does fentanyl, and to have side effects similar to those of placebo.[10,53,98,136]

7. Buprenorphine Is Not Immunosuppressive

There is a bidirectional communication between the brain and the immune system that is modulated by opioids.[137] Exogenous opioids are immunosuppressive, whereas endogenous opioids stimulate the immune system. In the late 19th century, morphine was used to suppress cellular immunity and to lower resistance in guinea pigs, which were used as an experimental model for infection.[138] Most potent opioids reduce antibody production, reduce natural killer cell activity, and impair the cytokine expression and phagocytic activity of white cells.[138–140] Both morphine and fentanyl are examples of immunosuppressive analgesics.[141,142] Immunosuppression is potentiated by exogenous corticosteroids, the coadministration of other immunosuppressive medications, and chemotherapy.[2,143] The cause of immunosuppression is through activation of the mu receptor within the central nervous system, which activates the sympathetic system and increases cortisol.[137,144–149] Tolerance develops over time to the immunosuppression associated with morphine and fentanyl.[150,151] Immunosuppression is also generated independent of mu receptor activation, and is not reversed by naltrexone or standard doses of methylnaltrexone.[146,152]

Pain, cancer, and surgery reduce and impair natural killer cell activity, and are associated with poorer outcomes in multiple common cancers.[153–158] In animal models, morphine is associated with increased morbidity and mortality from infection and cancer.[140] Paradoxically, the use of opioids after surgical injury in experimental animals reduces metastatic spread of cancer and reduces the adverse effect of surgery on natural killer cell function.[159–164] However, in 2 retrospective studies, the use of patient-controlled analgesia with morphine was associated with increased relapse rates in breast cancer patients post mastectomy and in prostate cancer patients post radical prostatectomy, compared with spinal local anesthetics.[165,166]

Unlike morphine, when buprenorphine is injected into the periaqueductal gray it does not reduce natural killer-cell function, increase cortisol, reduce adrenocorticotropic hormone levels, or alter norepinephrine or serotonin levels.[148,167] Unlike morphine and fentanyl, buprenorphine does not increase metastases in natural killer-cell–sensitive tumors when it is injected into animals.[147] Chronic buprenorphine does not adversely influence antimicrobial responses or tumor surveillance, in contradistinction to fentanyl.[140,151] Buprenorphine maintenance therapy also restores immune function in heroin addicts.[168,169] Recovery of immune function may be, in part, related to morphine abstinence.

Most of the studies regarding buprenorphine and the lack of immunosuppression have been conducted in animal. It is unclear whether the immunosuppression of most opioids is clinically relevant. Future studies will be needed to demonstrate either reduced infection or altered course of cancer with buprenorphine. However, it is good practice to avoid such opioids in patients who are already immunosuppressed by disease or therapy. Buprenorphine should be a consideration in this group of patients.[143,170]

8. Buprenorphine Does Not Adversely Affect the Hypothalamic-Pituitary-Adrenal Pathway or Cause Hypogonadism

Chronic use of most potent mu agonists is associated with hypogonadotropic hypogonadism, loss of libido, and fatigue.[171] Over time, hypogonadism can lead to osteopenia and loss of muscle mass. Medication exposures associated with osteoporosis risk include opioids, glucocorticoids, and antidepressants.[172] In animals, morphine and fentanyl rapidly reduces diencephalon testosterone levels, which does not occur with buprenorphine.[173] Because morphine and fentanyl reduce testosterone levels, testosterone replacement is frequently required to improve sexual function and quality of life.[174,175] When men on buprenorphine maintenance therapy are compared with those on methadone, those on buprenorphine have higher testosterone levels and less sexual dysfunction.[176–178] Lower testosterone levels were associated with a higher body mass index (calculated as the weight in kilograms divided by height in meters squared) and greater depression as reported in 2 studies.[177,178] TDS buprenorphine in women relieves pain without inducing hypogonadism, lowering testosterone levels, or influencing menstrual cycles or follicle-stimulating hormone, luteinizing hormone, or estrogen levels.[179]

Even in high doses, buprenorphine will minimally influence sexual hormone levels. As a result, it will have less of an adverse effect than will other potent mu agonists (such as morphine and fentanyl) on psychological function, libido, muscle mass, and bone mineral density. There are 3 nonrandomized studies that have provided data about buprenorphine and gonadal function[177–179]. More prospective data are needed.

9. Buprenorphine Does Not Significantly Prolong the QTc Interval, and Is Associated With Less Sudden Death Than Is Methadone

Methadone has been associated with a prolonged QTc interval and torsades de pointes, which are the assumed mechanism for sudden cardiac death. Recommendations for screening have been recently published.[180] Prolongation of the QTc interval greater than 500 ms increases the risk of torsades de pointes and sudden cardiac death. The prevalence of a prolonged QTc in methadone-maintained individuals is nearly 29%, with approximately 5% having a QTc interval greater than 500 ms. The risk of a prolonged QTc is particularly high when doses were greater than 120 mg daily. In contrast to methadone; buprenorphine at maintenance doses is not associated with a prolonged QTc interval.[181–183] Sudden cardiac deaths occur 4 times more frequently with methadone maintenance than with buprenorphine maintenance, which suggests less cardiac toxicity. All of these studies were done in individuals on maintenance therapy and not in those on buprenorphine for pain. Buprenorphine doses for maintenance therapy are usually higher than they are for analgesia; however, advanced cancer patients are on multiple medications, which may influence repolarization.[184] Such studies

need to be done in those with advanced cancer or serious illnesses.

10. Buprenorphine Is a Safe and Effective Analgesic for the Elderly

The elderly (those aged 65 years and older) frequently suffer from pain syndromes related to arthritis, diabetes, and neurologic and cardiovascular diseases as well as cancer.[185] Chronic pain in the elderly is frequently undertreated, and analgesics have a narrower therapeutic index secondary to reduced organ function and alterations in drug pharmacodynamics.[186–188] Certain analgesics such as NSAIDs are not recommended for use in the elderly.[189] Drug-drug interactions are more common in the elderly because of polypharmacy.

Several retrospective studies have reported the use of buprenorphine in the elderly.[16,52–54] A prospective observational study found that buprenorphine was equally effective for those aged 65 years and younger, those between 65 and 75 years, and those aged 75 years or older.[190] Responses were from 64% to 68%. Sleep improved in 60% to 65% of respondents, as did quality of life. Adverse events did not increase with age. A similar study demonstrated the same benefits of buprenorphine in those aged 65 years and older.[52] In addition, this study found no difference in efficacy in those aged 65 years and older, compared with those aged 50 years and younger. Other studies found that there was no increased toxicity in the elderly[99] and no dose adjustment needed.[191] Buprenorphine pharmacokinetics are not altered with age.[10] For all opioids except buprenorphine, drug half-life and the half-life of active metabolites are increased in the elderly and those with reduced renal function.[16] Buprenorphine interacts differently with CYP3A4 than does methadone, and is also rapidly conjugated. Drugs that block CYP3A4 do not appear to significantly influence buprenorphine pharmacokinetics.[3,192] Drug-drug interactions through cytochrome P450 enzymes are common in elderly patients who are on multiple medications.[193] Buprenorphine and its active metabolite are rapidly conjugated, and glucuronidation is associated with few drug interactions.[194] Buprenorphine is the only potent opioid that is not associated with an increased fracture risk in elderly individuals.[195] By consensus, buprenorphine is recommended as a first-line opioid in the elderly.[16] However, more studies of buprenorphine in the elderly need to be done. Most of the experience has been retrospectively derived.

11. Buprenorphine Is the Safest Opioid to Use in Patients With Renal Failure and in Those on Dialysis

Buprenorphine clearance is largely through the gastrointestinal tract; elimination is not influenced by renal function.[26,27,100,191,196–198] There is no change in pain rating or blood levels of buprenorphine or norbuprenorphine in individuals on hemodialysis.[197] Buprenorphine is one of the safest opioids to use in those whose renal function is worsening or unstable. Because buprenorphine has a ceiling effect on respiratory depression and is relatively safe in hepatic failure, it is an excellent analgesic to use in the intensive care setting or in the face of multiple-organ failure.

12. Patients Have Milder Withdrawal Symptoms and Less Drug Dependence With Buprenorphine

Buprenorphine selectively dampens central sensitization. Central sensitization is one of the mechanisms behind opioid withdrawal.[9,65,199] In addition, buprenorphine has a long half-life; its prolonged binding to the mu receptor dampens withdrawal mechanisms and delays withdrawal to more than 72 hours after discontinuation.[27,200,201] Buprenorphine produces fewer rewarding effects than do other potent mu agonists, and it blocks psychological dependence.[124,201–203] Buprenorphine can precipitate withdrawal in individuals on high doses of other potent mu agonists.[201] A single dose of buprenorphine can precipitate withdrawal in individuals on larger doses (100 mg) of methadone.[204] Splitting doses (ie, giving multiple small doses rather than a single large dose) minimized subjective withdrawal. Doses of a buprenorphine-naloxone combination (ranging from 1 mg:0.25 mg to 16 mg:4 mg, respectively) have been given to individuals who are also on hydromorphone (40 mg/day) as maintenance therapy without subjective withdrawal.[205] Heroin addicts can undergo rapid buprenorphine titration without withdrawal.[206,207] Individuals on lower doses of methadone (from 25 mg to 45 mg) who are switched to buprenorphine (2 mg to 4 mg) will not experience withdrawal.[208] With maintenance therapy, a gap (4 to 6 hours for short-acting opioids, 24 hours with high doses of methadone) is recommended between stopping the first opioid and starting buprenorphine to avoid inducing withdrawal. These conversion gaps are based on maintaining addiction therapy and managing withdrawal symptoms, rather than on providing analgesia.[209–212] Options when managing individuals might involve starting with a low-dose of buprenorphine and overlapping with the first opioid which is then weaned over several days, or provide a gap between opioids to allow the levels of the first opioid to fall before starting buprenorphine.[213] There are no clinical studies where buprenorphine was used as an analgesic to give guidance to the proper approach to converting to buprenorphine when individuals are on high doses of potent mu agonists such as morphine, hydromorphone, fentanyl or methadone. On the other hand, intravenous buprenorphine has been used to treat withdrawal in medically ill, hospitalized heroin addicts. Symptoms of withdrawal were decreased when buprenorphine was used to manage withdrawal; its use resulted in neither respiratory depression nor a psychological high.[214] Buprenorphine is better than clonidine in managing withdrawal symptoms; symptoms resolve more quickly when buprenorphine rather than methadone is used to manage withdrawal.[215]

CONCLUSION

In the past, morphine has been considered the opioid of choice for moderate to severe pain, largely based on efficacy. However, no objective criteria have been established as a reference for choosing opioids for pain. Additional criteria

include versatility, safety, tolerability, and cost.[216] Buprenorphine has several advantages over other potent mu agonists. Besides being effective, it is uniquely antihyperanalgesic, lacks respiratory depression, is not immunosuppressive, and does not produce hypogonadism. There is less cognitive impairment than with certain other opioids. It is not cardiotoxic, is safe to use in renal failure, and is relatively safe in hepatic failure. Buprenorphine has few drug interactions and is versatile in its routes of administration. Other than methodone, it is one of the few long-acting sublingual potent mu agonists, which is an advantage if patients are unable to swallow or suffer from nausea and vomiting. The average wholesale price for sublingual buprenorphine in the Cleveland area is approximately half that of sustained-release oxycodone, and is equal to that of the analgesic dose of the fentanyl transdermal patch. In the United States, commercial low-dose TDS buprenorphine is expensive, compared with the equivalent sublingual dose. In Germany, according to a Markov model, TDS buprenorphine was more cost effective per quality-adjusted life-year gained than were TDS fentanyl and sustained-release oxycodone for chronic pain.[217] Buprenorphine is not a drug to be used for spinal analgesia, but this is also true for fentanyl and other lipophilic opioids because of their rapid redistribution and lack of regional confinement. It is therefore reasonable to consider buprenorphine as a first- or second-line potent analgesic based on clinical circumstances. More studies are needed to compare buprenorphine with other opioids that have not only analgesia as outcomes, but also various side effects including cognitive effects, immunosuppression, hypogonadism, substance abuse, and addiction. Buprenorphine needs to be tested in individuals with well-defined pain phenotypes, as most studies have included individuals with poorly defined phenotypes or with various pain syndromes.

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Brief Report: Access to Treatment for Opioid Use Disorders: Medical Student Preparation

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The current opioid epidemic requires new approaches to increasing access to treatment for patients with opioid use disorders and to improve availability of medication assisted treatment. We propose a model where medical students complete the necessary training to be eligible for the waiver to prescribe opioid medications to treat these disorders by the time of medical school graduation. This plan would increase the number of Drug Abuse Treatment Act of 2000 (DATA 2000) waivered physicians who could gain additional experience in treating substance use disorders during residency and provide the access to clinical care needed for individuals suffering with opioid use disorder. (Am J Addict 2017;26:316–318)

Opioid use disorder and overdose deaths continue to be one of the major public health issues in the United States. In 2014 there were over 29,000 accidental overdose deaths with opioids, in the form of prescription opioid analgesics and heroin, being the major sources of morbidity and mortality.[1] Treatment access for opioid use disorders continues to be a challenge, with states having far fewer physicians available and willing to provide medication assisted treatments such as buprenorphine products[2] and injectable naltrexone than needed for the affected population. Methadone is also an effective pharmacotherapy for opioid use disorder, but its utilization is often limited by the requirement that it be administered through programs that are strictly regulated at both the federal and state level.[3]

Currently, most physicians obtain a waiver to prescribe medications on Schedules III, IV or V specifically approved by the US Food and Drug Administration (FDA) for the treatment of opioid use disorders through a requirement outlined in DATA 2000 of at least 8 hours of training endorsed by one of several national stakeholder groups.[4] However, while approximately 33,000 physicians have obtained this waiver, less than half offer this treatment to patients, although the reasons for this are likely multifaceted. Physicians may lack confidence to take on the challenges of patients with active opioid use disorder including co-occurring mental illness and/or other co-occurring substance use disorders (SUDs) and potentially, liability concerns with only 8 hours of training. Despite the availability of national training and mentoring programs such as the Providers' Clinical Support System for Medication Assisted Treatment (PCSS-MAT, www.pcssmat.org) there may be a sense of a lack of a support system for providers to assist with patients having these greater needs. It is also possible that some physicians may simply decide upon exposure to training that this is not a practice in which they wish to engage which may be influenced by the unfortunate stigma that surrounds opioid use disorder. Whatever the reason(s), the reality is that Americans with opioid use disorders have great difficulty finding evidence-based, medication treatment for their disorder.

This situation requires that novel approaches be considered for management of opioid use disorders and we provide one such concept. DATA 2000 contains a clause that allows states to determine what training would qualify for a waiver to prescribe opioids for opioid use disorders in their jurisdictions. Specifically, the law states that one means of becoming a "qualifying physician" includes the requirement that "the physician has such other training or experience as the State medical licensing board (of the State in which the physician will provide maintenance or detoxification treatment) considers to demonstrate the ability of the physician to treat and manage opiate-dependent patients."

The Warren Alpert Medical School of Brown University has engaged in a partnership with the Rhode Island Department of Health to offer a comprehensive addiction medicine/psychiatry curriculum that is deemed by the Rhode Island Board of Medical Licensure and Discipline to qualify for the waiver

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necessary to prescribe approved opioids for the treatment of opioid use disorder. This curriculum has been developed to provide medical students with a comprehensive training experience on the spectrum of substance misuse and use disorders and includes a component specifically focusing on clinical use of buprenorphine for the treatment of opioid use disorder to address the additional requirements of a DATA waiver training. It spans the entire 4 years of medical school with 3 hours of classroom didactics providing an overview of the assessment and treatment of substance use disorders; training on behavior change, screening, brief intervention and referral to treatment (SBIRT); and use of the opioid overdose antidote naloxone in years 1 and 2. In years 3 and 4, a case-based approach is taken for training on pain management including assessment and appropriate use of opioid and non-opioid alternatives and implementation of SBIRT (Table 1).

TABLE 1. Alpert Medical School, Brown University Substance Misuse Curriculum Outline

Pre-clerkship years (MS I and II)	Clerkship and clinical years (MS III and IV)
Doctoring I and II (Year I) Introduction to behavioral change counseling (1 h) Substance use counseling/behavior change practice (2 h) All students must screen at least five patients for substance abuse disorders; those who screen positive will receive brief intervention and referral for treatment; students must document (2 h)	Family medicine clerkship All students must screen at least five patients for substance use disorders; those who screen positive will receive brief intervention and referral for treatment; students must document (2 h) Completion of Family Medicine Computer Assisted Simulations for Educating Students (fmCASES) modules on chronic pain (1 h)
Integrated medical sciences (Year I) Lectures on substance use disorders and their treatment (3 h total including 1 h on opioids)	Internal medicine clerkship All students must screen at least five patients for substance use disorders; those who screen positive will receive brief intervention and referral for treatment; students must document (2 h)
Doctoring III and IV (Year 2) All students must screen at least five patients for substance use disorders; those who screen positive will receive brief intervention and referral for treatment; students must document (2 h)	Emergency medicine elective Training on SBIRT for all 4th year medical students, including simulation cases (Elective)
Interprofessional Education Workshop (Year I); four stations: Panel with individuals affected by substance use disorders and providers (1 h) Standardized patient case to perform SBIRT in interprofessional education teams (1 h) Naloxone training (preceded by training on http://prescribetoprevent.org/; 1 h in person; 1 h online preparation) Case study; interprofessional development of care plan with consideration of diverse medical problems (HIV, hepatitis) and social challenges that impede medical care such as homelessness, stigma, and lack of social support (1 h)	4th year OSCE case on SBIRT (4th year; all students) (0.5 h)
Clinical skills clerkship (Transition between Years II and III) Lecture on pain management/opioids and alternatives to opioids (1 h) Small group cases on pain management/opioids/opioid alternatives (1.5 h)	
Prior to 4th year Objective Structured Clinical Examination (OSCE): Lecture on medication assisted treatment: Clinical use of buprenorphine in the treatment of Opioid Use Disorder (1 h)	

Patient simulations provide practical experience in the evaluation and management of substance-related conditions in the fourth year. Each year, students are required to use SBIRT skills to assess five patients for hazardous substance use. In year 4, a 1 hour lecture with a focus on clinical use of buprenorphine is presented. The total number of hours of training completed by all graduating medical students is 24 which is far in excess of the 8 hours required by DATA 2000. This course of study provides the necessary preparation for the graduating physician to qualify for a waiver in Rhode Island upon meeting the additional two requirements generally obtained in residency training of a full medical license and a DEA registration for prescribing controlled substances.

This mechanism for DATA waiver qualification applies only to physicians practicing in Rhode Island. However, the Rhode Island Department of Health will be reaching out to other states to encourage them to consider partnering with medical schools in their states to certify addiction medicine curricula that would qualify for a DATA waiver. States could then agree to provide reciprocity for medical students who have obtained similar training from a medical school in a different state. This would allow physicians to prescribe approved opioids to treat opioid use disorder in the state in which they undertake residency training and/or choose to practice following completion of residency. Similarly, states might also collaborate with nurse practitioner and physician assistant training programs to certify a curriculum that would lead to eligibility for a DATA waiver in their states now that Congress has passed legislation expanding the provider base for the prescribing of these medications.

Effectively addressing the opioid epidemic requires urgent action and novel thinking. Congress has given the tools in DATA 2000 and in the Comprehensive Addiction and Recovery Act[5] legislation to rapidly increase the number of buprenorphine providers in the United States. We have described a novel approach to obtaining the DATA waiver for young physicians. Going forward, additional curriculum could also be developed to complement this training if a significant period of time passes between completing the medical school curriculum and treating patients with opioid use disorder in practice. Making addiction medicine a standard part of medical school curriculum helps to normalize this area of practice and may contribute to reduction in stigma and increased likelihood that physicians will engage in the treatment of opioid use disorder. It is up to leadership in the medical professions to help to curb this epidemic through training that will result in large numbers of clinicians able and willing to provide care to their patients struggling with opioid use disorder.

Declaration of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

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Domain	Sub-domain	Competency
Pain	**What is Pain?** Multi-dimensional nature of pain	Describes the complex, multidimensional, and individual-specific nature of pain[1a]
		Describes how cultural, institutional, societal, and regulatory influences affect assessment and management of pain[1a]
		Demonstrates knowledge of the theories and science for understanding the physiology of pain and pain transmission[1a]
		Demonstrates knowledge of the terminology for describing pain, including acute, chronic, and pain at the end of life[1a]
	How is pain assessed? Pain assessment and measurement	Uses a biopsychosocialspiritual model to evaluate persons with pain[2a]
		Describes patient, clinician, and system factors that can facilitate or interfere with effective pain assessment and management[1a]
		Recognizes patient preferences and values to determine pain-related goals and priorities, including quality of life [1a]
		Uses valid and reliable tools for measuring pain, function, and associated symptoms to assess and reassess related outcomes appropriate to the clinical context and population[1a]
		Uses and models language that destigmatizes pain, reflects a whole-person perspective, builds a therapeutic alliance, and promotes behavior change[1a]
		Demonstrates use of proper patient assessment, including physical exam and history, when treating pain[3a]
		Demonstrates empathic, compassionate and professional communication during pain assessment[1]
		Evaluates a patient's pain using culturally appropriate evidence-based methodologies and considering age and gender[4a]
	How is pain treated (safely and effectively)?	Uses a biopsychosocialspiritual model to develop a whole-person care plan and prevention strategies for persons with pain[2a]
		Demonstrates knowledge of risk stratification, patient selection, and ongoing monitoring for pharmacological pain treatment[5]
		Differentiates between physical dependence, substance use disorder, misuse, tolerance, and nonadherence in patients[1]
		Identifies appropriate multimodal pain treatment options as part of a comprehensive pain management plan[1a]
		Identifies and describes potential pharmacological and non-pharmacological treatment options [4a]
		Develops a treatment plan that takes into account the differences between acute pain, acute-on-chronic pain, chronic/persistent pain, and pain at the end of life[1]
		Develops a pain treatment plan based on benefits and risks of available treatments[1a]
		Demonstrates the inclusion of the patient and others, as appropriate, in the shared decision-making process for pain care[1]
		Monitor the effects of pain management approaches to adjust the plan of care as needed, with respect to functional outcomes[1a]
		Empowers patients to recognize and apply health promotion and self-management strategies[2a]
	How is pain affected by context?	Describes the unique pain assessment and management needs of special populations[1]
		Describes the role, scope of practice, and contribution of the different professions within multidisciplinary pain management care teams[1a]
		Demonstrates how to assess and manage pain across settings and transitions of care[1a]
		Recognizes the role of the clinician as an advocate in assisting patients in meeting treatment goals including recognizing own and societal bias against patients with chronic pain. [1]
		Utilizes an individualized pain management plan (including risk mitigation) that integrates the perspectives of patients, family and social support systems, and clinicians in the context of available resources[1]

Competencies are taken directly from: 1= North American Pain Competencies, 2 = Arizona Pain and Addiction Curriculum, 3 = Pennsylvania State Core Competencies for Education on Opioids and Addiction, 4 = Massachusetts Medical Education Core Competencies for the Prevention and Management of Prescription Drug Misuse, 5 = Specific Disciplines Addressing Substance Use: AMERSA in the 21st Century – 2018 Update

Competencies are adapted from: 1a= North American Pain Competencies, 2a = Arizona Pain and Addiction Curriculum, 3a = Pennsylvania State Core Competencies for Education on Opioids and Addiction, 4a = Massachusetts Medical Education Core Competencies for the Prevention and Management of Prescription Drug Misuse, 5a = Specific Disciplines Addressing Substance Use: AMERSA in the 21st Century – 2018 Update

Domain	Sub-domain	Competency
Substance Use Disorder	**What is SUD?**	Describes the interrelated nature of pain and opioid use disorder, including their neurobiology [2a]
		Demonstrates knowledge of the pathophysiology of substance use disorders[5]
		Recognizes the spectrum of and differences between substance use, misuse, use disorders, physical dependence, tolerance, withdrawal, and pain[1a,5a]
		Identifies the impact of substance (alcohol, cannabis, tobacco, opioid, sedative, and stimulant) use on health. [5]
	How is SUD assessed?	Uses a biopsychosocialspiritual model to screen for and evaluate persons with substance use disorder[2a]
		Recognizes and stratifies patient risk for opioid use disorder and other adverse effects, including overdose[4a,5a]
		Demonstrates sufficient knowledge to perform proper assessment, diagnosis, and referral for treatment of substance use disorder[3,5]
		Demonstrates empathic and compassionate communication during SUD assessment[1a]
		Uses and models language that destigmatizes addiction, reflects a whole-person perspective, builds a therapeutic alliance, and promotes behavior change[4a,5a]
	How is SUD treated (safely and effectively)?	Uses a biopsychosocialspiritual model to develop a whole-person care plan for persons with substance use disorder[2a,4a]
		Recognizes signs and symptoms of controlled substance overdose and demonstrates fundamental knowledge of management strategies[4a]
		Displays knowledge of substance use disorder treatment, including pharmacologic (opioids, nicotine, and alcohol use disorder), behavioral and social options, using a chronic disease model. [4a,5a]
		Demonstrates effective communication skills in counseling patients and families on the use of medical therapies
		Uses an integrated, team-based approach to substance use disorder treatment[2a,5a]
		Engage patients who use drugs in harm reduction and other secondary prevention interventions to reduce morbidity[5]
		Engages patients' family and social support in the care of substance use disorder[2a]
	How is SUD affected by context?	Recognizes their own and societal biases and stigmatization against patients with substance use disorders, including barriers faced by special populations[4a,5a]
		Identifies and incorporates relevant data regarding social determinants of health into treatment planning for substance use disorders[4a]
		Identifies strategies to mitigate the risk of substance use disorder and promote wellness in clinicians
		Critically evaluates systems and seeks evidence-based solutions that deliver quality care in the treatment of substance use disorders[2a]

Competencies are taken directly from: 1= North American Pain Competencies, 2 = Arizona Pain and Addiction Curriculum, 3 = Pennsylvania State Core Competencies for Education on Opioids and Addiction, 4 = Massachusetts Medical Education Core Competencies for the Prevention and Management of Prescription Drug Misuse, 5 = Specific Disciplines Addressing Substance Use: AMERSA in the 21st Century – 2018 Update

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Domain	Sub-domain	Competency
Public Health	**Lessons learned from the opioid epidemic**	Describes the impact of pain, opioid use disorder, and other substance use disorders on society [1]
		Describes the social, environmental, healthcare systems, industry, and regulatory drivers that have shaped opioid prescribing and approach to pain care including the social determinants of health in the distribution of morbidity and mortality.[2a]
		Describes population health and policy efforts intended to address the opioid misuse and overdose epidemics, including co-prescribing of naloxone. [5]
		Recognizes the role of health and healthcare disparities in pain and substance use treatment
		Recognizes pain, opioid use disorder, and other substance use disorders as multidimensional, public health problems.
		Demonstrates knowledge of the epidemiology of medical and nonmedical opioid use and overdose in the United States[5]
		Identifies primary, secondary, tertiary prevention strategies to address opioid misuse and overdose

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