The Opioid Epidemic: How, Where, and What Can Be Done?

NIH Demystifying Medicine Lecture Series

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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

Source: NIDA, IMS Health, National Prescription Audit, years 1997-2011
Pain is at the root of the opioid epidemic
“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.

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<thead>
<tr>
<th>Region</th>
<th>Pleasure/reward</th>
<th>Pain</th>
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</thead>
<tbody>
<tr>
<td>Lateral prefrontal cortex</td>
<td>Humans, fMRI, taste reward</td>
<td>Humans, H2O PET, hyperalgesic pain</td>
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<tr>
<td>Anterior insula</td>
<td>Humans, fMRI, food craving</td>
<td>Humans, fMRI, pain</td>
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<td>Posterior insula</td>
<td>Humans, fMRI, Hypothetical reward</td>
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<td>Orbitofrontal cortex</td>
<td>Humans, fMRI, pleasant touch</td>
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<td>Medial prefrontal cortex</td>
<td>Humans, H2O PET, pleasurable music</td>
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<td>Anterior cingulate gyrus</td>
<td>Monkeys, electrophysiology</td>
<td>Humans, fMRI, pain</td>
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<td>Dorsal striatum</td>
<td>Humans, fMRI, fruit juice</td>
<td>Humans, opioid PET</td>
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<tr>
<td>Nucleus accumbens/ventral striatum</td>
<td>Humans, fMRI and dopamine ligand PET, monetary reward</td>
<td>Humans, dopamine ligand PET, pain</td>
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<td>Ventral pallidum</td>
<td>Rodents, taste reactivity</td>
<td>Rodents, tracing, pain affect</td>
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<tr>
<td>Thalamus</td>
<td>Humans, H2O PET, chocolate reward</td>
<td>Humans, fMRI, placebo analgesia</td>
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<tr>
<td>Hypothalamus</td>
<td>Humans, H2O PET, pleasurable music</td>
<td>Rodents, tracing of nociceptive pathway</td>
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<tr>
<td>Midbrain</td>
<td>Humans, H2O PET, chocolate reward</td>
<td>Humans, fMRI, anticipation of pain</td>
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<tr>
<td>Amygdala</td>
<td>Humans, H2O PET, pleasurable music</td>
<td>Humans, fMRI, pain</td>
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<tr>
<td>Hippocampus</td>
<td>Humans, fMRI, unexpected reward</td>
<td>Humans, fMRI, pain</td>
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<tr>
<td>Cerebellum</td>
<td>Humans, fMRI, unexpected reward</td>
<td>Humans, fMRI, pain</td>
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<tr>
<td>Brainstem</td>
<td>Rodents, taste reactivity</td>
<td>Humans, fMRI, pain</td>
</tr>
<tr>
<td></td>
<td>Rodents, conditioned place preference</td>
<td>Humans, fMRI, pain</td>
</tr>
</tbody>
</table>

Pain v. reward

Shared pathway

- OFC
- NAc
- VP
- Amy

Eg. naloxone

Opioid receptor mediates reward and analgesia and....death

- Morphine
- μ-opioid receptor
- G protein
- β-arrestin

- Analgesia
- TRV130
- Increased Analgesia

- ↓ Respiration
- ↓ GI function

Eg. morphine


Pain. 2014 Sep;155(9):1829-35.
In 2016, NIH invested $483 million on pain research.

Pain cuts across all 27 of the NIH Institutes and Centers.
The NIH Pain Consortium Membership

Mission

To enhance pain research and promote collaboration among researchers across the NIH Institutes and Centers that have programs and activities addressing pain

http://painconsortium.nih.gov/

National Cancer Institute
National Eye Institute
National Institute on Aging
National Institute on Alcohol Abuse and Alcoholism
National Institute of Arthritis and Musculoskeletal and Skin Diseases
National Institute of Biomedical Imaging and Bioengineering
National Institute of Child Health and Human Development
National Institute of Deafness and Other Communication Disorders
National Institute of Dental and Craniofacial Research
National Institute of Diabetes and Digestive and Kidney Disorders
National Institute on Drug Abuse
National Institute of General Medical Sciences
National Institute of Mental Health

National Institute of Minority Health and Disparities
National Institute of Neurological Disorders and Stroke
National Institute of Nursing Research
National Heart Lung and Blood Institute
National Center for Advancing Translational Science
National Center for Complementary & Integrative Health
John E. Fogarty International Center
Warren Grant Magnuson Clinical Center
Office of Science Policy and Analysis
Office of Behavioral and Social Sciences Research
Office of Technology Transfer
Office of Research on Women’s Health
Office of Rare Diseases
Institute of Medicine report led to the National Pain Strategy

The NPS is the government’s first broad-ranging effort to improve how pain is perceived, assessed, and treated: a significant step toward the ideal state of pain care.

Coordinated roadmap toward improving U.S. pain care in:

- population research;
- prevention and care;
- disparities;
- service delivery and payment;
- training and professional/public education

OASH is coordinating trans-agency implementation
National Pain Strategy

- Disparities
- Prevention & Care
- Services & Payment
- Professional Education & Training
- Public Education & Communication
- Population Research

Research
Federal Pain Research Strategy

Research Priorities to Guide the Federal Pain Research Agenda
Released June 2017

Continuum of Pain

PREVENTION OF ACUTE & CHRONIC PAIN
ACUTE PAIN & ACUTE PAIN MANAGEMENT
TRANSITION FROM ACUTE TO CHRONIC PAIN
CHRONIC PAIN & CHRONIC PAIN MANAGEMENT

WHAT HAPPENS AND TO WHOM?
WHY AND HOW DOES IT HAPPEN?
HOW TO MANAGE?

BASIC SCIENCE
CLINICAL SCIENCE
UNDERSTAND MECHANISMS
TRANSLATE/TREAT

DISPARITIES

Research Priorities:
- Continuum of Pain
- Prevention of Acute & Chronic Pain
- Acute Pain & Acute Pain Management
- Transition from Acute to Chronic Pain
- Chronic Pain & Chronic Pain Management

Questions:
- What happens and to whom?
- Why and how does it happen?
- How to manage?

Resources:
https://iprcc.nih.gov/
NIH funded Centers of Excellence in Pain Education were created to develop, evaluate, and distribute pain management curriculum resources (case based studies) for medical, nursing, dental, and pharmacy schools to enhance and improve how health care professionals are taught about pain and treatment of pain.

Edna, 70, chronic low back pain

Beverly, 46, burning mouth syndrome

Morgan, 14, headaches

Edna, Beverly, Morgan

Harvard University
University of Connecticut
University of Iowa
University of Washington
Johns Hopkins University
University of Rochester

Southern Illinois University
St. Louis University
University of Alabama at Birmingham
University of Pennsylvania
Pittsburgh University

https://painconsortium.nih.gov/NIH_Pain_Programs/CoEPES.html
Opioids act on reward circuits as well as pain circuits. There are multiple non-opioid control nodes in the pain circuits that should be targeted for non-addictive pain treatments.

25.5 M adults have pain every day
23.4 M report a lot of pain
10.5 M adults report a lot of pain every day
8 M have pain interfering with lifestyle

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Advances in pain research: New Targets for Pain

- HSV vector driven expression of analgesic signals in DRG
- Transient receptor potential channels (TRPA1/4)
  - TRPA1 gain of function mutation causes familial episodic pain syndrome
- Voltage activated Ca++ channel blockers
- K+ channels blockers
- Chemokine receptor antagonists
- Tetrahydrobiopterin from GTP release from injured neurons, polymorphisms in BCH1 enzyme linked to pain vulnerability
- Alpha2 adrenergic agonist
- Bivalent MOR with linked mGluR5 antagonist, CCR5 antagonist, delta OR antagonist
- Epigenetic mechanisms involved in chronic pain
- microRNA cluster 183

*Nat Rev Drug Discov.* 2017 Aug;16(8):545-564
• Calcitonin gene-related peptide (cGRP) levels:
  – rise during spontaneous migraine attacks
  – Increased levels in serum in chronic migraine patients
  – decrease in response to triptans in parallel with symptomatic relief
• Kappa Opioid Receptor (KOR) antagonists block increased cGRP
• Anti-cGRP Monoclonal antibodies are in phase 3 clinical trials for migraine prevention

Advances in pain research: Spinal Cord Stimulation and Opioid Use

- 86 patients underwent SCS for chronic pain
  - 53 had used opioids for pain prior to surgery
- 64% of patients who were using opioids prior to SCS reduced (n = 2) or eliminated opioid use (n = 29) at 1 yr postoperatively
- Patients who eliminated opioid use or never used opioids had superior clinical outcomes to those who continued use.

Advances in Pain Research: FDA Approval for Vagus Nerve Stimulation in Headache

gammaCore® Receives FDA Clearance for the Acute Treatment of Pain Associated with Migraine Headache in Adult Patients
First non-invasive vagus nerve stimulation therapy applied at the neck provides new option for Americans living with migraine

FDA Releases gammaCore®, the First Non-Invasive Vagus Nerve Stimulation Therapy Applied at the Neck for Acute Treatment of Pain Associated with Episodic Cluster Headache in Adult Patients

Live cell imaging of GCaMP responses in Nav1.8+ trigeminal ganglion neurons.
Pragmatic clinical trial

Hypothesis: patients who receive an interdisciplinary biopsychosocial intervention at their primary care clinic will have a greater reduction in pain impact in the year following than patients receiving usual care.
HEAL Initiative

Helping to End Addiction Long-term (HEAL) Initiative

1. Prevent addiction through enhanced pain management
   • Understand Origins of Chronic Pain
   • Develop New Non-Addictive Treatments for Pain
   • Build Clinical Trial Network for Chronic Pain
   • Enhance Precision Pain Management

2. Improve treatments for opioid misuse disorder and addiction
   • Improve Therapeutic Approaches to Addiction
   • Evaluate Treatments, Consequences of NOWS
   • Optimize Effective Treatments through Pilot Demonstration Projects

Announced April 4, 2018
The goal is to discover, optimize, and validate objective mechanistic markers associated with pain conditions to:

1. Enrich clinical study population:
   - Allow or improve cohort stratification
   - Provide predictors of treatment response
2. Demonstrate therapeutic target engagement

NINDS Pain Biomarker Efforts
- Workshop focused on “Best Practices for Biomarker Discovery” early 2019
- NINDS funding opportunities
- Centralized NINDS “one-stop” biomarker web page

**Analytical Validation of a Candidate Biomarker For Neurological Disease**
*PAR-NS-18-549, PAR-18-550*

**Clinical Validation of a Candidate Biomarker For Neurological Disease**
*PAR-NS-18-548, PAR-NS-18-664*

Cooperative Agreement Grant Mechanisms: U01 (Academic) and U44 (SBIR)
fMRI as a Biomarker for Pain

**A Component Process Approach**
- Clinical/functional outcomes
- Component process
- Brain biomarkers

**B Stimulus Intensity Independent Pain Signature-1 (SIIPS1)**
- Left: 3.07 t = 5.0
- Right: 3.07 t = -5.0
- vmPFC: 11
- mPFC: 11
- MCC/SMA: 11

**C Neurologic Pain Signature (NPS)**
- dACC
- dpINS/S2
- Predictive weights

**D NPS ‘Receptive Field’**
- Specificity (Not activated by)
  - Aversive images
  - Social rejection
  - Observed pain
  - Pain anticipation
  - Cognitive demand
  - Nausea
  - Cognitive reappraisal
  - Pain recall
  - Warmth
- Sensitivity (Activated by)
  - Gastric distention
  - Esophageal distention
  - Rectal distention
  - Vaginal distention
  - Cold pain
  - Noxious pressure
  - Electric shock
  - Noxious heat

**E Benefits of a Combinatorial Model**
- Explained variance (%)
- NPS-SIIPS1
- NPS
- SIIPS1
- Standard

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Neural Circuitry Changes with Chronic Pain

Nerve fibers
Peripheral sensors
Spinal cord
Nociceptor
Altered brain volume structure activity
Volume Control
Spinal cord
Peripheral nerve
Common Fund: Can we prevent chronic pain?

**Gap:** Risk predictors of the transition from acute to chronic pain

**Goal:** Identify those at risk for transition to chronic pain through mechanistic objective signatures

- Phenotyping, genotyping
- Imaging
- Omics

**Justification**

- Pain mechanisms
- Novel druggable targets
- Cohort stratification
- Prevention strategies

**Outcomes**

- Identification of combined biomarkers with clinically meaningful predictive value
- Comprehensive data set
Thank You!

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