The Future of Pain Medicine

Principles and Practice of Pain Medicine

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Today’s Talk

- Established and emerging trends
  - Which treatments will be provided?
  - Who will provide/receive pain care?
  - Reframing pain from synapse to society

- Translational science
  - Personalized ("precision") medicine
  - Formulation science (opioid ADFs)

- References: Bonney & Carr (AAPM 2013); Carr & Cousins (Eger 2014); ACTTION, IMMPACT

- Breaking news: CDC, National Pain Strategy

- Presenter conflicts of interest: None
3 Key Concepts

◆ Pain is a disease
  - High prevalence and burden
  - New interest in acute ➔ chronic transition
  - BUT: lagging evidence base c/w other diseases
◆ Pain management is a human right
  - We didn’t say “zero pain”!
◆ Pain is a public health problem
  - Disease = pathology + host + environment
  - Disparities, inequities, social justice
  - Prevention models: 1°, 2°, 3°
  - 2011 IOM report; 2016 National Pain Strategy
PAIN BEHAVIOR

SUFFERING

PAIN

NOCICEPTION
“The Fundamental Unit of Pain is the Cell”

- Above is title of 2014 review article in Pain supplement by Reichling, Green and Levine.
- However, no figures in that supplement depict individual cells.
- Figure from Ji R-R et al, Glia and pain: Is chronic pain a gliopathy? Pain 154 (2013) S10-S28
Pain is a Disease (1)

- Injury triggers a cascade of responses
- PNS, CNS promptly adapt, reorganize, remember
- “Programmed instability” links pain, memory
- Acute and chronic pain = continuum
- Increasing documentation of chronic neuropathic pain after surgery (NNH 2-7)
- Unclear why NNH isn’t = 1
Pain is a Disease (2)

- **Peripheral Nervous System**
  - damaged axons sprout, overexpress Na$^+$ channels, alpha receptors, form collaterals
  - “active” nociceptors become sensitized
  - “sleeping” nociceptors awaken
  - firing rates increase
  - SNS fibers invade dorsal root ganglia

- **Central Nervous System:**
  - activity-dependent sensitization (PKC, NMDA)
  - plasticity (reorganization, apoptosis)
  - widespread deafferentation, disinhibition
Pain is a Disease (3)

- Chronic pain: an initially adaptive, advantageous process gone awry
- In the dorsal horn: C fibers die, A betas sprout
- Aberrant circuits established
- Is prevention feasible? (pre-emptive analgesia, growth/ transcription factor antagonism)
- Is combination analgesic chemotherapy the future? (multimodal analgesia)
“Druggable Targets”

- Voltage-gated ion channels: Ca\(^{++}\) (gabapentin, pregabalin, ziconitide); Na\(^{++}\) (lidocaine, mexiletine)
- IL-1, TRPV1 antagonists (on hold)
- Kinase antagonists
- NGF antagonists (Tanezumab, REGN475, JNJ-42160443 on hold)
- Cannabinoids (Sativex [GW Pharma], marijuana)
- CGRP antagonists/ Abs (migraine)
- Angiotensin-2 receptor antagonists
- Epoxide inhibitors
- Also: Botox, stem cells, IN/ SL/ TD routes…
Future of Pain Pharmacotherapy (Carr & Bonney, AAPM 2013)
Precision Medicine

- Genetic: SNPs, epigenetics
- Gender, age, weight
- Prior sensitization (often present on Hx)
- Psychosocial (litigation/ compensation, job/ family satisfaction, spousal solicitousness, premorbid depression, abuse)
- Clinician-patient interaction (?enabling, medicalizing a somatoform disorder)
AEDs Better for “Irritable Nociceptor” Peripheral NPP?

Demant et al, Pain 2014: Oxcarbazepine [Trileptal]
Sodium Channels and Inherited Erythromelalgia vs PolyN

- Gain-of-function mutation in SCN9A gene encoding the Nav1.7 sodium channel → IEM
- Pharmacologic (Pfizer, Cao 2016) treatment of patients or in vitro sensory neurons from induced pluripotent stem cell lines reversed abnormalities, e.g., heat-induced
- Carbamazepine also attenuated pain in 2 family members with IEM (Geha 2016)
- BUT, limited usefulness of phenotyping to predict drug response in polyneuropathy (Holbech 2016)
“Imprecise” Analgesia can be Safe, Effective [AP/SE 3, NB4]

  – NSAIDs, Coxibs, APAP
  – Ketamine
  – Regional anesthesia LA
  – Alpha-2 agonist, beta-blocker

◆ Continuation of preop opioid (e.g., methadone, ? buprenorphine)

◆ Nondrug Rx

◆ “Personalization” not always necessary for successful pain management
  – Analogies to life: cars, meals, clothes etc

◆ Glucocorticoid
  – AEDs
  – Nondrug
Pain Intensity vs Technique
(Closed/Open), Opioid w/d, OLH
Differences in Analgesic Efficacy: Opioids, NSAIDs etc
Basic Science of Analgesiology: Following a Typical Paradigm

- Mold, penicillin, synthetic antibiotics, antivirals
- Willow bark, salicin, aspirin, COX-2
- Opium, morphine, opioids, peptides, abuse- and tamper resistant formulations
- Now: pain = diverse conditions, hosts
- Future: “combination analgesic chemoRx”
  - embrace diversity, not homogeneity
  - multifunctional molecule(s), co-administered agents
  - tailor agent(s) to mechanisms of disease, host
“OVER 80 FOUR-STAR RAVE REVIEWS!”

“GETTING LOST NEVER FELT SO GOOD!”

— Thelma Adams, Us Weekly

BILL MURRAY  SCARLETT JOHANSSON

LOST in TRANSLATION

Written and directed by Sofia Coppola
Translating Efficacious Rx (40% applicability per step)

<table>
<thead>
<tr>
<th>ISSUE</th>
<th>IMPACT</th>
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<tr>
<td>Exciting evidence-based Rx</td>
<td>100%</td>
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<tr>
<td>Subpopulation of responders</td>
<td>40</td>
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<tr>
<td>Clinic participation rate</td>
<td>16</td>
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<tr>
<td>Within-clinic clinician participation</td>
<td>4</td>
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<tr>
<td>Patient participation</td>
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<tr>
<td>Delivery/adherence fidelity</td>
<td>0.4</td>
</tr>
<tr>
<td>Longer-term effects</td>
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Glasgow RE, Diabetes Care 2003
[RCTs], while of clear utility in establishing efficacy, are nevertheless remarkably artificial in the sense of not resembling the real-life application of medicaments to treatment of the ill. Once marketed, a drug will be used by doctors of all levels of expertise and wisdom, on heterogeneous populations, usually in conjunction with other drugs, without informed consent, protocol forms, or specified lab tests as criteria for success or failure.
Given these differences, it seems inevitable that the prediction of "naturalistic" performance from controlled clinical trials will be faulty, the only point at issue is how flawed will be the prognostications.

What, then, is needed? Certainly not more clinical trials. Rather, we must study the medicine in its natural habitat, i.e. the doctor's office, the patient's home, and the hospital.
Have We Gotten it Backwards?
Pain Equals… (1)

\[ \int_{t=0}^{t=\infty} \text{Action Potentials (t)} \, dt \]
Pain Equals... (2)

\[ \sum_{i=1}^{\infty} \int_{t=0}^{t=\infty} f_i(\text{Action Potentials (t)}) \]
But: Pain \textit{Really} Equals

\[
\sum_{i=1}^{\infty} \int_{t=0}^{t=\infty} f_i(\text{Action Potentials}) + \int_{t=\infty}^{t=\infty} (\text{Social Cues + Bereftness (t)})
\]
Darwin: Social Neuroscience

All sentient beings developed through natural selection in such a way that pleasant sensations serve as their guide, and especially the pleasure derived from sociability and from loving our families.

Charles Darwin (1809-1882)
Pain Sufferers: Outsiders

- Much literature on pervasive under-Rx of pain
- Emerging literature links pain and stigma, humiliation (e.g., torture), marginalization
- Outsiders – racial, ethnic, linguistic minorities; young; old; those with cancer, HIV, substance abuse; the poor or homeless -- at special risk
  - N.B. Morris, Lasch on culture, ethnicity in P:CU
- Above suggests a link between valuing/devaluing an individual’s subjective experience and aggressiveness of pain Rx
Stigma, Marginalization (IOM)

- It has been hell. First, you have to find someone who believes you. [#135]
- Doctors don't recognize pain they cannot see or diagnose as a specific issue. [#314]
- The stigma is one of the biggest barriers. I have been treated like a lowlife by medical people when I disclose that I have chronic pain and use opioids for it. [#383]
fMRI Pain Signature (Wager 2013)
“Comparisons of rejecter versus friend and pain versus warmth yielded similar levels of self-reported negative affect, and overlapping portions of many regions related to pain intensity were activated (bilateral anterior insula, medial thalamus, secondary somatosensory cortex, and dorsal posterior insula).”
The Perfect Analgesic?
Dyadic vs Supradyadic Healthcare Models

Social Determinants of Health Framework (WHO)

SOCIOECONOMIC POLITICAL CONTEXT
- Governance
- Macroeconomic Policies
- Social Policies (Labour market, Housing, Land)
- Public Policies (Education, Health, Social protection)
- Culture and Societal value

Socioeconomic Position
- Social Class
- Gender
- Ethnicity (racism)
- Education
- Occupation
- Income

Material Circumstances (Living and Working, Conditions, Food Availability, etc)
- Behaviors and Biological Factors
- Psychosocial Factors

Social cohesion & Social Capital

Impact on Equity in Health and Well-being

Interstitial Determinants of Health

Structural Determinants of Health Inequities

Health System
CDC: Opioid Trends

Prescription Painkiller Sales and Deaths

- Sales (kg per 10,000)\(^a\)
- Deaths (per 100,000)\(^b\)

Year: 1999 to 2013

Sources:
\(^a\) Automation of Reports and Consolidated Orders System (ARCOS) of the Drug Enforcement Administration (DEA), 2012 data not available.
CDC: Abuse Trends

Unintentional Drug Poisoning Deaths Involving Opioid Analgesics, Cocaine and Heroin: United States, 1999–2011

% CHANGE 2006-11
+ 28%
- 35%
+ 119%

Number of Deaths


- opioid analgesic
- cocaine
- heroin

- 16,000
- 14,000
- 12,000
- 10,000
- 8,000
- 6,000
- 4,000
- 2,000
- 0
US Opioid Death Rates
Opioid Crisis: Consequences

- Multidimensional response: legislative, regulatory (NASPER), educational, scientific (ADFs)
- Myriad efforts, not all coordinated
  - Not all evidence-based (e.g., dose thresholds, MEDD)
  - Climate of fear for prescribers
- Rifts between government agencies (FDA, CDC)
- Reduction of opioid availability across the board
- Impetus to reformulate/develop new drugs
- Increased interest and data to support behavioral & interventional techniques (HF SCS, cold RF…)
- Calls to end pain assessment, delink $ HCAHPS
- Polarized, volatile, ultimately unstable situation
IOM, WHO have declared pain a public health issue:

- High prevalence, burden
- Amenable to prevention (e.g., acute-to-chronic)
- Population-based, clear relation to SES
- Human rights dimension including inequities
- Moral imperative to transform our thinking
- \textit{Unexpected consequences}
From the 2011 IOM Report

Value of a public health and community-based approach:

- Many features of the problem of pain lend themselves to public health approaches -- a concern about the large number of people affected, disparities in occurrence and treatment, and the goal of prevention cited above. Public health education can help counter the myths, misunderstandings, stereotypes, and stigma that hinder better care.
Educational Changes if Pain Were a Public Health Issue

- **BIO PSYCHO SOCIAL**

**SOCIO PSYCHO BIOLOGICAL**

- Informed by “social neuroscience” (= the study of neural mechanisms that subserve social processes, behaviors)
- Interprofessional team teaching, training
- Population-based context: social, cultural, environmental and economic
Current Fee-for-Service Payment System

The Problem
Care is fragmented instead of coordinated. Each provider is paid for doing work in isolation, and no one is responsible for coordinating care. Quality can suffer, costs rise and there is little accountability for either.

Patient-Centered Global Payment System

The Solution
Global payments made to a group of providers for all care. Providers are not rewarded for delivering more care, but for delivering the right care to meet patient’s needs.

$   $   $   $
Hospital  Specialist  Primary Care  Home Health

$  Primary Care
Hospital
Specialist
Home Health
ACO Key Features

- Drive down total medical expense
  - Right care, right time, right place
  - Decrease variation, over-utilization
- Local accountability for continuum of care
  - Integrated delivery systems
  - Designated patient population
- Shared savings
  - Bonus for high quality, low cost
- Performance measurement including
  - Meaningful outcome
  - Patient experience of care
Pain Management in ACO

- Creation of data registries from claims and EHR
- Identification of patients’ utilization profiles
  - Medication profile (number, type)
  - Services utilization profile
- Team-based care delivery
  - PCP, Specialist, Mid-level practitioner, Care manager, Patient educator
- Patient empowerment
- Cross continuum care coordination
  - Office, Community programs, Home Care, ED, Hospital, SNF
- Payment methods now (June 2016) being hashed out in MACRA
Institute of Medicine:
Relieving Pain in America
A Blueprint for Transforming Prevention, Care, Education, and Research
October 2012: Assistant Secretary for Health, Department of Health and Human Services tasked IPRCC and NIH to address IOM Recommendation 2-2.

“develop a comprehensive, population health-level strategy for pain prevention, treatment, management, education, reimbursement, and research that includes specific goals, actions, time frames, and resources.”
Most common causes of disability

2013*

- Lower back pain
- Major depression
- Iron deficiency
- HIV
- Diabetes
- War
- Other
- No data

Source: The Lancet

*Adjusted for severity
IN AN IDEAL WORLD...

- Prospective identification, plans for patients at risk
- Prompt (?pre-emptive) effective, individualized antinociceptive and behavioral interventions
- Effective treatments, rationally chosen and combined
- Ongoing titration, strategies to minimize adverse effects and bridge gaps
- Monitoring of standardized outcomes to validate/calibrate practice, accomplish CQI, meet JCAHO standards, identify best practices
- Followup to assess long-term costs, benefits
- Supportive climate: policies, payment, attitudes