Helping to End Addiction Long-term. The Intersection of Pain and Addiction

May 17, 2021
Walter Koroshetz, M.D.
• NIGMS-Anesthesia is a medical treatment that prevents patients from feeling pain during surgery- implies loss of sensation.

• From Hippocrates ~ 300 BC
  • Anesthesia, [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]
  
  • Analgesia- [analgetoi] to mean insensible to pain in patient who is [anesthetoi] also deaf to what is spoken and blind to what is happening.
  
  • Narcotic- [Narkoo], the word from which narcosis is derived means loss of senses and to grow numb. Is used by Hippocrates along with [anaestheteta] to indicate when very hot water can be used on a patient. In other texts the words are used jointly.
  
  • Hippocratic texts frequently prescribe opium extracts for painful gynecologic disorders. Referred to for both analgesic and sleep producing.
  
  • Greek philosopher Dioskourides (1st century AD) first uses the word [anaesthesia] to describe the narcotic effects of the mandrake plant to cause loss of sensation.
• 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 19th 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

Source: NIDA, IMS Health, National Prescription Audit, years 1997-2011
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.
• 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 substance abuse, chronic use of benzodiazepine
    • Past history or family history of substance use disorder, sexual abuse, peer group OUD, mental health disorder, history of sexual abuse
    • Pain catastrophizing—irrationally negative forecast 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?
• The Challenging Questions:
  • How to best treat patients presenting with pain and an opioid overuse disorder?
    • Patients with a painful condition—estimated at 20% of those treated for pain with opioids
      • How to distinguish worsening pain frequency/intensity vs. drive to obtain “rewarding effects”?
        • 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 concomitant disorders such as anxiety/depression/catastrophizing to which opioids are perceived to provide relief?
      • How to manage patients with chronic pain who are “noncompliant” 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:

- Fatigue/Cognitive
- Injury
- Obesity
- Inactivity
- Sedentary life-style
- Medical Conditions
  - Depression
  - Anxiety
  - Medication Overuse
  - Alcohol Abuse
  - Sleep Disorder
Patient Burden is Complex and Extends Beyond Pain

Fatigue and cognition

- General adult population
- Chronic pain
- High Impact Chronic Pain

Pitcher et al. 2019

Mental health

Health care usage

- Medical specialist consult (last 12 months)
- >10 health office visits (last 12 months)
- >1 surgical procedures (last 12 months)
• Studies about primary care treatment of chronic pain report providers feel they have inadequate training, limited confidence in their ability to provide effective treatment, and a low level of satisfaction 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.
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
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

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

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

An amygdalar neural ensemble that encodes the unpleasantness of pain

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

Electrophysiological and transcriptomic correlates of neuropathic pain in human dorsal root ganglion neurons
The case for basic pain research: Calcitonin gene-related peptide antagonists

Molecular Mechanisms of Cell-Specific and Regulated Expression of the Calcitonin/α-CGRP and β-CGRP Genes

MICHELE M. BENNETT, SUSAN G. AMARA


Figure adapted from Edvinsson et al., 2018.
HEAL Analgesic Development Program

Planning for Therapeutic Devel.
- Team building
- Mechanisms
- Feasibility

Initial Therapeutic Devel.
- Mechanisms
- Assays
- Models
- Biomarkers
- Proof of efficacy/concept

Optimization Stage
- Optimization of leads & Target Engagement Biomarkers
- IND
- 1st in human trials

- Type of pain
- Pain Condition
- ID Patient specific targets
- Molecular Pathway
- Cell type

Identified “HIT to Lead”
IND approved, PHASE I complete asset
## Enhancing Pain Management

### Accelerating Research to Improve Pain Care

<table>
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<tr>
<th>Discovery</th>
<th>Preclinical Development</th>
<th>Clinical Studies</th>
<th>Implementation/Dissemination</th>
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<tr>
<td><strong>Target Discovery</strong></td>
<td>Are new drugs safe?</td>
<td>Safety testing</td>
<td>Preclinical Development</td>
</tr>
<tr>
<td>How can we find novel drugs?</td>
<td>Longitudinal Studies</td>
<td>Effectiveness Trials</td>
<td>Longitudinal Studies</td>
</tr>
<tr>
<td><strong>Pre-screening platforms</strong></td>
<td>Who will develop chronic pain?</td>
<td>Mann et al.</td>
<td>Longitudinal Studies</td>
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<tr>
<td>What novel molecule, biologic, device might relieve pain?</td>
<td><strong>Therapeutics Development</strong></td>
<td>Which therapies work best?</td>
<td>Longitudinal Studies</td>
</tr>
<tr>
<td>How can we develop or improve drugs &amp; devices to relieve pain?</td>
<td><strong>Biomarkers &amp; Endpoints</strong></td>
<td>For whom?</td>
<td>Longitudinal Studies</td>
</tr>
<tr>
<td>How do we assess pain?</td>
<td><strong>Longitudinal Studies</strong></td>
<td><strong>Pragmatic Trials</strong></td>
<td>Longitudinal Studies</td>
</tr>
<tr>
<td>Who will respond to a treatment?</td>
<td>Who will develop chronic pain?</td>
<td>How do we get treatments into the clinic?</td>
<td>Longitudinal Studies</td>
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Thank You!

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Follow me @NINDSdirector
How will COVID affect those with chronic pain?

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

PROMIS-PI bank
- pain interference with:
  - physical activities
  - cognition
  - emotional state
  - Recreation
  - sleep
  - enjoyment in life
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.
# Prevalence and Profile of High-Impact Chronic Pain in the US

<table>
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<tr>
<th>Chronic pain</th>
<th>Pain experience on most days in last 3 months</th>
<th>Population Estimates</th>
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<tr>
<td>Chronic Pain Without Limitation (CPWL)</td>
<td>no activity limitations/participation restrictions.</td>
<td>29.9 m, 13.6%</td>
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<tr>
<td>High Intensity Chronic Pain (HICP)</td>
<td>as above with addition of ≥1 activity limitation</td>
<td>10.6 m, 4.8%</td>
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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

The Journal of Pediatrics, 1/29 2021
Data From the 2007-2015 National Ambulatory Medical Care Survey: Feldman, PT, PhD\textsubscript{1,2}, and Nahin, PhD, MPH\textsubscript{3}
HEAL Harmonization of Patient-reported Pain Outcomes Data

Provide quality data for interpretability of findings across studies, pain conditions, populations, interventions

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<tr>
<th>Core CDEs</th>
<th>Supplemental CDEs</th>
<th>370 supplemental questionnaires</th>
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<td>Demographic Questions</td>
<td>Adult and Pediatric Questionnaires</td>
<td>Chronic and Acute Pain Questionnaire</td>
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<th>BACPAC</th>
<th>Bio-markers</th>
<th>EPPIC Net</th>
<th>ERN</th>
<th>HOPE</th>
<th>PRISM</th>
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<tr>
<th>Pain Intensity</th>
<th>Pain Interference</th>
<th>Physical Functioning/QOL</th>
<th>Sleep</th>
<th>Pain Catastrophizing</th>
<th>Depression</th>
<th>Anxiety</th>
<th>Global Satisfaction</th>
<th>Substance Use Screener</th>
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NIH HEAL INITIATIVE