What's New in My Field:
Pain Management

Kirsten Baca, MD
Board Certified Anesthesiology
Board Certified Pain Management

Financial Relationship Disclosures

- I have none

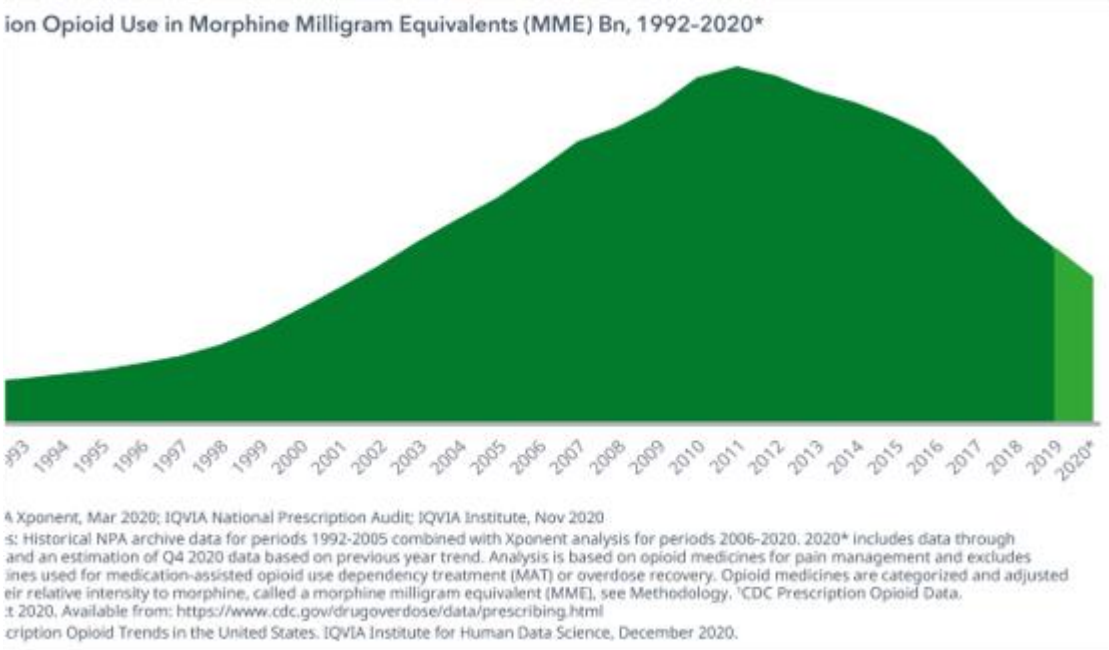
After this lecture, learners will know about:

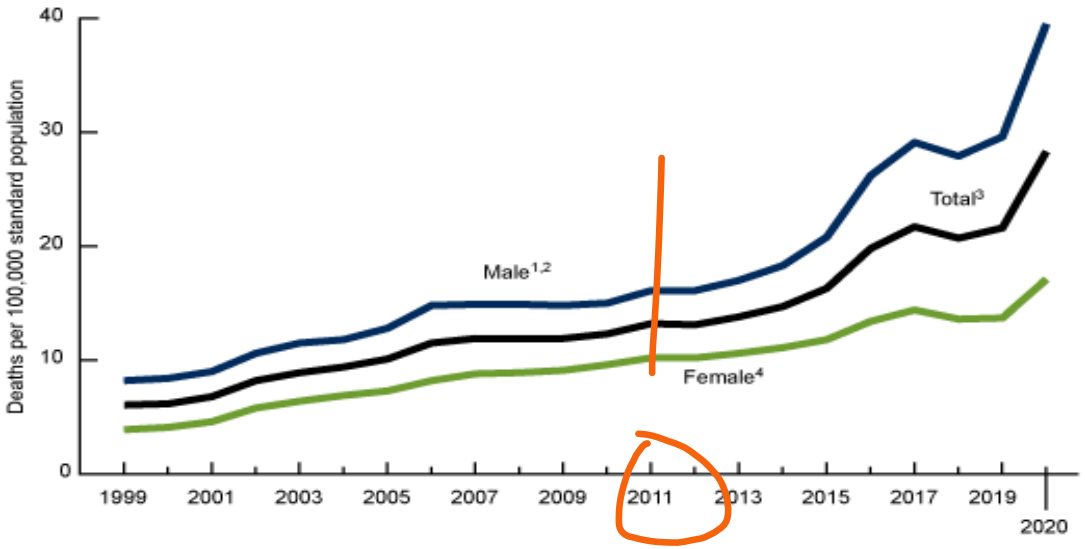
- The opioid epidemic, street fentanyl, and designer drugs
- The current draft of CDC Opioid Prescribing Guidelines
- Buprenorphine as a primary, first line analgesic
- Ketamine for pain management
- Emerging non-opioid therapies for pain
- Long COVID and chronic pain

Opioid Epidemic

- The pendulum swings from periods of opioid abundance lead to periods opioid misuse, overdose crisis, and reaction

- Current epidemic rooted in 1990's OxyContin marketing





1Rates for males were significantly higher than for females for all years, $p < 0.05$.
2Significant increasing trend from 1999 to 2006, stable trend from 2006 to 2012, and increasing trend from 2012 through 2020, $p < 0.05$.
3Significant increasing trend from 1999 to 2006, stable trend from 2006 to 2013, and increasing trend from 2013 through 2020, $p < 0.05$.
4Significant increasing trend from 1999 through 2020, with different rates of change over time, $p < 0.05$.
NOTES: Drug overdose deaths are identified using the *International Classification of Diseases, 10th Revision* (ICD–10) underlying cause-of-death codes X40–X44, X60–X64, X85, and Y10–Y14. The number of drug overdose deaths in 2020 was 91,799. Access data table for Figure 1pdf icon.
SOURCE: National Center for Health Statistics, National Vital Statistics System, Mortality.

- 1999-2011: opioid prescriptions and deaths quadrupled
- 2011-2020: opioid prescriptions **cut in half** while deaths **have doubled**

State of Opioid Epidemic: 2021 data

- Drug overdose deaths in 2021: **107,622**
- Opioid overdose deaths in 2021: **80,816**
  - Synthetic opioids other than methadone (street fentanyl) in 2021: **71,238**
  - Prescription opioids in 2021: **13,503**

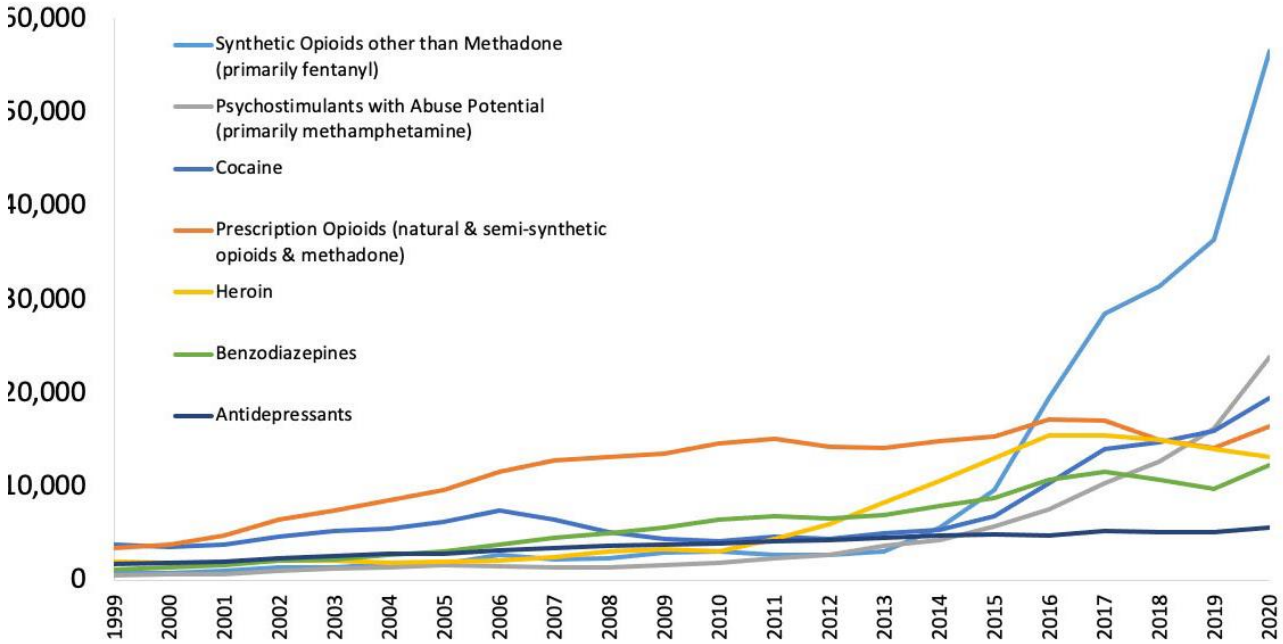
DRUG TYPE	(DEATHS 2021)	(DEATHS 2020)
Synthetic Opioids (fentanyl)	71,238	57,834
Psychostimulants (meth)	32,856	24,576
Cocaine	24,538	19,927
Natural/semi-synthetic (prescription)	13,503	13,722

https://www.cdc.gov/nchs/pressroom/nchs_press_releases/2022/202205.htm
Page last reviewed: May 11, 2022
Content source: CDC/National Center for Health Statistics

Ahmad FB, Rossen LM, Sutton P. Provisional drug overdose death counts. National Center for Health Statistics. 2021.

Figure 2. National Drug-Involved Overdose Deaths by Specific Category—Number Among All Ages, 1999-2020. Overall, drug overdose deaths rose from 2019 to 2020 with 91,799 drug overdose deaths reported in 2020. Deaths involving synthetic opioids other than methadone (primarily fentanyl) continued to rise with 56,516 overdose deaths reported in 2020. Those involving psychostimulants with abuse potential (primarily methamphetamine) also continued to increase to 23,837 (Source: CDC WONDER).

Figure 2. National Drug-Involved Overdose Deaths*, Number Among All Ages, 1999-2020



*Includes deaths with underlying causes of unintentional drug poisoning (X40–X44), suicide drug poisoning (X60–X64), homicide drug poisoning (X85), or drug poisoning of undetermined intent (Y10–Y14), as coded in the International Classification of Diseases, 10th Revision.
Source: Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple Cause of Death 1999-2020 on CDC WONDER Online Database, released 12/2021.

- Counterfeit pills are **widely available** and may or may not be advertised as opioids

- DEA lab testing reveals **4 out of 10** counterfeit pills laced with fentanyl contain a **lethal dose of fentanyl**

https://www.dea.gov/sites/default/files/2021-12/DEA-OPCK_FactSheet_December%202021.pdf

A lethal dose

These vials show the lethal dosage of each drug. As you can see, Carfentanil is significantly more potent. The dosages shown are enough to kill an average-sized adult male.

* About the size of a snowflake.

https://www.bostonglobe.com/metro/2017/11/15/comparing-lethality-and-potency-opioid-drugs/6iEmKXzFDc2rjg9IIZeXWP/story.html

2022 CDC Clinical Practice Guidelines for Prescribing Opioids (public comments closed)

- Released February 2022 for public comments
- Closed April 2022 to public comments
- Final document due late 2022
- Some changes of note:
  - Removes 90 MME threshold: Instead “prescribe lowest dose to achieve effects”
  - Relaxes definition of acute pain timeline
  - Reports evidence that demonstrates **small** improvements v. placebo in pain and function in the **short term**
- Encourages dose reduction where possible with emphasis on individualized treatment plans
- Continues to emphasize NON-OPIOID medications and interventions including exercise and PT

https://www.federalregister.gov/documents/2022/02/10/2022-02802/proposed-2022-cdc-clinical-practice-guideline-for-prescribing-opioids

Buprenorphine as First Line Opioid Therapy

- Originally designed as an ANALGESIC in 1977
- As effective as morphine in treating pain
- Built in safety with a respiratory depression ceiling
- Short-acting naloxone is not meaningfully absorbed
- Can co-dose with pure MOR agonists and have additional analgesia
- Profoundly anti-hyperalgesic with less tachyphylaxis (or none)

FACT: Buprenorphine is an effective analgesic

Journal of
Clinical Pharmacy and Therapeutics
Journal of Clinical Pharmacy and Therapeutics, 2014 doi: 10.1111/jcpt.12196

Commentary

The clinical analgesic efficacy of buprenorphine

R. B. Raffa* PhD, M. Haidery* PharmD, H.-M. Huang* PharmD, K. Kalladeen* PharmD, D. E. Lockstein* PharmD, H. Ono* PharmD, M. J. Shope* PharmD, O. A. Sowunmi* PharmD, J. K. Tran* PharmD and J. V. Pergolizzi†‡§ Jr MD
*Temple University School of Pharmacy, Philadelphia, PA, †Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, ‡Department of Anesthesiology, Georgetown University School of Medicine, Washington, DC, and §Department of Pharmacology, Temple University School of Medicine, Philadelphia, PA, USA

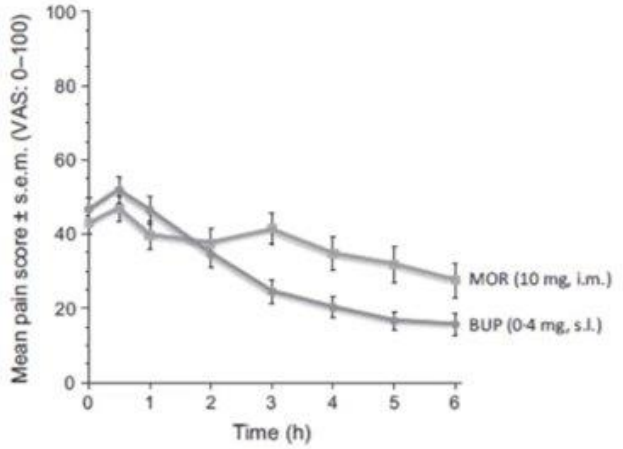


Fig. 2. The analgesic efficacy of s.l. buprenorphine (0·4 mg) was compared with that of i.m. morphine (10 mg) in a randomized, double-blind study of post-op pain of 101 patients (mean age: 40–45 years). Pain was measured using a 10-cm pain scale (0 = none, 10 = as much as imaginable). Buprenorphine produced the same pain relief as did morphine during the first 2 h and modestly greater pain relief from 2 to 6 h. Redrawn from Edge *et al.*[22]

FACT: Buprenorphine has a respiratory depression ceiling

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PAIN

Comparison of the respiratory effects of intravenous buprenorphine and fentanyl in humans and rats

A. Dahan[1]*, A. Yassen[2], H. Bijl[1], R. Romberg[2], E. Sarton[1], L. Teppema[1], E. Olofsen[1] and M. Dunbar[3]

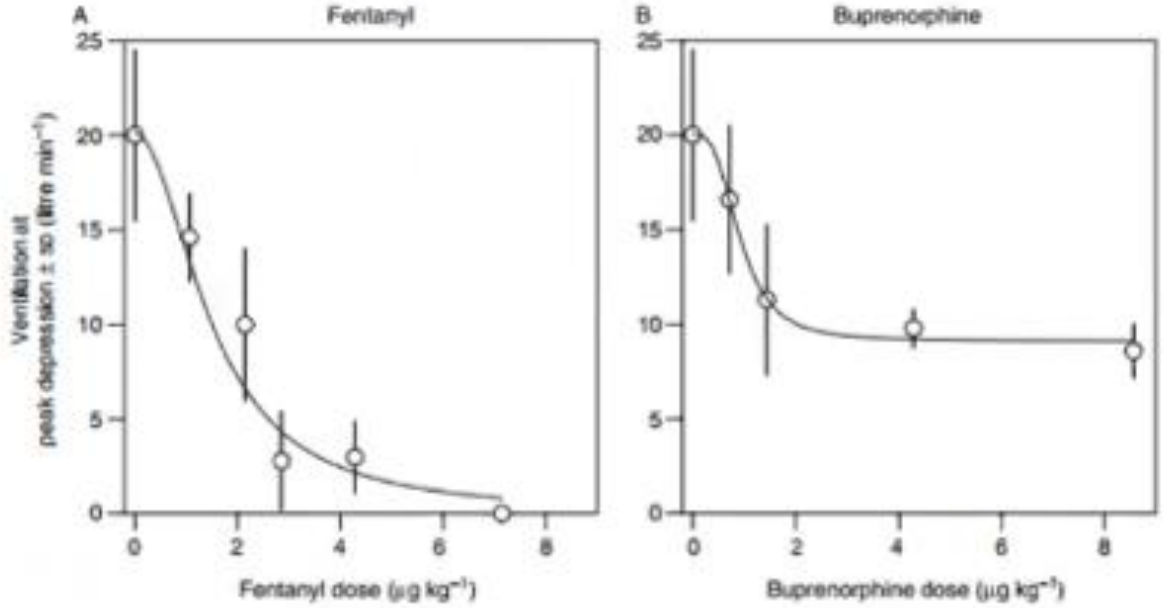


Fig 4 Dose–response relationships for (A) fentanyl and (B) buprenorphine. The response is the peak ventilatory depression. The line through the data is the fit to the Hill equation. 0 μg kg^{-1} is placebo. Data are mean (SD).

FACT: Naloxone packaged with Suboxone is not meaningfully absorbed

- The sublingual combination tablet formulation of buprenorphine and naloxone at a fixed dose ratio of 4:1 has been shown to be as effective as the tablet formulation containing only buprenorphine in treating opiate addiction. The addition of naloxone does not affect the efficacy of buprenorphine for two reasons: (1) naloxone is poorly absorbed sublingually relative to buprenorphine and (2) the half-life for buprenorphine is much longer than for naloxone (32 vs. 1 h for naloxone). The sublingual absorption of buprenorphine is rapid and the peak plasma concentration occurs 1 h after dosing. The plasma levels for naloxone are much lower and decline much more rapidly than those for buprenorphine.

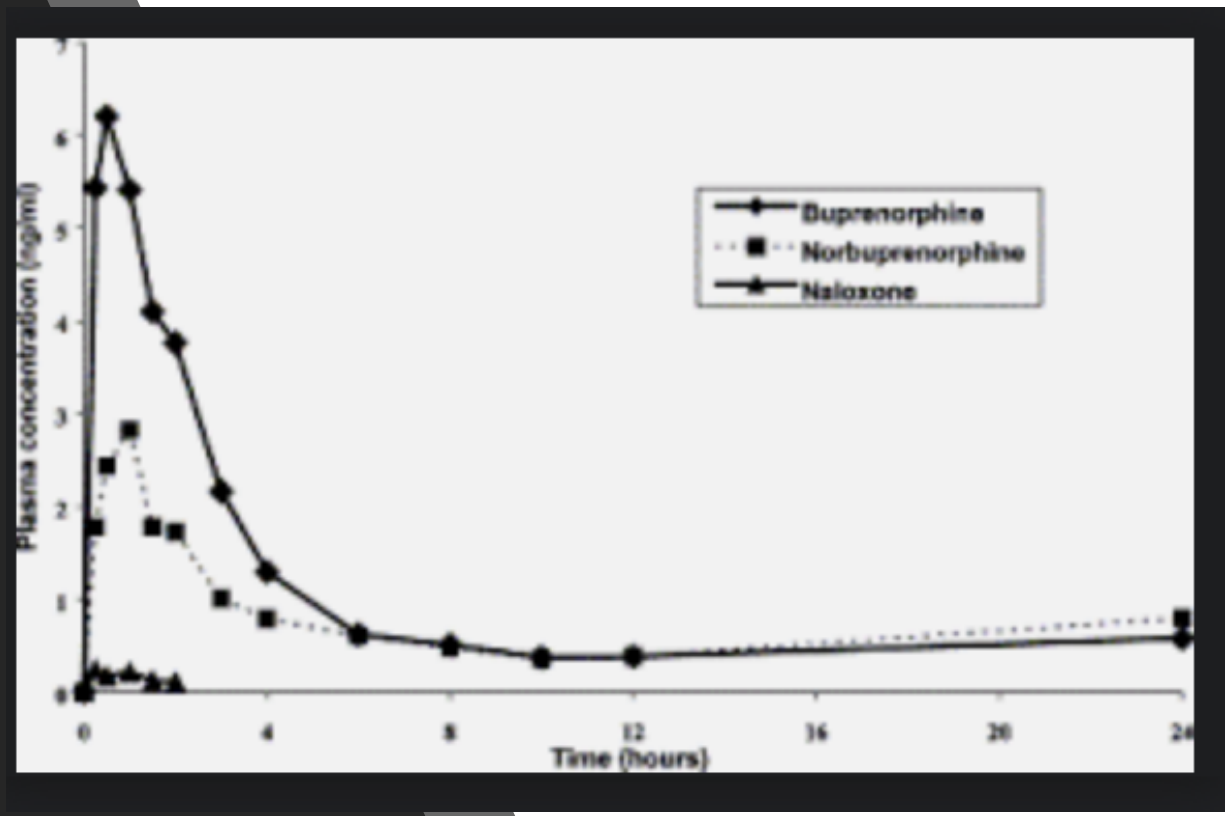
ELSEVIER

Drug and Alcohol Dependence
Volume 70, Issue 2, Supplement, 21 May 2003, Pages S39-S47

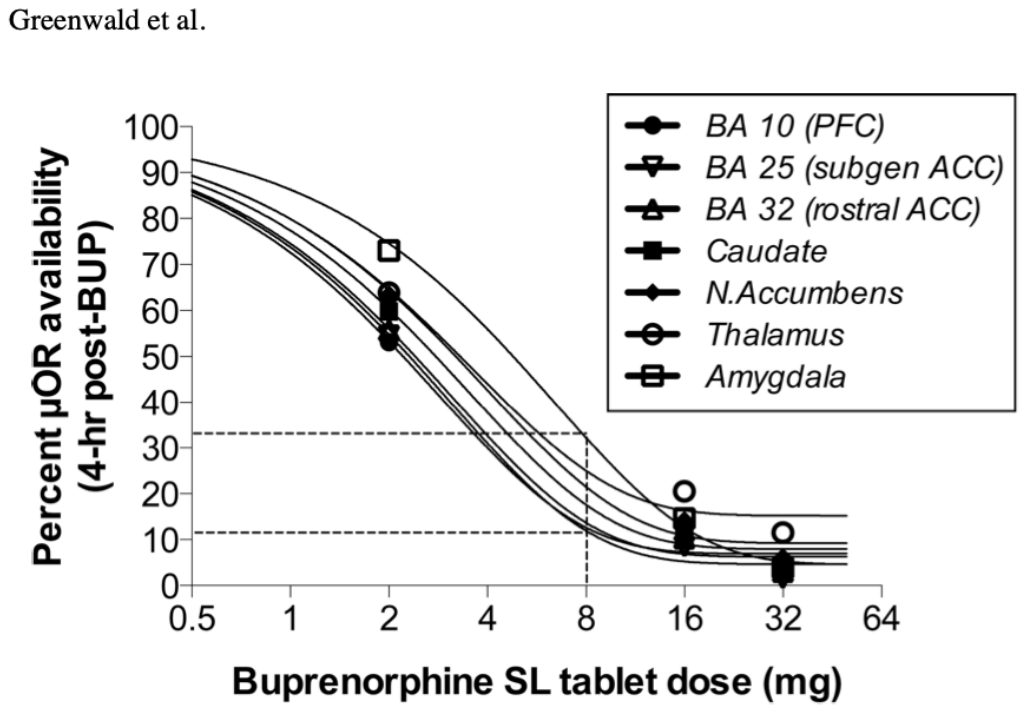
Review

Pharmacokinetics of the combination tablet of buprenorphine and naloxone

C.Nora Chiang, Richard L Hawks



FACT: Pure mu-opioid receptor agonists can be dosed and felt while one is taking buprenorphine

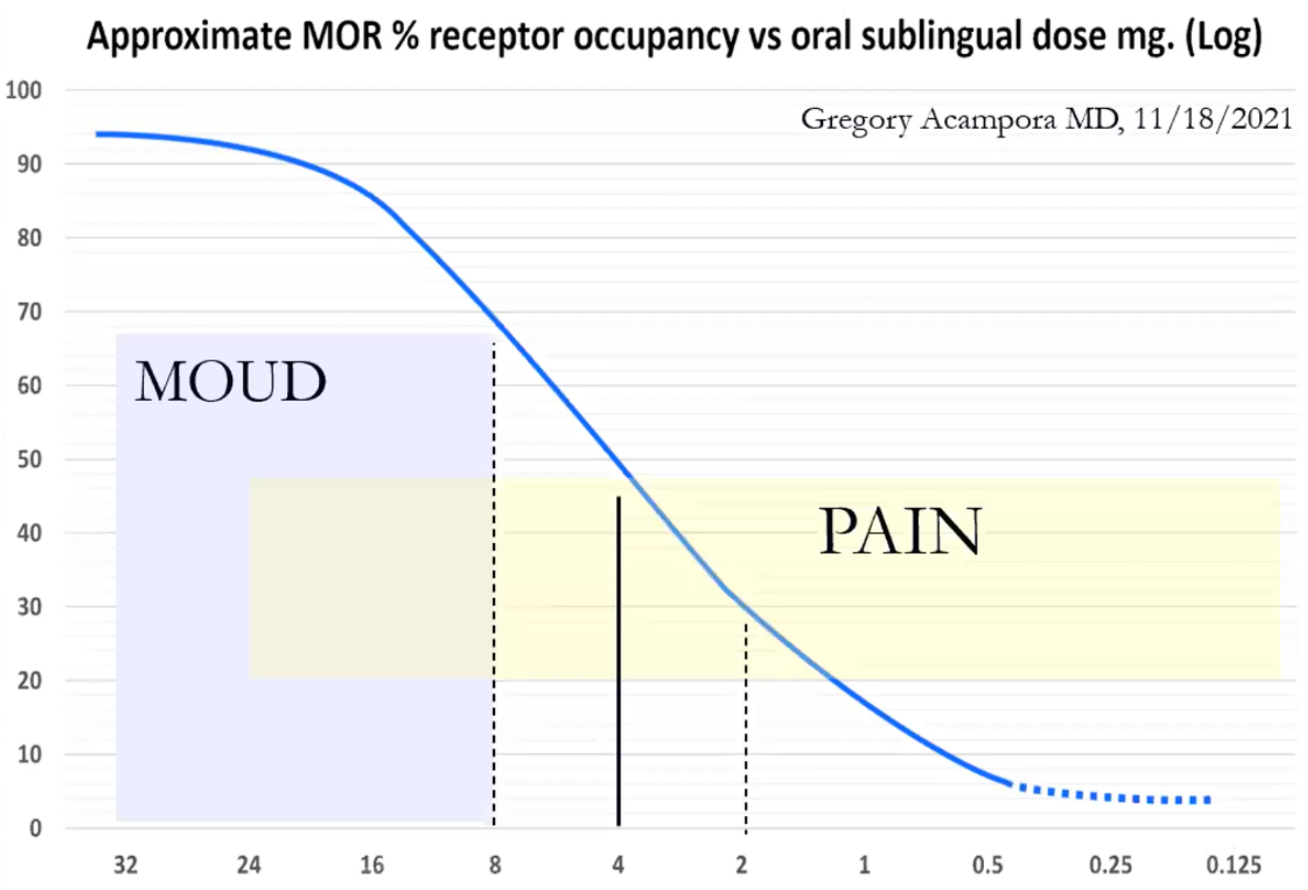


Dose	Occupied μ-OR	Free μ-OR
2 mg	40%	60%
4 mg	56-64%	36-44%
8 mg	65-80%	20-35%
12 mg	76-87%	13-24%
16 mg	80-91%	9-20%

Greenwald MK, Comer SD, Fiellin DA. Buprenorphine maintenance and mu-opioid receptor availability in the treatment of opioid use disorder: implications for clinical use and policy. Drug and Alcohol Dependence. 2014 Nov;144:1-11. DOI: 10.1016/j.drugalcdep.2014.07.035. PMID: 25179217; PMCID: PMC4252738.

FACT: Buprenorphine can treat pain in OUD

- Analgesia with 10-60% receptor occupation (0.25-1 ng/ml; 0.5-4 mg/day)
- Craving/withdrawal prevented with 50% occupation (~1 ng/ml; ~4 mg/day)
- Euphoria prevented with 75% occupation (2-3 ng/ml; ~8-12 mg/day)



FACT: Buprenorphine is anti-hyperalgesic

Pain 118 (2005) 15–22

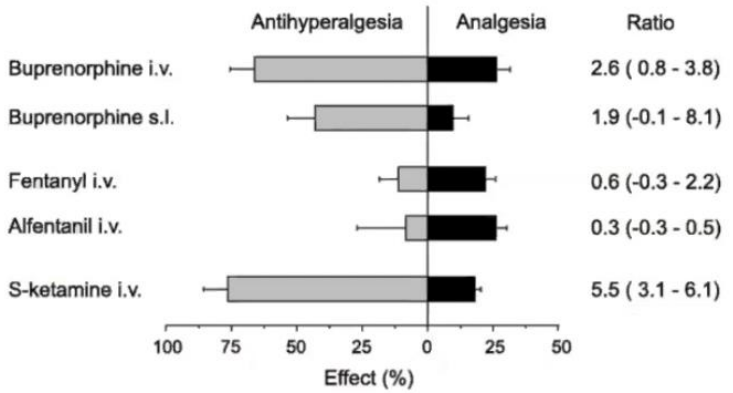
PAIN

www.elsevier.com/locate/pain

Research papers

Different profiles of buprenorphine-induced analgesia and antihyperalgesia in a human pain model

Wolfgang Koppert[a,*], Harald Ihmsen[a], Nicole Körber[a], Andreas Wehrfritz[a], Reinhard Sittl[a], Martin Schmelz[b], Jürgen Schüttler[a]



Ratios of antihyperalgesic and analgesic effects after application of the respective medication, based on the areas under the curve of the individual ratings ($AUC_{antihyperalgesia}/AUC_{analgesia}$). The data for fentanyl, alfentanil and S-ketamine are re-analyzed from previous studies (Koppert et a., 2001; Treister et al., 2004). Data are expressed as mean and SD (n=12–15 each).

FACT: Additional benefits of buprenorphine

- Less constipation, less cognitive impairment, not immunosuppressive (morphine, fentanyl)
- Does not cause hypogonadism
- Does not prolong QTc (methadone, oxycodone)

- Safe in elderly, renal failure
- Is not reenforcing, causes less dependence, and withdrawal is milder

Davis MP. Twelve reasons for considering buprenorphine as a frontline analgesic in the management of pain. J Support Oncol. 2012 Nov-Dec;10(6):209-19. doi: 10.1016/j.suponc.2012.05.002. Epub 2012 Jul 17. PMID: 22809652.

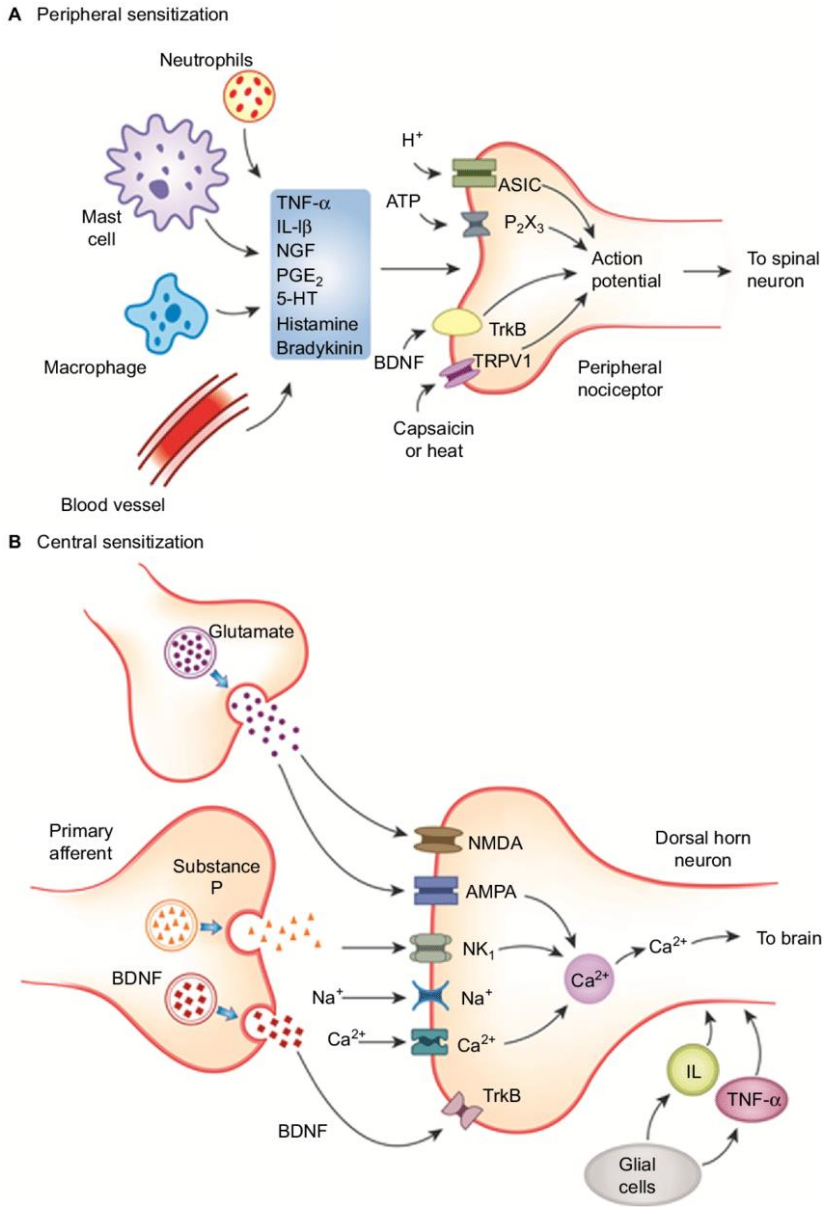
Ketamine for Pain Management

- Increasing use of office based ketamine infusions for the treatment of chronic pain and mood disorders
- Clinical evidence suggest that a single administration of ketamine can treat pain and produce long-lasting, though not permanent, pain relief

Yang Y, Maher DP, Cohen SP. Emerging concepts on the use of ketamine for chronic pain. Expert Rev Clin Pharmacol. 2020 Feb;13(2):135-146. doi: 10.1080/17512433.2020.1717947. Epub 2020 Jan 28. PMID: 31990596.

Chronic pain development

- The *N*-methyl-D-aspartate receptor (NMDA) plays a crucial role in the development and chronification of NP
  - (A) Peripheral sensitization: Activation of peripheral nociceptors on the skin in response to stimuli (heat, trauma, pressure) releases chemical mediators at the site of injury.
  - (B) Central sensitization: Persistent pain or inflammation causes repetitive firing in afferent C-fiber nociceptors, triggering release of glutamate, substance P, etc. in the dorsal horn, and activation of NMDAR which stimulate release of pro-inflammatory mediators by the microglia.

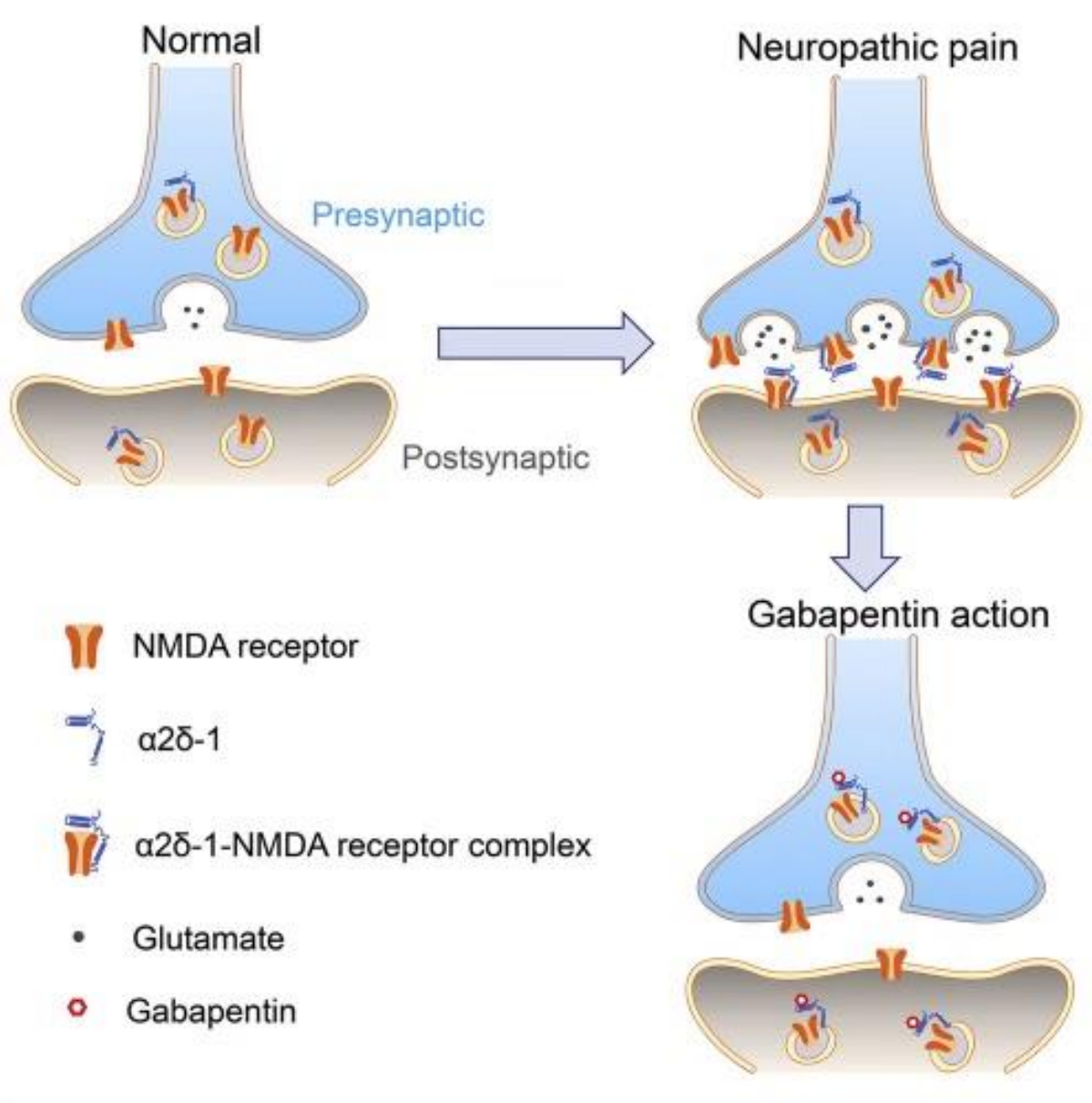


Dureja, Gur & Iyer, Rajagopalan & Das, Gautam & Ahdal, Jaishid & Narang, Prashant. (2017). Evidence and consensus recommendations for the pharmacological management of pain in India. Journal of Pain Research. Volume 10. 709-736. 10.2147/JPR.S128655.

Kamp J, Van Velzen M, Olofsen E, Boon M, Dahan A, Niesters M. Pharmacokinetic and pharmacodynamic considerations for NMDA-receptor antagonist ketamine in the treatment of chronic neuropathic pain: an update of the most recent literature. Expert Opin Drug Metab Toxicol. 2019 Dec;15(12):1033-1041. doi: 10.1080/17425255.2019.1689958. Epub 2019 Nov 13. PMID: 31693437.

NMDA-R activity is increased in neuropathic pain

- $\alpha 2\delta{-}1$ gene overexpression potentiates pre- and post-synaptic NMDA-R activity of the spinal dorsal horn neurons
- Over-expression is the mechanism of hyperalgesia in neuropathic pain



Jinjun Chen, Lingyong Li, Shao-Rui Chen, Hong Chen, Jing-Dun Xie, Rita E. Sirrieh, David M. MacLean, Yuhao Zhang, Meng-Hua Zhou, Vasanthi Jayaraman, Hui-Lin Pan, *The α2δ-1-NMDA Receptor Complex Is Critically Involved in Neuropathic Pain Development and Gabapentin Therapeutic Actions*, Cell Reports, Volume 22, Issue 9, 2018, Pages 2307-2321, ISSN 2211-1247, https://doi.org/10.1016/j.celrep.2018.02.021 (https://www.sciencedirect.com/science/article/pii/S221112471830189X)

Affective-Motivational Pain

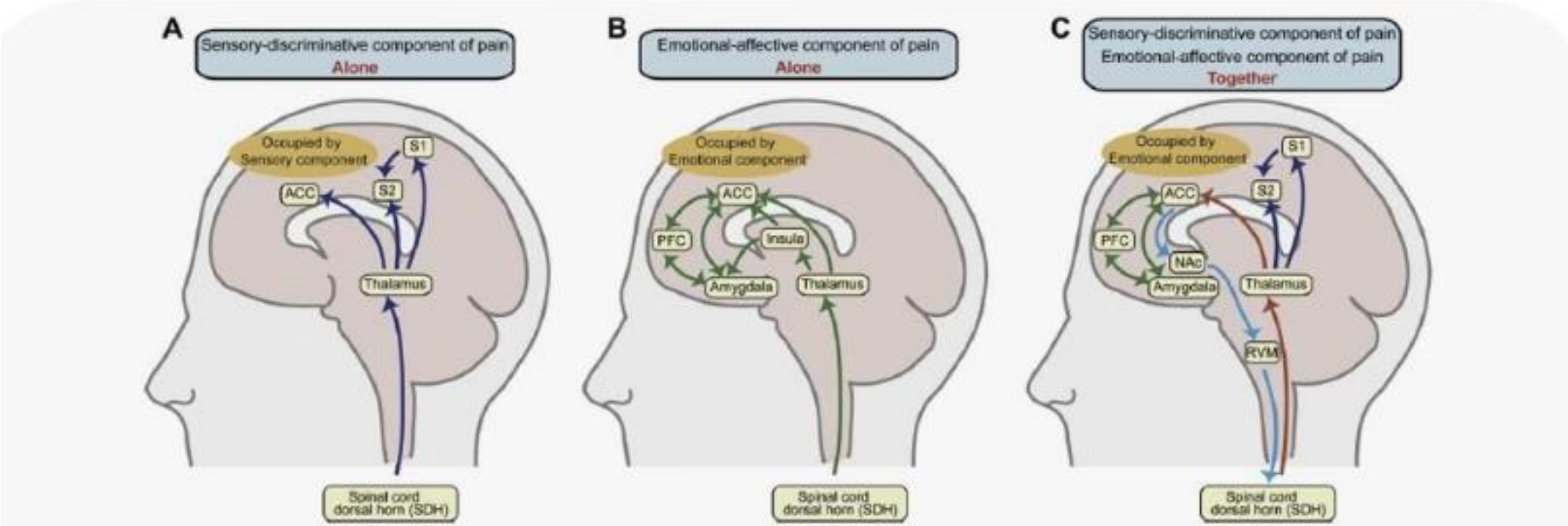


Fig. 1. The ACC encodes pain processing in priority levels.
(A) The sensory-discriminative component of pain has been ascribed to the lateral nociceptive system.
(B) The affective-motivation component of pain is mediated by the medial nociceptive system.
(C) The sensory-discriminative component of pain (blue arrow) and the emotional-affective component of pain (green arrow) may be considered the two levels in pain processing. The emotional-affective component is preferentially processed in the ACC (green arrow). This priority of pain processing in the ACC causes descending facilitation (light blue arrow) in the downstream brain areas, which then facilitate spinal nociception.

Xiao Xiao, Yu-Qiu Zhang, A new perspective on the anterior cingulate cortex and affective pain, Neuroscience & Biobehavioral Reviews, Volume 90,2018, Pages 200-211, ISSN 0149-7634, https://doi.org/10.1016/j.neubiorev.2018.03.022.

Diseases and syndromes associated with neuropathic pain

Table 1. Examples of diseases and syndromes associated with neuropathic pain. (Table view)

Trauma to the peripheral or central nervous system	Surgical trauma, spinal cord injury, traumatic peripheral nerve damage, amputation with phantom limb pain, complex regional pain syndrome, complex regional pain syndrome
Nerve or spinal cord compression	Disc herniation, canal stenosis
Vascular disease	Stroke, ischemia of the lower extremities
Degenerative neurological disease	Multiple sclerosis, amyotrophic lateral sclerosis, syringomyelia, Parkinson's disease, Huntington's disease, Alzheimer's disease
Infectious disease	HIV/AIDS, leprosy, shingles, neuritis
Hereditary neuropathic syndromes	Erythromelalgia, Fabry's disease, sodium channelopathy
Metabolic syndromes	Diabetes mellitus, sarcoidosis, alcoholism, amyloidosis, malnutrition, obesity
Drugs and toxins	chemotherapeutics, thalidomide, arsenic
Cancer	Paraneoplastic, dysglobulinemia, nerve damage (in cancer pain often both neuropathic and nociceptive components are present)
Other	Idiopathic, fibromyalgia

Jasper Kamp, Monique Van Velzen, Erik Olofsen, Martijn Boon, Albert Dahan & Marieke Niesters (2019)Pharmacokinetic and pharmacodynamic considerations for NMDA-receptor antagonist ketamine in the treatment of chronic neuropathic pain: an update of the most recent literature, Expert Opinion on Drug Metabolism & Toxicology, 15:12, 1033-1041, DOI: 10.1080/17425255.2019.1689958

Emerging non-opioid pain therapies

- Emphasis on multimodal perioperative care (blocks, non-opioids, etc)
- CGRP-R antagonists and migraine management
- Botox and migraine, chronic spasm pain management
- Evolution of RFA, first used for low back pain in 1975
  - Lumbar, cervical, thoracic, sacral
  - Also, knee, hip, shoulder, peripheral nerves
- SCS neuromodulation at high frequency, mixed paresthesia
- Dorsal root and peripheral nerve stimulation
- SIJ fusion techniques, interspinous spacers

Long COVID

- Chronic pain condition with musculoskeletal, neuropathic, and psychological features
- Overlap with treatment approach to fibromyalgia and other syndromes

Plos One 2021; 16[8]:e0254347. Cardiovascular diabetology (2021;20:172). Proceedings of the national Academy of Sciences (2021;118[34]:e2024358118)

Thank you

- Questions?
  - Email: kirsten.e.baca@gmail.com
  - Office: 385-333-7123