Homeland Defense & Security
Information Analysis Center

Battlefield Pain Management

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University of California, Berkeley

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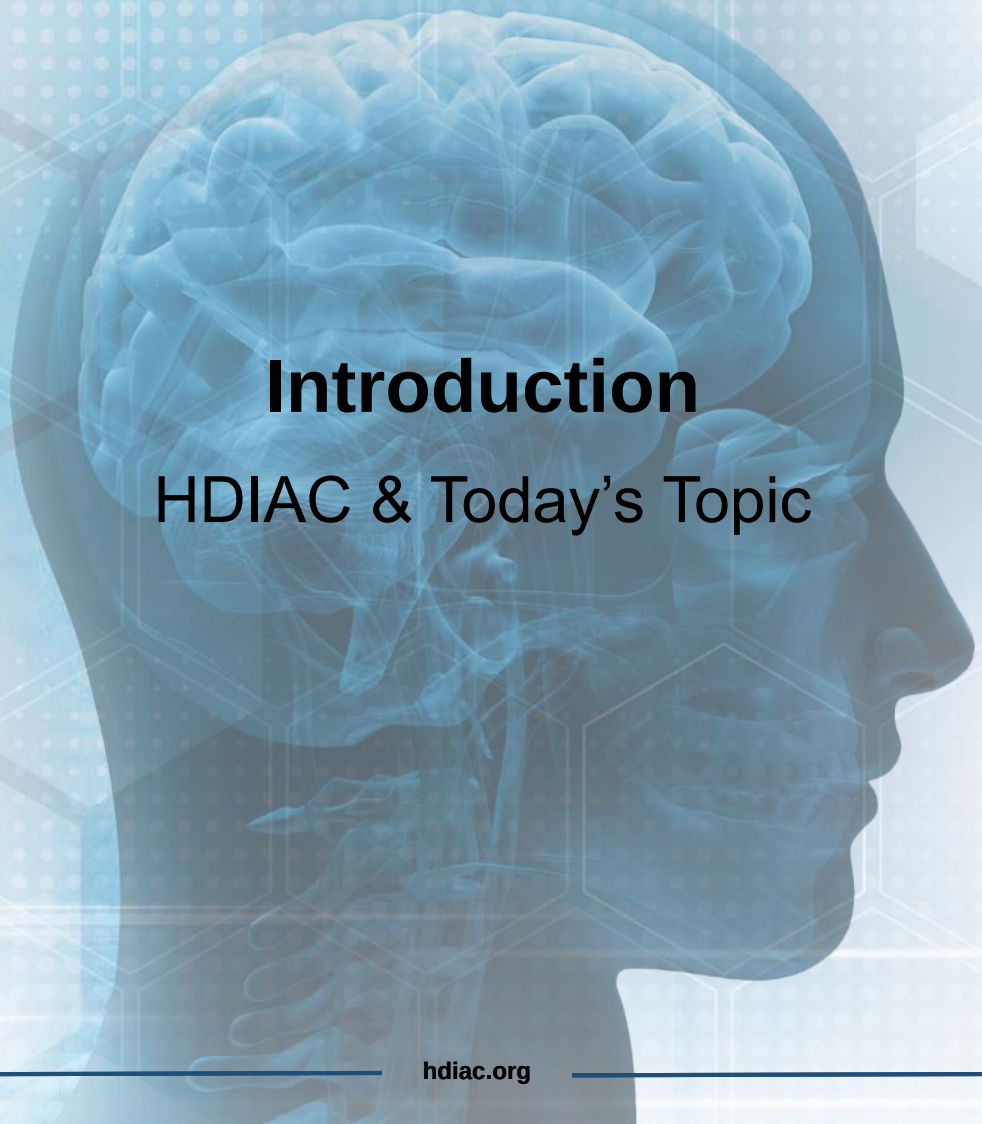
The views presented are those of the speaker and do not necessarily represent the views of DoD or its components.



Introduction

HDIAC & Today's Topic

HDIAC Overview

What is the Homeland Defense & Security Information Analysis Center (HDIAC)?

One of three Department of Defense Information Analysis Centers

Responsible for acquiring, analyzing, and disseminating relevant scientific and technical information, in each of its eight focus areas, in support of the DoD and U.S. government R&D activities

HDIAC's Mission

Our mission is to be the go-to R&D/S&T and RDT&E leader within the homeland defense and security (HDS) community, by providing timely and relevant information, superior technical solutions, and quality products to the DoD and HDS Communities of Interest/Communities of Practice.

HDIAC Overview

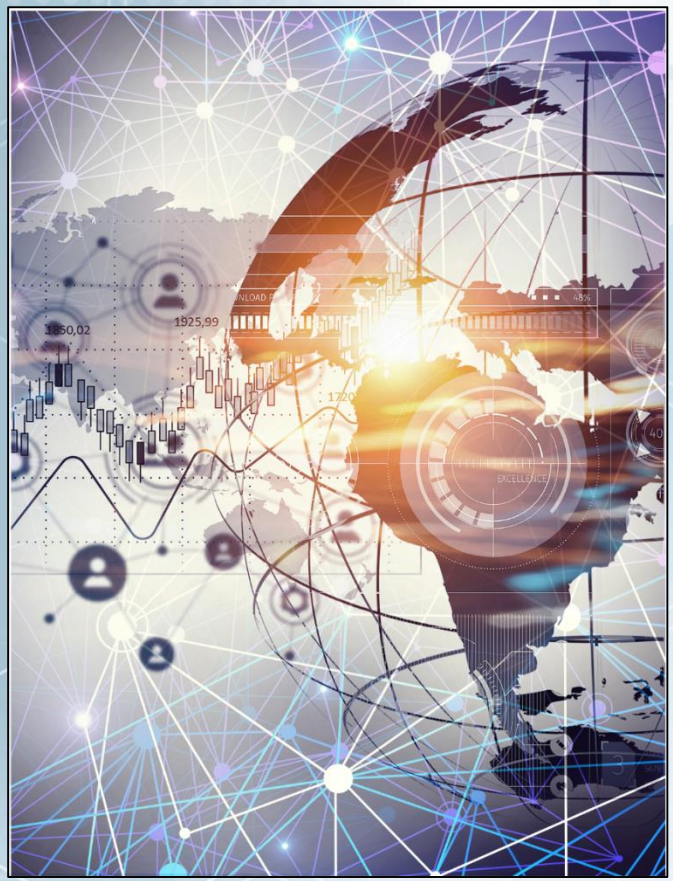
HDIAC Subject Matter Expert (SME) Network

HDIAC SMEs are experts in their field(s), and, typically, have been published in technical journals and publications.

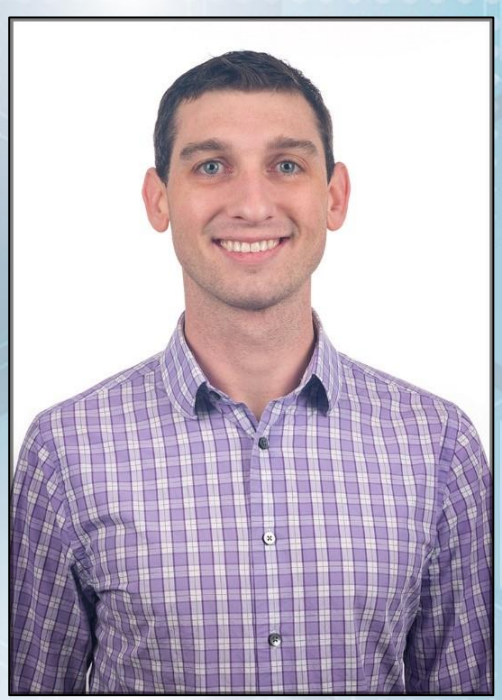
SMEs are involved in a variety of HDIAC activities

- Authoring HDIAC Journal articles
- Answering HDIAC Technical Inquiries
- Engaging in active discussions in the HDIAC community
- Assisting with Core Analysis Tasks
- Presenting webinars

If you are interested in applying to become a SME, please visit HDIAC.org or email info@hdiac.org.



Presenters



Kyle E. Giesler, Ph.D.
Postdoctoral Scholar
University of California, Berkeley

Kyle E. Giesler is a postdoctoral scholar at the University of California, Berkeley investigating non-viral delivery strategies for CRISPR/Cas9 and other emerging biologics. He received his Ph.D. in medicinal chemistry from Emory University under the tutelage of Dennis Liotta where he designed novel small molecules for the treatment of HIV and other chronic viral infections. From 2015 to 2017, he interned with the former Senior Vice President and Chief Patent Counsel at GlaxoSmithKline, Sherry Knowles. His research interests include pharmacology, drug delivery, immunology, virology, stereoelectronic effects, and high-risk drug discovery ventures. He also has a keen interest in medical research relating to military operations, regenerative medicine, medical countermeasures, and CBRN defense strategies.

Overview

Injuries and Pain on the Battlefield

- **Survival from battlefield injuries has significantly increased**
- **Acute battlefield injuries often result in severe pain and require immediate intervention**
- **Ineffective pain management has both short and long-term consequences (chronic pain and post-traumatic stress disorder)**
- **Incidence of acute pain is second only to trauma experiences on the battlefield**
  - Blast injury (56 percent)
  - Gunshot wounds (32 percent)
  - Motor vehicle crash (4.5 percent)
  - Non-combat injury (2.2 percent)

Shackelford, S. A., Fowler, M., Schultz, K., Summers, A., Galvagno, S. M., Gross, K. R., . . . Butler, F. K. (2015). Prehospital pain medication use by U.S. Forces in Afghanistan. *Military Medicine, 180*(3), 304-309. doi:10.7205/milmed-d-14-00257

Image source: https://www.eucom.mil/media-library/Article/35827/us-soldiers-hone-explosive-capabilities-at-saber-strike-17

Available Treatment Options

- Sodium ion channel inhibitors
- NMDA Antagonists
- NSAIDs
- Nerve blocks
- Opioids
- Gabapentinoids
- Alpha-2 agonists
- Tricyclic anti-depressants
- Others

The complexity and intensity of battlefield injuries coupled with the availability of pain management and/or evacuation prohibits a universal approach for treating these injuries

Where do Analgesics Operate?

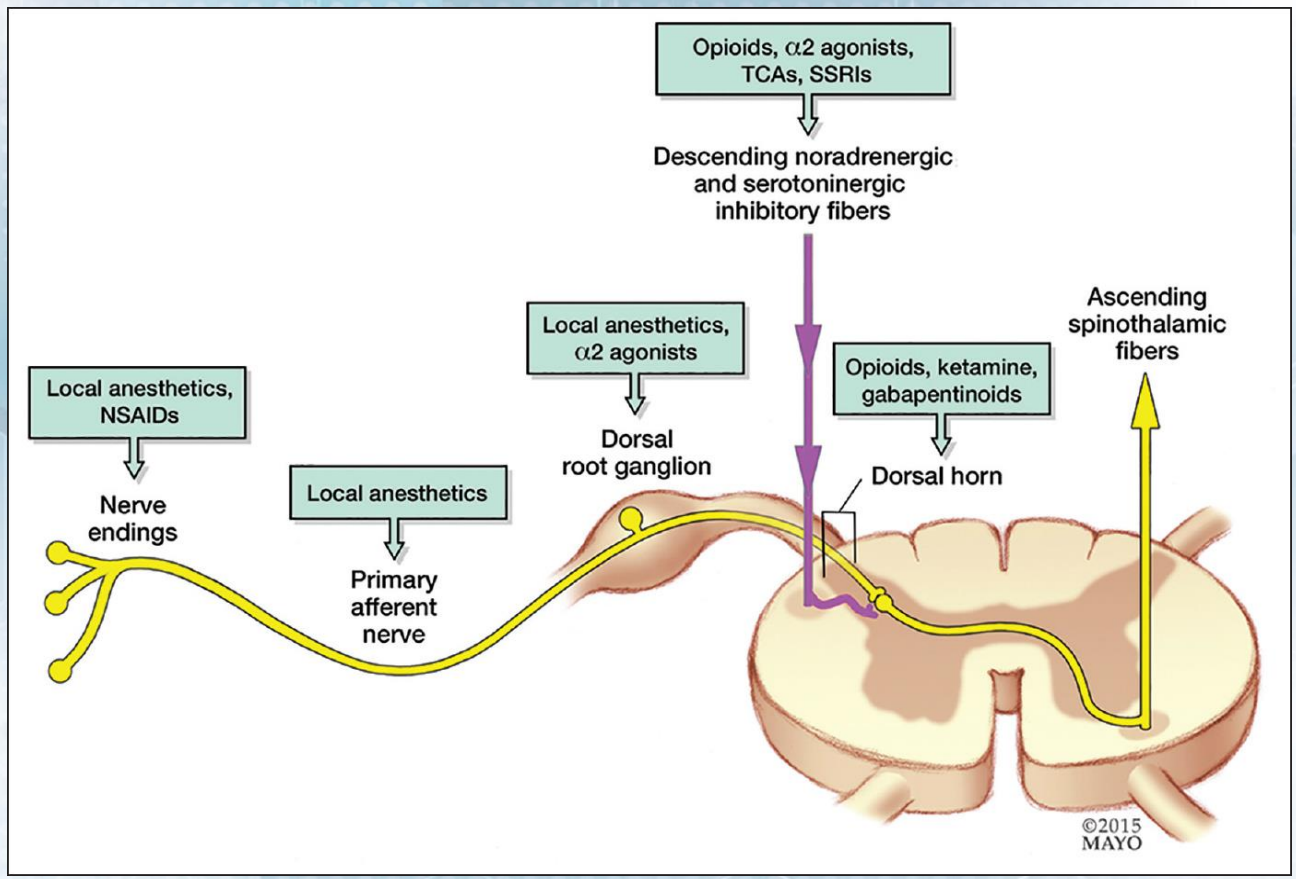


Image credit: *Journal of Anaesthesiology Clinical Pharmacology, 32*(2), 160-167. Reproduced under a Creative Commons license

Morphine on the Battlefield

- **Opiates have been in use since at least 4300 B.C.E.**
  - Morphine did not exist until German pharmacist Friedrich Wilhelm Serturner successfully crystallized the compound from the poppy flower in 1804
- **Morphine has seen extensive battlefield use since the 19th century**
  - Widespread use amongst soldiers during the American Civil War
  - Touted as a “miracle drug” for its analgesic properties
  - Originally developed as a less addictive alternative to opium
  - Soldiers began suffering from severe morphine addiction
  - Morphine overdose and addiction continued into WWII
- **Today, morphine is generally regarded as the standard of care for pain management for military personnel**
  - 10 mg auto-injectors for personal use
    - Inconsistent absorption. Delayed onset
  - IV morphine provides more rapid pain relief

Fentanyl & Dsuvia™

- **Actiq® is a fentanyl "lollipop" that supplants morphine on the battlefield**
  - Fentanyl is ~100x more potent than morphine
  - Actiq® delivers fentanyl across the buccal mucosa
  - Oral transmucosal fentanyl was added in 2004 to DoD's Tactical Combat Casualty Care (TCCC) Guidelines as an option for battlefield analgesia
  - Easily administered and can be removed once the deserved level of analgesia is achieved.
  - Used by the US Army, Navy, and Marine Corps
- **Dsuvia™ is a new opioid, 500x more potent than morphine**
  - FDA approval in November 2018
  - Approved for the treatment of moderate to severe pain
  - Developed in collaboration with the Department of Defense
  - Not available in retailer pharmacies
  - Needle-free application

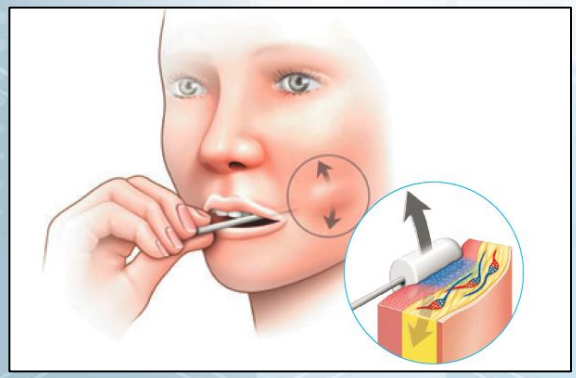


Image credit: https://www.tevauk.com/hcp/actiq

Image credit: http://www.dsuvia.com/

Rogers, E., Wright, C., & King, P. (2018). Fentanyl lozenge story part 2: from military procurement to package. *Journal of the Royal Army Medical Corps, 164*(6), 458-462. doi:10.1136/jramc-2017-000901

How Opioids Work: A Spotlight on Morphine

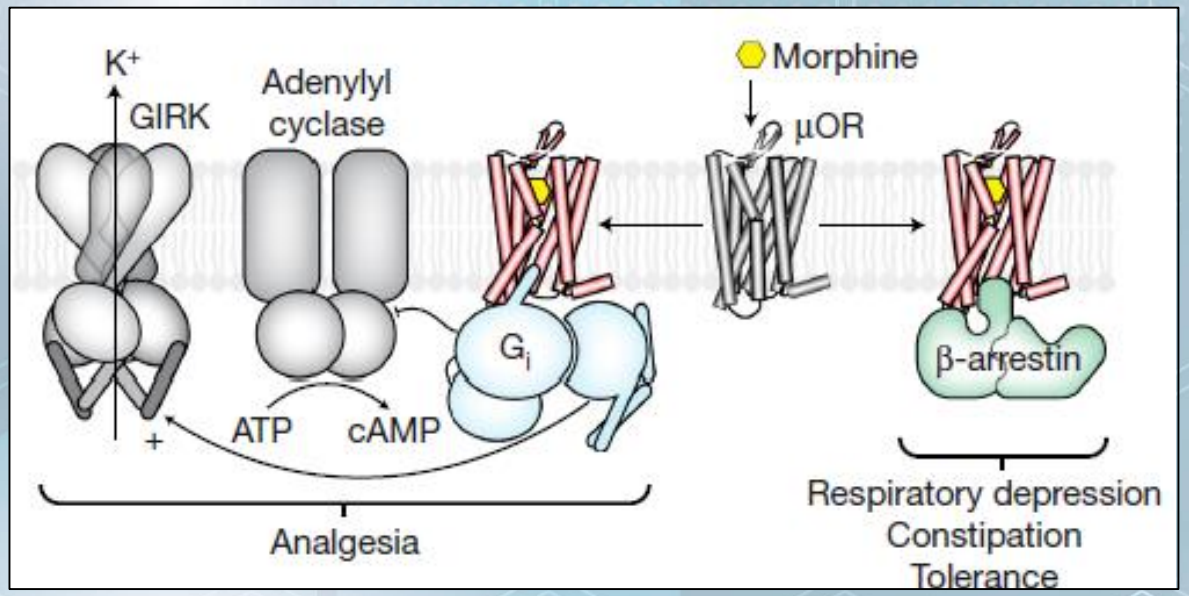


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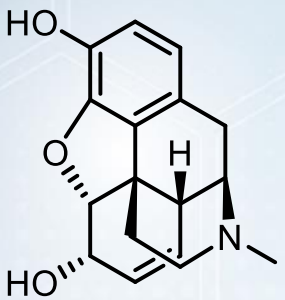
Image credit: https://en.wikipedia.org/wiki/Venus_flytrap



morphine

Raehal, K. M., & Bohn, L. M. (2014). β-arrestins: regulatory role and therapeutic potential in opioid and cannabinoid receptor-mediated analgesia. *Handbook of experimental pharmacology*, *219*, 427-43.

Opioids: Risk-to-Benefit Ratio
Push for an Alternative

Advantages

- Highly efficacious for the treatment of moderate to severe pain
- Relatively safe when administered under medical supervision
- Opioids do not produce end-organ toxicity commonly observed with NSAIDs (e.g., gastrointestinal bleeding, kidney failure, cardiovascular toxicity)
- No ceiling effect (i.e., more opioids produces more analgesia)

Disadvantages

- High potential for abuse
- Respiratory suppression
- Tolerance
- Constipation
- Nausea
- Vomiting
- Narrow therapeutic window

The Quest for Non-Opioid Analgesics

- **Most non-opioid analgesics have failed clinical trials**
- **Why?**
  - Animal models rarely predict human efficacy
  - Flaw in preclinical target validation
- **Pain is subjective to a number of clinical trial participants**
  - Questionnaires and surveys offer the only insight as to how a patient is feeling
- **The molecular mechanisms that characterize pain are incompletely understood**
- **High placebo effect**
  - Therapeutic misconception
- **Despite a high risk of failure, a few drugs have made it to the clinic**

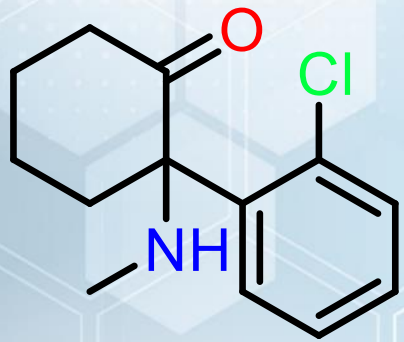
Image credit: https://www.clinicalleader.com

Hewitt, D. J., Hargreaves, R. J., Curtis, S. P., & Michelson, D. (2009). Challenges in analgesic drug development. *Clinical Pharmacology and Therapeutics, 86*(4), 447-450. doi:10.1038/clpt.2009.161

Yaksh, T. L., Hunt, M. A., & Dos Santos, G. G. (2018). Development of New Analgesics: An Answer to Opioid Epidemic. *Trends in Pharmacological Sciences, 39*(12), 1000-1002. doi:10.1016/j.tips.2018.10.003

The Rise of Ketamine

- **NMDA receptor antagonist**
- **Synthesized and discovered in the 1960s**
- **Approved by the FDA in 1970**
- **Extensively used for surgical anesthesia during the Vietnam War**
  - Fell out of favor as newer anesthetics came to market
- **Sub-anesthetic doses produces analgesia**
- **Multiple routes of administration**
  - IV injection (100 percent bioavailability, onset of action: seconds)
  - IM injection (93 percent bioavailability, onset of action: 1-5 minutes)
  - Intranasal delivery (25–50 percent bioavailability, onset of action 5–10 minutes)
  - Oral elixir (17 percent bioavailability, onset of action 15–20 minutes)
  - Rectal, intrathecal, and transdermal applications are also possible
- **Widely used off-label in hospitals and emergency rooms for the treatment of acute pain**
  - Not currently FDA-approved to treat pain
  - Post-surgical pain and pediatrics
  - No standardized dose or guidelines

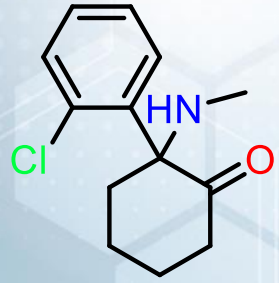


Note: Ketamine is not currently FDA-approved to treat pain

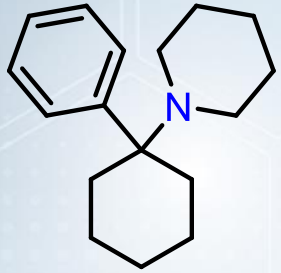
Effects of Ketamine

- **Dissociative Anesthesia = Ataranalgesia**
- **Greek: *Ataraxia* = without soul**

- **Hallucinations/dissociation from reality**
- **"Fast-on" and "Fast-off" analgesia**
  - Fast onset of action and short half-life
- **Efficacy is comparable to opioids**
- **Preserved pharyngeal reflexes & respiratory drive**
  - No respiratory suppression
  - Bronchodilatory effects
- **Anti-depressant properties**
- **Increases blood pressure and heart rate**
- **Potential for dependence**
- **Nausea/vomiting**



Ketamine
"K"



Phencyclidine
(PCP)

Note: Ketamine is not currently FDA-approved to treat pain

Ketamine vs. S-Ketamine

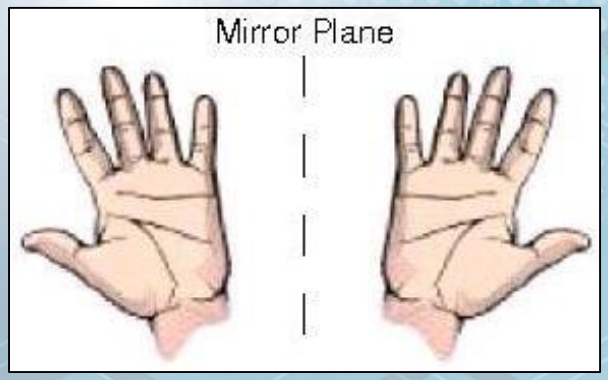
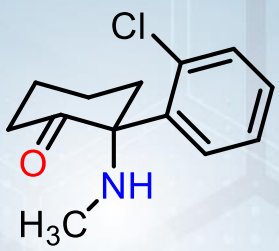
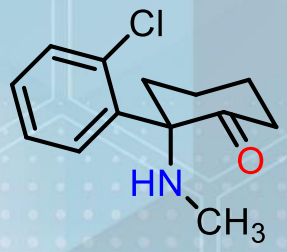


Image credit: http://www.simsoup.info/Origin_Issues_Homochirality.html



(R)-ketamine
"arketamine"



(S)-ketamine
"esketamine"

Advantages of (S)-ketamine

- 2x the analgesic potency of racemic ketamine
- 4x greater affinity for the NMDA receptor
- 10x higher neuroprotective effects
- Wider therapeutic range
- Faster elimination (10–15 mins)

Note: Ketamine is not currently FDA-approved to treat pain

Ketamine's Mechanism of Action

Morphine: Agonist
Ketamine: Antagonist

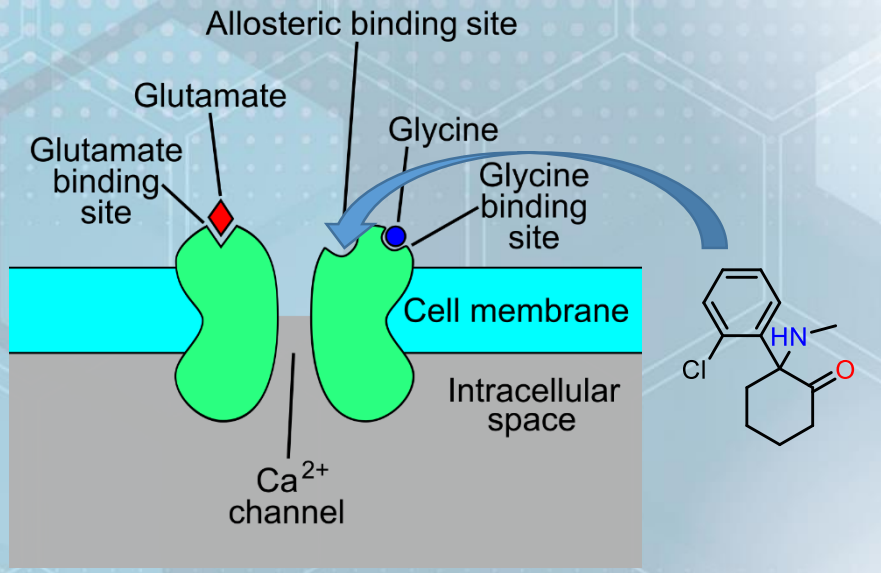


Image credit: https://en.wikipedia.org/wiki/NMDA_receptor

- **Ketamine is a non-competitive NMDA-receptor antagonist**
  - Inhibits activation of the NMDA-receptor by glutamate
- **Reduces presynaptic release of glutamate**
  - Potentiates the effects of GABA

Note: Ketamine is not currently FDA-approved to treat pain

Ketamine on the Battlefield

- **Ketamine was added by the Committee on Tactical Combat Casualty Care's list of approved battlefield analgesic options in 2011**
  - However, Navy SEAL medics do not routinely carry ketamine
- **Warfighters with severe burns who received ketamine during surgery developed post-traumatic stress injury (PTSI) at lower rates than those who received placebo (27 percent vs. 46 percent, respectively)**
- **Tactical benefits of ketamine:**
  - Minimal impact on medic carrying capacity
  - Can withstand environmental extremes
  - Fast and consistent pain relief
  - Well-suited for individuals who are also in shock or at risk for going into shock
    - Opioids increase mortality in individuals suffering from hemorrhagic shock

McGhee, L. L., Maani, C. V., Garza, T. H., Gaylord, K. M., & Black, I. H. (2008). The correlation between ketamine and posttraumatic stress disorder in burned service members. *Journal of Trauma, 64*(2 Suppl), S195-198; Discussion S197-198. doi:10.1097/TA.0b013e318160ba1d

Butler, F. K., Kotwal, R. S., Buckenmaier 3rd, C. C., Edgar, E. P., O'Connor, K. C., Montgomery, H. R., ... & Gross, K. R. (2014). A triple-option analgesia plan for tactical combat casualty care: TCCC guidelines change 13-04. *J Spec Oper Med*, *14*(1), 13-25.

Note: Ketamine is not currently FDA-approved to treat pain

The Future of Ketamine in Military Medicine

Several hurdles must be addressed in order to advance ketamine's future in military medicine:

1. **FDA-approval for acute pain**
2. **Standardized dosing and guidelines**
3. **The development of novel delivery devices (e.g., auto-injectors, infusion pumps) for battlefield use**
    I. Ketamine wafers (Wafermine, iX Biopharma)
    II. IN delivery not ideal for sandy or dusty battlefield environments
    III. Is there a civilian market for such devices?
4. **Assessment of abuse potential**
    I. Potential for dissociative effects on the battlefield

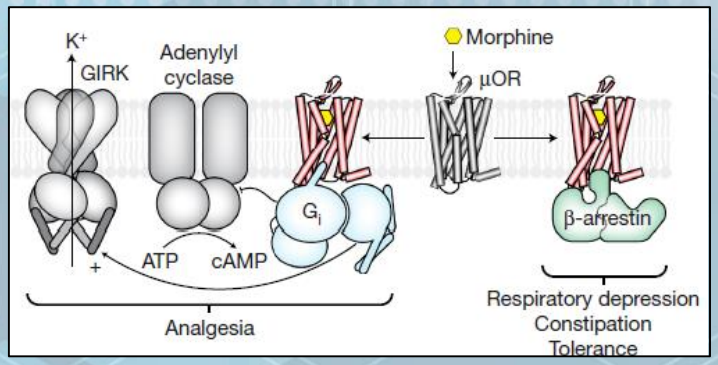
Other potential indications for military personnel

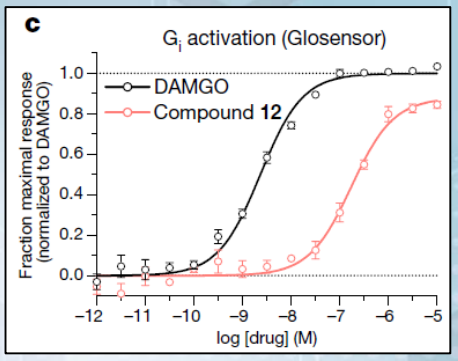
1. Depression
2. Post-traumatic stress disorder

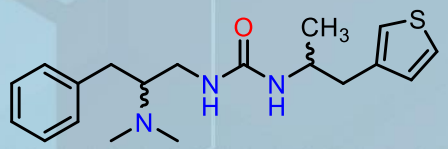
Note: Ketamine is not currently FDA-approved to treat pain

Towards Safer Opioid Analgesics

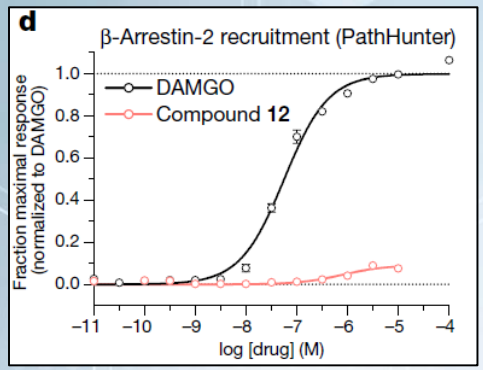
Structure-based Discovery of Opioid Analgesics with Reduced Side Effects







Compound **12**
Ki = 42 nM



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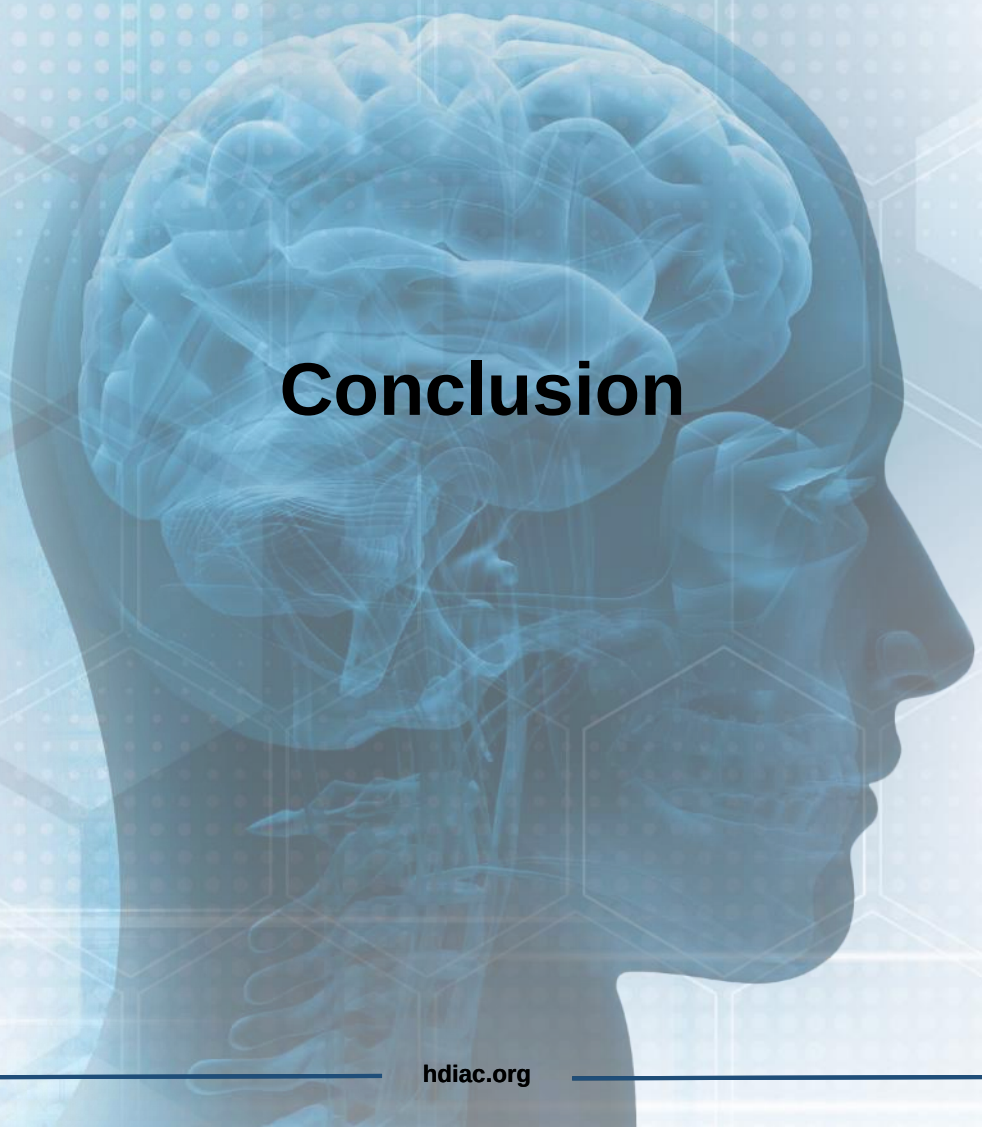
Manglik, A., Lin, H., Aryal, D. K., McCorvy, J. D., Dengler, D., Corder, G., . . . Shoichet, B. K. (2016). Structure-based discovery of opioid analgesics with reduced side effects. *Nature, 537*(7619), 185-190. doi:10.1038/nature19112

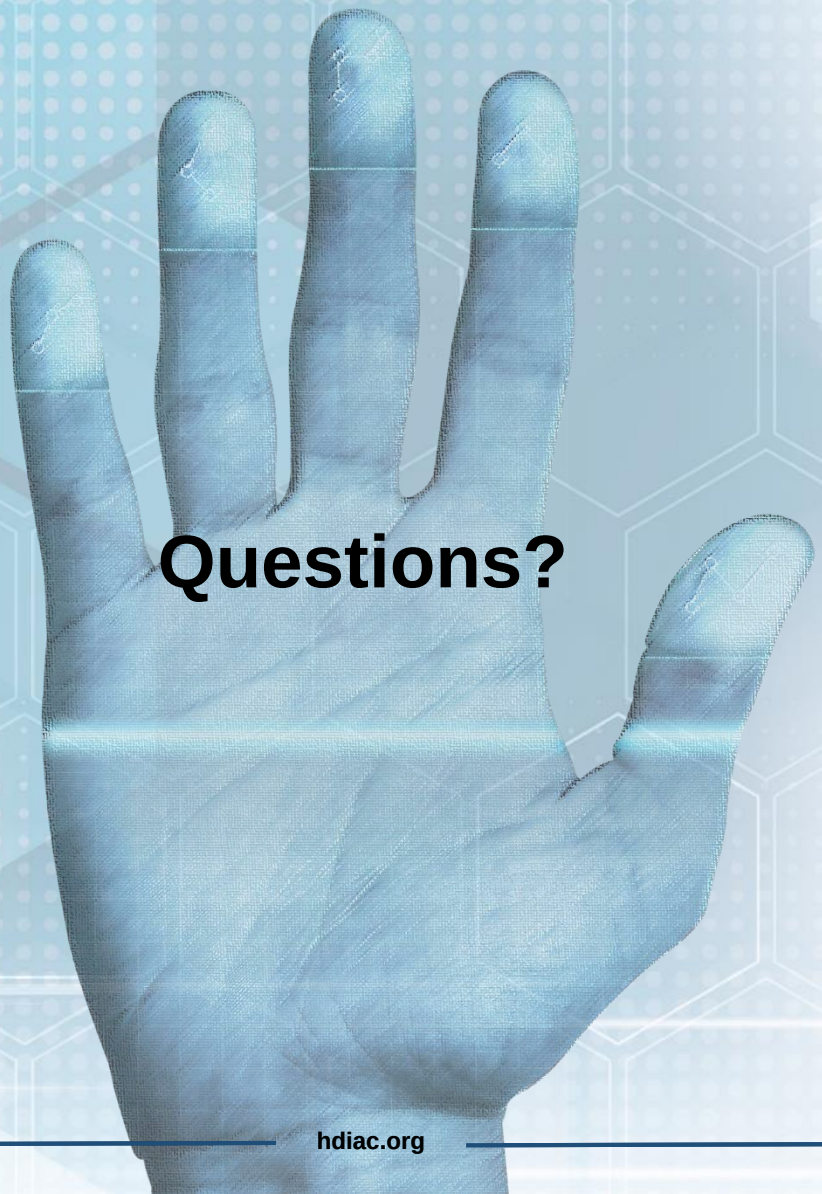


Conclusion

Battlefield Pain Management: Conclusions

- **Opioids remain the preferred analgesics on the battlefield**
  - Morphine, fentanyl, Dsuvia™
  - Effective drugs with many caveats
- **There are many challenges associated with developing non-opioid analgesics**
- **Ketamine is an attractive NMDA antagonist with analgesic properties**
  - Extensive battlefield use
  - Benefits over morphine
  - Delivery devices needed
- **New opioids with fewer side effects are being pursued by academia**

Note: Ketamine is not currently FDA-approved to treat pain



Questions?