

### NIH HEAL INITIATIVE

## Helping to End Addiction Longterm. The Intersection of Pain and Addiction



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National Institutes of Health HEAL Initiative NIH HEAL Initiative and Helping to End Addiction Long-term are service marks of the U.S. Department of Health and Human Services.

# Pain and Opioids: <u>The Web of Anesthesia, Analgesia and Narcosis</u>

- NIGMS-Anesthesia is a medical treatment that prevents patients from feeling pain during surgery- implies loss of sensation.
- From Hippocrates ~ 300 BC
  - <u>Anesthesia</u>, [anaesthoetos], used to describe parts of body that lose the power of feeling, but mixed with descriptions of depressed level of consciousness- case of a patient who "took no notice" [anaesthetos]
  - <u>Analgesia-</u> [analgetoi] to mean insensible to pain in patient who is [anesthetoi] also deaf to what is spoken and blind to what is happening.
  - <u>Narcotic-</u> [Narkoo], the word from which narcosis is derived means loss of senses and to grow numb. Is used by Hippocrates along with [anaestheta] to indicate when very hot water can be used on a patient. In other texts the words are used jointly.
  - Hippocratic texts frequently prescribe <u>opium extracts</u> for painful gynecologic disorders. Referred to for both analgesic and sleep producing.
  - Greek philosopher Dioskourides (1<sup>st</sup> century AD) first uses the word [anaesthesia] to describe the narcotic effects of the mandrake plant to cause loss of sensation.



A statue of Hippocrates stands at the place where he died, in Larissa, Greece. (Image credit: Georgios Alexandris/Shutterstoc k)

# US History of Addiction after Opioids for PAIN

- In mid-nineteenth century opiates used to treat pain, cough, neuralgia, alcoholism, insomnia, anxiety, fatigue, diarrhea, etc.
- During Civil War- 10 million opioid pills distributed to Union forces led to wave of addiction after the war.
- Opium imports increased four-fold between 1840 and 1890
- From mid to late 19<sup>th</sup> century drug use increased most rapidly in women. By 1895 2/3 of opium addicts were women treated for "female problems"
- In 1898 Bayer introduced heroin as a nonaddictive analgesic
- By 1900 1/200 Americans were addicted to opioids
- 1914 Harrison Narcotic Act passed to regulate medical opium



# **Balancing act of treating pain**

- 100 million American adults have pain
  - 40 million have severe pain
  - 25 million report daily pain
  - 8 million have pain that interferes with lifestyle









# Nature has placed mankind under the governance of two sovereign masters, Pain and Pleasure- Jeremy Bentham

Brain regions implicated in pain and reward processing by neuroimaging and electrophysiology studies who striking overlap.

Region	Pleasure/reward	Pain
Lateral prefrontal cortex	• Humans, fMRI, taste reward <sup>101</sup>	<ul> <li>Humans, H<sub>2</sub>O PET, hyperalgesic pair</li> <li>Humans, fMRI, pain<sup>103</sup></li> </ul>
- Anterior insula	<ul> <li>Humans, fMRI, food cravings<sup>104</sup></li> <li>Humans, H<sub>2</sub>O PET, chocolate reward<sup>75</sup></li> </ul>	<ul> <li>Humans, fMRI, pain<sup>105</sup></li> <li>Humans, fMRI, placebo analgesia<sup>106</sup></li> </ul>
Posterior insula	<ul> <li>Humans, fMRI, hypothetical reward<sup>107</sup></li> </ul>	<ul> <li>Humans, direct brain stimulation<sup>108</sup></li> <li>Humans, fMRI, pain<sup>105</sup></li> </ul>
Orbitofrontal cortex	<ul> <li>Humans, fMRI, pleasant touch<sup>74</sup></li> <li>Humans, fMRI, chocolate reward<sup>75</sup></li> </ul>	<ul> <li>Humans, fMRI, pain<sup>74</sup></li> <li>Humans, fMRI, placebo analgesia<sup>106</sup></li> </ul>
Medial prefrontal cortex	<ul> <li>Humans, H<sub>2</sub>O PET, pleasurable music<sup>64</sup></li> <li>Humans, fMRI, monetary reward<sup>109</sup></li> </ul>	• Humans, fMRI, pain <sup>130,113</sup>
Anterior cingulate gyrus	<ul> <li>Monkeys, electrophysiology<sup>112</sup></li> <li>Humans, H<sub>2</sub>O PET, chocolate reward<sup>75</sup></li> </ul>	<ul> <li>Humans, fMRI, pain<sup>133</sup></li> <li>Humans, opioid PET<sup>83</sup></li> </ul>
Dorsal striatum	<ul> <li>Humans, fMRI, fruit juice<sup>114</sup></li> <li>Humans, fMRI, monetary reward<sup>115</sup></li> </ul>	<ul> <li>Humans, dopamine ligand PET, pain</li> <li>Humans, fMRI, pain<sup>116</sup></li> </ul>
Nucleus accumbens/ ventral striatum	<ul> <li>Humans, fMRI and dopamine ligand PET<sup>4</sup>, monetary reward <sup>65</sup></li> <li>Rodents, hedonic hotspot, taste reactivity</li> <li>Humans, dopamine ligand PET<sup>45</sup>, drug reward</li> </ul>	<ul> <li>Humans, dopamine ligand PET<sup>43</sup></li> <li>Humans, fMRI, expectation of pain<sup>4</sup></li> <li>Rodents, pain-induced analgesia<sup>20</sup></li> </ul>
Ventral pallidum	<ul> <li>Rodents, taste reactivity<sup>62,65</sup></li> </ul>	<ul> <li>Rodents, tracing, pain affect<sup>12</sup></li> <li>Humans, μ-opioid PET, sustained pa</li> </ul>
Thalamus	* Humans, H <sub>2</sub> O PET, chocolate reward <sup>75</sup>	* Humans, fMRI, placebo analgesia <sup>108</sup>
Hypothalamus	* Humans, H <sub>2</sub> O PET, pleasurable music <sup>117</sup>	<ul> <li>Rodents, tracing of nociceptive path</li> <li>Humans, direct brain stimulation<sup>118</sup></li> </ul>
Midbrain	<ul> <li>Humans, H<sub>2</sub>O PET, chocolate reward<sup>75</sup></li> <li>Humans, H<sub>2</sub>O PET, pleasurable music<sup>64</sup></li> </ul>	<ul> <li>Humans, fMRI, anticipation of pain<sup>1</sup></li> <li>Humans, fMRI, pain<sup>120</sup></li> </ul>
Amygdala	<ul> <li>Humans, H<sub>2</sub>O PET, pleasurable music<sup>64</sup></li> <li>Primates, reward anticipation/learning<sup>63</sup></li> </ul>	Humans, fMRI, pain <sup>20,129</sup>
Hippocampus	<ul> <li>Humans, fMRI, unexpected reward<sup>121</sup></li> <li>Humans, H<sub>2</sub>O PET, pleasurable music<sup>64</sup></li> </ul>	<ul> <li>Humans, fMRI, pain<sup>122</sup></li> <li>Humans, fMRI, anticipation of pain</li> </ul>
Cerebellum	* Humans, fMRI, unexpected reward <sup>121</sup>	* Humans, fMRI, pain <sup>123</sup>
Brainstem	<ul> <li>Rodents, taste reactivity<sup>124</sup></li> <li>Rodents, conditioned place preference<sup>40</sup></li> </ul>	<ul> <li>Humans, fMRI, pain<sup>121</sup></li> <li>Rodents, pain<sup>40</sup></li> </ul>

### Facing Opioid Overuse Disorder in Pain Management

### • The Challenging Questions:

- How to best prescribe opioids to patients with pain who are at high risk for developing opioid misuse.
  - Alcohol, cocaine, or other <u>substance abuse</u>, chronic use of benzodiazepine
  - Past <u>history</u> or family history of substance use disorder, sexual abuse, peer group OUD, mental health disorder, history of sexual abuse
  - <u>Pain catastrophizing-</u>irrationally negative fore-cast of future events, pain related worry and fear, feel hopeless in the context of pain, consumed by thoughts of pain anticipation
- How to differentiate patients without a painful condition who complain of pain seeking opioids for other reasons?
  - How to best avoid prescribing opioids that are diverted and sold for profit?

### Facing Opioid Overuse Disorder in Pain Management

### • The Challenging Questions:

- How to best treat patients presenting with pain <u>and</u> an opioid overuse disorder?
  - Patients with a painful condition- estimated at 20% of those treated for pain with opioids
    - <u>How to distinguish worsening pain frequency</u>/intensity vs. drive to obtain "<u>rewarding effects"</u>?
      - 85% of those with prescription OUD have a chronic pain condition
      - Physicians frequently "distrust" that patients indeed suffer from "genuine pain," due to previous encounters with manipulative "drug seekers". This negative regard leads to undertreatment of pain.
    - How to negotiate treating patients with <u>concomitant disorders</u> such as anxiety/depression/catastrophizing to which opioids are perceived to provide relief?
    - How to manage patients with chronic pain who are "<u>noncompliant</u>" with prescribed opioids?
      - They are commonly dismissed from medical practice, but then seek another physician, or obtain opioids illegally.
  - How to coordinate the complex care of persons with pain and OUD?

### Why is pain treatment so challenging?

### Chronic pain is often set in a web of disorders contributing to disability



# Patient Burden is Comples and Extends Beyond Pain

Fatigue and cognition





Pitcher et al. 2019



Health care usage

#### **Mental health**



Frequency ("daily")

Intensity ("a lot")

# The Problem @ The Ground Level: Primary Care.

JGIM

#### INNOVATIONS IN EDUCATION

#### Primary Care Provider Concerns about Management of Chronic Pain in Community Clinic Populations

Carole C. Upshur, EdD,<sup>1</sup> Roger S. Luckmann, MD, MPH,<sup>1</sup> Judith A. Savageau, MPH<sup>1</sup> <sup>1</sup>Department of Family Medicine and Community Health, University of Massachusetts Medical School, Worcester, MA, USA.

- Studies about primary care treatment of chronic pain report providers feel they have <u>inadequate</u> <u>training</u>, <u>limited confidence</u> in their ability to provide effective treatment, and a <u>low level of</u> <u>satisfaction</u> with their care of chronic pain patients.
- 81.5% of primary care physicians rated their undergraduate medical education in chronic pain as insufficient, with 54.7% rating their chronic pain training as residents as insufficient.



POSTGRADUATE MEDICINE, 2017 VOL. 129, NO. 3, 332–335 http://dx.doi.org/10.1080/00325481.2017.1297668



🔍 Cheok for update

CLINICAL FEATURE EDITORIAL

Chronic pain management in medical education: a disastrous omission

John D. Loeser<sup>a</sup> and Michael E. Schatman<sup>b</sup>

#### Pain Education in North American Medical Schools

Lina Mezei, Beth B. Murinson, and the Johns Hopkins Pain Curriculum Development Team. J of Pain 2011



Pain teaching hours by school. Main figure shows schools teaching 0 to 5 hours, 5 to 10 hours aetc.. U.S. medical schools/ dark gray bars, Canadian schools/light gray. Inset shows expanded x-axis for 0 to 10 hours, U.S. schools only.



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### Research: Managing patients with pain and OUD

- Frequent use of opioids for the treatment of chronic pain along with increasing frequency of opioid-related problems in military veterans
- Research: Integrated psychosocial treatment in veterans with chronic pain, who are taking buprenorphine for the treatment of OUD.
- Acceptance and Commitment Therapy for chronic pain and Mindfulness Based Relapse Prevention for substance use and misuse.
- Identify meaningful outcomes for both pain and OUD



### Kevin Vowles and Katie Witkiewitz, University of New Mexico



### Research: Peri operative pain management: mitigate risks of opioid exposure in naïve youth

5-7% of adolescents prescribed an opioid after surgery develop opioid misuse or persistent opioid use.

Research: mHealth psychosocial intervention "SurgeryPal" to prevent chronic postsurgical pain in adolescents who are undergoing spinal surgery

- Identify psychosocial risk factors for chronic pain
- Teach pain self-management skills
- Reduce opioid exposure
- Track opioid use 6 months post op





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PI: Jennifer Rabbits, & Tonya Palermo Seattle Children's Hospital



### **Research: Hemodialysis Opioid Prescription Effort:** HOPE

Opioid use rates in people on dialysis are 3 times higher than the general population over 65: significant risk for addiction.

More than half had one or more opioid prescriptions during any 12-month period.

Opioid use is linked to poor health outcomes: more hospitalizations, fractures, and deaths.

**HOPE:** safer and more effective treatments: non-pharmacological approaches with conversion to buprenorphine for pain in dialysis patients



# The Final Solution: Science Resulting in More Effective Non-Addictive Treatment for Pain

#### PAIN

### Anti–PD-1 treatment impairs opioid antinociception in rodents and nonhuman primates

Zilong Wang<sup>1</sup>\*, Changyu Jiang<sup>1</sup>\*, Qianru He<sup>1</sup>, Megumi Matsuda<sup>1</sup>, Qingjian Han<sup>1</sup>, Kaiyuan Wang<sup>1</sup>, Sangsu Bang<sup>1</sup>, Huiping Ding<sup>2</sup>, Mei-Chuan Ko<sup>2,3</sup>, Ru-Rong Ji<sup>1,4,5†</sup>

nature ARTICLES https://doi.org/10.1038/s41593-020-0632-8

# General anesthetics activate a potent central pain-suppression circuit in the amygdala

Thuy Hua<sup>©</sup><sup>1,3</sup><sup>⊠</sup>, Bin Chen<sup>1,3</sup>, Dongye Lu<sup>1</sup>, Katsuyasu Sakurai<sup>1</sup>, Shengli Zhao<sup>1</sup>, Bao-Xia Han<sup>1</sup>, Jiwoo Kim<sup>1</sup>, Luping Yin<sup>©</sup><sup>1</sup>, Yong Chen<sup>2</sup>, Jinghao Lu<sup>1</sup> and Fan Wang<sup>©</sup><sup>1</sup><sup>⊠</sup>

#### NEUROSCIENCE

### An amygdalar neural ensemble that encodes the unpleasantness of pain

Gregory Corder<sup>1,2,3,4</sup>\*†, Biafra Ahanonu<sup>5,6,7</sup>\*, Benjamin F. Grewe<sup>5,7</sup>‡, Dong Wang<sup>1</sup>, Mark J. Schnitzer<sup>5,6,7,8</sup>§, Grégory Scherrer<sup>1,2,3,4,9</sup>§ Electrophysiological and transcriptomic correlates of neuropathic pain in human dorsal root ganglion neurons

Robert Y. North,<sup>1,\*</sup> Yan Li,<sup>2,\*</sup> Pradipta Ray,<sup>3,\*</sup> Laurence D. Rhines,<sup>4</sup> Claudio Esteves Tatsui,<sup>4</sup> Ganesh Rao,<sup>4</sup> Caj A. Johansson,<sup>5</sup> Hongmei Zhang,<sup>2</sup> Yeun Hee Kim,<sup>6</sup> Bo Zhang,<sup>6</sup> Gregory Dussor,<sup>3</sup> Tae Hoon Kim,<sup>6</sup> Theodore J. Price<sup>3</sup> and Patrick M. Dougherty<sup>2</sup>





### The case for basic pain research: Calcitonin gene-related peptide antagonists

#### **ANNALS** *of* the New York ACADEMY OF SCIENCES

#### 🔂 Full Access

Molecular Mechanisms of Cell-Specific and Regulated Expression of the Calcitonin/ $\alpha$ -CGRP and  $\beta$ -CGRP Genes

MICHELE M. BENNETT, SUSAN G. AMARA

First published: June 1992 | https://doi.org/10.1111/j.1749-6632.1992.tb22755.x | Citations: 12

# THE BRAIN PRIZE

The world's largest brain research prize is Danish and is awarded by the Lundbeck Foundation. Each year, we award 10 million DKK (approx. 1,3 million€) to one or more brain researchers who have had a groundbreaking impact on brain research.

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#### Winners of The Brain Prize 2021

Figure adapted from Edvinsson et al., 2018.

Professors Lars Edvinsson, Peter Goadsby, Michael Moskowitz, and Jes Olesen have been awarded The Brain Prize 2021, worth 10 million Danish kroner, for their groundbreaking work on the causes and treatment of migraine.



### **HEAL Analgesic Development Program**







# Enhancing Pain Management

Accelerating Research to Improve Pain Care







# **Thank You!**

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### How will COVID affect those with chronic pain?



**PROMIS-PI bank** pain interference with:

- physical activities
- cognition
- emotional state
- Recreation
- sleep
- enjoyment in life

Cross-lagged longitudinal analysis showed that social isolation (SI) predicted pain interference (PI), but PI did not predict SI



### Persistent Symptoms of COVID-19 in Non-hospitalized Patients: (2-3 wks post test)



#### **NEW NIH FOA NIH:**

Post-Acute Sequelae of SARS-CoV-2 Initiative to understand how SARS-CoV-2 can lead to long-lasting and widespread effects and to identify ways to prevent and treat these conditions.



Centers for Disease Control and Prevention CDC 24/7: Saving Lives, Protecting People™

July 31, 2020

Morbidity and Mortality Weekly Report (MMWR)

### **Prevalence and Profile of High-Impact Chronic Pain in the US**

2011 National Health Interview Surv	vey Sample Questionnaire N=15, 670	Population Estimates
Chronic pain	pain experience on most days in last 3 months	40 m, 18.4%
Chronic Pain Without Limitation (CPWL)	no activity limitations/participation restrictions.	29.9 m, 13.6%
High Intensity Chronic Pain (HICP)	as above with addition of <a>1</a> activity limitation	10.6 m, 4.8%



# US Estimates of Chronic Musculoskeletal Pain Treatment in Children, Adolescents, Young Adults

- Average Annual visits to health care provider
  - 0.6 million for children <13 years
  - 1.0 million adolescents 13-17 years
  - 1.6 million for young adults 18-24 years
- Most prevalent chronic musculoskeletal pain types across all age groups
  - joint pain
  - back pain
  - limb pain
  - muscle pain
  - Neck pain

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The Journal of Pediatrics, 1/29 2021

Data From the 2007-2015 National Ambulatory Medical Care Survey: Feldman, PT, PhD<sub>1,2</sub>, and Nahin, PhD, MPH<sub>3</sub>



### **HEAL Harmonization of Patient-reported Pain Outcomes Data**



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