When Pain is Real, but Opioids are Contraindicated: Chronic-on-acute Pain in Children with Hematologic and Oncologic Diseases

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Learning Objectives

• Explore obstacles to treat “chronic-on-acute” pain through a rehabilitative pediatric pain program
• Discuss successful interdisciplinary approaches in managing primary pain disorders in children with underlying recurrent acute pain episodes
• Explore treatment choices and appreciated low importance of pharmacotherapy

Case Example: Barbette Payn

• (not a real case): 14-year-old with 4-year history of periumbilical abdominal pain (in remission following ALL treatment age 5)
• Worsened in early September of last year (coinciding with attending new school)
• Previous work-up: Several endoscopies, repeated laboratory investigations, and imagery (CT, MRI, ultrasound) - all normal/negative
• Was prescribed numerous medications, all of which where non-helpful, some causing odd side effects
• Has trouble falling asleep - usually sleeps with mum in bed, with dad now sleeping downstairs

Thanks to Neil Schechter
Barbette Payn

- Mum very well organized (color coded folder)
- Mother attends to her until she falls asleep, or when waking up at night
- Often too much headache and too tired in the morning to go to school, now frequently sleeps until 11:30 am and takes naps in afternoon
- Missed > 35 days at school last school year, usually goes to school nurse x1-2/day
- Constant bi-frontal headache developed 8 months ago with her eyes going blurry, occasionally “blackout”: workup by ophthalmologist and neurologist, incl. CT, MRI, EEG normal

Barbette Payn

- Constant neck, shoulder and bilateral knee, ankle pain for > 5 months; work-up by rheumatologist, orthopedic surgeon incl. X-rays, exhaustive laboratory investigations, all negative/normal
- Barbette has been in Emergency Rooms a total of 5 times in last 12 months, resulting in 2 hospital admissions at Mrs. Payn’s “request”
- One out of city clinic diagnosed her with “POTS”; another with “autonomic dysfunction”; a third with Chronic Lyme Disease” (despite negative titers x3)
- Chiropractor found yeast in stool (=prescribed antifungals), clots behind the eyes (=blood thinner), and heavy metal toxicity (=chelation therapy) and performed several adjustments

Barbette Payn

- Mrs. Payn is worried that a terrible disease is missed by the physicians and is requesting a exploratory laparoscopy
- She herself has been diagnosed with Fibromyalgia and quit her job to stay home with her daughter to care for her
- Three months ago the overwhelming pain and fatigue resulted in Barbette’s inability to attend school anymore and Mrs. Payn has arranged with school for home tutoring / Online school
- Barbette has stopped meeting with friends and attending social activities and sports activity (competitive dancing)
### Case Example

What now?

### Pain Assessment

1. **Nociceptive Pain**: arises from the activation of peripheral nerve endings (nociceptors) that respond to noxious stimulation
   - Somatic (for example, muscles, joints)
   - Chronic somatic pain typically well localized & often results from degenerative processes (such as arthritis)
   - Visceral (internal organs)

2. **Neuropathic Pain**: resulting from injury to, or dysfunction of, the somatosensory system.
   - Central pain: caused by a lesion or disease of the central somatosensory nervous system

3. **Psycho-social-spiritual-emotional Pain / Total Pain**

4. **Chronic Pain**

   - Pain lasting > 3-6 months: Time definition arbitrary
   - Pain that extends beyond the expected period of healing and hence lacks the acute warning function of physiological nociception


   Chronic Pain in children is the result of a dynamic integration of biological processes, psychological factors, and sociocultural factors considered within a developmental trajectory. [Pediatric Chronic Pain Task Force. 2012 American Pain Society]
Pain versus Disability


Metaanalysis 2011 (King et al.)

  - girls > boys
  - increasing with age
  - psychosocial variables impacting prevalence: anxiety, depression, low-self-esteem, other chronic health problems, lower socio-economic status
  - Range
    - Headaches: 8-83%
    - abdominal pain: 4-53%
    - musculoskeletal (incl. back) pain: 4-49%
    - pain combinations: 4-49%
  - Mean prevalence
    - Headaches: 23%
    - abdominal pain, musculoskeletal pain, and pain combinations: 11-38%

Catastrophizing [“Awfulizing”]

- A set of negative emotional / cognitive processes such as magnification, rumination and pessimism about pain sensations and feelings of helplessness when in pain.
  - Rumination: Parent anxious preoccupation with pain
  - Magnification: Parent amplification of the significance of pain

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Pain Catastrophizing

- (1) Caregiver expectations/cognitions can significantly influence child memory formation and (2) parental (> than child) pain catastrophizing seems to be driver for negative memory biases.

- Caregivers' expectations and cognitions can significantly influence child memory formation and parental (> than child) pain catastrophizing seems to be a driver for negative memory biases.


- Parental catastrophizing associated with greater pain in children with IBD.


- Catastrophizing delays analgesic effect of distraction.


- Assessment Tool: Pain Catastrophizing Scale-child version.


Fear of Pain

- Plays a significant role in relation to functional disability and depressive symptoms in the context of pediatric chronic pain.


- Appears to play both a facilitative and inhibitory role in relation to treatment response:

  - may hinder improvements in disability & depressive symptoms
  - declines are strongly associated with positive functional outcomes

Chronic Pain Pathophysiology

- Many different chronic and recurrent pain syndromes, in both adult and pediatric populations, are now considered manifestations of an underlying vulnerability rather than separate disorders.


- Considerable evidence, especially from twin studies, points to a role of shared biological sensitivity: "pain vulnerability","pain sensitivity", or "central sensitivity syndrome".


- (3) Williams FM, Spector TD, MacGregor AJ. Pain reporting at different body sites is explained by a single underlying genetic factor. Rheumatology (Oxford). 2010 Sep;49(9):1753-5.

**Chronic Pain Pathophysiology**

**Biological**
- Genetics
- Microtrauma
- Infection
- Injury

**Psychological**
- Anxiety
- Depression
- Stress Sensitivity

**Social**
- School
- Adverse Events

**Disordered Pain Processing**

**Functional Primary Pain Disorder**

- Chronic pain disorder that after appropriate medical assessment cannot be explained in terms of conventionally defined medical disease based on biochemical or structural abnormalities.
- Not typically responsive to conventional medical therapy but responsible for the consumption of enormous medical resources.
- Associated with significant disruption of everyday life and often incapacitation.
- Often pejorative implication, i.e. pain is not organic and therefore not real or serious.

Primary Pain Disorders

• Chronic daily headache
• Dys-Functional abdominal pain
• Chronic musculoskeletal pain ("fibromyalgia")
  • CRPS ???
• Majority of children experience pain at multiple sites

The Porcupine

“I Guess That Explains The Abdominal Pains”
Gary Larson, The Far Side

Primary Pain Disorder

Pain Problem

Medical Workup

Positive

Negative

Assume manifestations of underlying vulnerability

Medical Treatment

Referral to:
Integrative Medicine
Mental Health Therapist
Pain Clinic
Pain Perception Gender Dependent?

Chronic-on-acute Pain

- At least (!) 5% of children with sickle cell disease, inflammatory bowel disease, rheumatoid arthritis, congenital heart disease, or cancer are expected to display chronic pain in addition to their underlying somatic pain episodes

Transition from acute to chronic pain?

Joel Katz (ISPP 2015)
### Chronic Pain Survivors of Childhood Cancer


- **Prevalence of pain conditions after treatment:** 12% pain/abnormal sensation; 15.5% migraines; 20.5% other headaches; using prescription analgesics higher among survivors than siblings

### Risk factors
- Younger age at diagnosis
- Pain: non-Hodgkin lymphoma, Wilms tumor, neuroblastoma (vs leukemia)
- Prescription: bone cancer, soft tissue sarcoma
- Female gender; lower educational attainment, minority status, unemployment, being single

### Chronic-on-acute pain (SCD)

- Limited longitudinal and cross-sectional data suggest that Sickle Cell Pain is largely episodic in young school-age children
- Increasing frequent and in some cases persistent in preteens and adolescents
- Frequently chronic in adults

- Treatment of persistent/chronic pain has also largely relied on opioids
- Underlying mechanism poorly understood
- Few studies examining role of peripheral and/or central sensitization
- Opioid-induced hyperalgesia seems likely in some cases but lacks definitive studies

### Chronic Sickle Cell Pain

- Does chronic SCD pain state only result from patients with nociceptive or inflammatory (vasculopathic) pain, recurrent nearly every day?
- Ischemic veno-occlusive pain not opioid-responsive?
- Model of “Chronic post surgical pain” transition from acute to chronic pain applies?
- Does persistent pain state represent neuropathic pain?
- “Daily” SCD pain in fact chronic musculo-skeletal pain?

**The answer is YES**
Chronic post surgical pain (CPSP)

- CPSP after Surgery: last at least 2 months, other causes were excluded
  - Intraoperative nerve transection/injury
  - Preventive analgesia can reduce incidence/intensity of adult CPSP
  - Psychological, emotional, social, family/peers might play role in development & maintenance of CPSP in children


- How long can we wait?
- Unknown at what point clinical deterioration begins

Who do we need? 
Physical Therapy

- Physical activity reduces risk for depression in female adolescents

- Adolescents with chronic pain: lower physical activity level

Who do we need? 
Psychology

- Affective, anxiety, & behavior disorders early risk factors of chronic pain (rather than vice versa)

- Psychological Treatments significantly reduce pain intensity reported by children and adolescents with headache, abdominal pain, and fibromyalgia.

- Delivered face-to-face effective in reducing pain intensity & disability for children / adolescents with headache

- CBT led to significant improvements in pain coping, catastrophizing, and efficacy that were sustained over time in adolescents with juvenile fibromyalgia.

Psychological Treatments

- Cognitive-behavioral therapy (CBT) increases prefrontal cortex gray matter in patients with chronic pain - associated with reduced pain catastrophizing.

- CBT effective online increases prefrontal cortex gray matter in patients with chronic pain and is associated with reduced catastrophizing.

- Psychological therapies delivered online appear effective for management of chronic / recurrent pain in kids

- However, none of these Internet interventions are publicly available. Costly to develop and out of date quickly!

- Cognitive-behavioral therapy increases prefrontal cortex gray matter in patients with chronic pain - associated with reduced pain catastrophizing.
Interdisciplinary Pain Clinic

- **Meta-Analysis:** Yoga may be useful for several pain-associated disorders

- **Iyengar Yoga:** n=5 adolescents; rheumatoid arthritis, 6-week, bi-weekly: improvements in pain, pain disability, depression, mental health, vitality, self-efficacy
  Iyengar Yoga for Young Adults with Rheumatoid Arthritis: Results From a Mixed Methods Pilot Study. J Pain Symptom Manage 2010 May. 39:904-13

- **RCT:** Acupuncture superior to sham acupuncture for fibromyalgia - Positive effect, but influenced by SSRIs?

Integrative Medicine

"Healing Environment" Pain, Palliative & Integrative Medicine Clinic @ChildrensMN

https://vimeo.com/122654881

The Exit Interview

- **Pain is real!**
- **Positive Expectation = Self-fulfilling prophecy!**
  - Expectations predict chronic pain treatment outcomes.

- **Chronic-on-acute:** Close collaboration with specialist of underlying acute condition to ensure no injury will be caused by rehab treatment
  - Pediatrics
  - Rheumatology
  - Gastroenterology
  - Hematology/Oncology
  - Cardiology
  - etc.
Exit Interview:
What is the Hard Work...and non-negotiable...?

- Physical Therapy
  - Daily home exercise
- Integrative Medicine
  - Self-Hypnosis
  - Biofeedback
  - Progressive Muscle relaxation, etc.
  - Daily home exercise
    - Passive: Massage, Acupuncture
- Deep Breathing
- Weight bearing 1 second
- Running Marathon
- Self-Hypnosis
Exit Interview

Exit Interview:
What is the Hard Work...and non-negotiable...?

- **Physical Therapy**
  - Daily home exercise

- **Integrative Medicine**
  - Self-Hypnosis
  - Biofeedback
  - Progressive Muscle relaxation, etc.
  - Daily home exercise
    - Passive: Massage, Acupuncture

- **Psychology**
  (...if missing school, anxiety, depression...)

Sleep & Chronic Pain

Majority of children with chronic pain have sleep difficulties; problems with:
- Sleep initiation
- Maintaining sleep
- Early morning awakening

- Insomnia: 12-18 years with chronic pain: 54% (vs 20% control)

- Sleep problems are persistent (50% vs 20%) and associated with negative impact for youths with chronic pain

- Treatment of insomnia in youths with chronic pain may lead to improvements in QoL and reduction in healthcare cost.
School & Chronic Pain

- Long-term school impairment -> poorer academic and occupational achievement, increase educational costs, development of psychiatric disorders
  

- Parental pain catastrophizing and parental protective response to child pain each individually predict school attendance rates and reports of overall school impairments
  

Exit Interview:
What is the Hard Work...and non-negotiable...?

- Physical Therapy
  - Daily home exercise

- Integrative Medicine
  - Self-Hypnosis
  - Biofeedback
  - Progressive Muscle relaxation
  - Daily home exercise
  - Passive Massage, Acupuncture

- Psychology (...if missing school)

- Normalize Life
  - Sports/Exercise
  - Sleep-hygiene
  - Social: Having daily fun
  - School: Attending full-time (or school-re-entry plan)

- Home Schooling
- Re-entry plan
- Full-time School Attendance
- Contract

Exit Interview

↑ Pain

↑ Stress Grumpy Anxiety

Attending School
Exit Interview:
What is the Hard Work...and non-negotiable...?

- Physical Therapy
  - Daily home exercise
- Integrative Medicine
  - Self-hypnosis
  - Biofeedback
  - Progressive Muscle relaxation
  - Daily home exercise
  - Passive: Massage, Acupuncture
- Psychology (...if missing school)
- Normalize Life
  - Sports/Exercise
  - Sleep-hygiene
  - Social: Having daily fun
  - School: Attending full-time (or school-re-entry plan)
- Family Coaching
- Medications...???

Medications?

Opioids & Chronic Pain

- Lack of evidence supporting long-term effectiveness
- Escalating misuse of prescription opioids including abuse and diversion
- Symptoms of depression associated with opioid use regardless of pain severity and physical functioning among patients with chronic pain
- Uncertainty about incidence of adverse drug events
  - Endocrine dysfunction (Androgen deficiency)
  - Immunosuppression & infectious disease
  - Opioid-induced hyperalgesia
  - Xerostomia
  - Overdose
  - Falls & fractures
  - Psychosocial complications
Opioids & Chronic Pain


- Even after adjusting for substantial number of potential confounders, opioids were associated with worse functioning in back pain patients at 6-month follow-up. Ashworth, J., et al., Opioid use among low back pain patients in primary care: Is opioid prescription associated with disability at 6-month follow-up? Pain, 2013. 154(7): p. 1038-44.


1. Low-dose Amitriptyline (stimulates)
2. Gabapentin (inhibits)
3. Acetaminophen
4. Ibuprofen (Celecoxib)
5. Lidocain 5% patch
6. Melatonin
7. Vitamin D?
8. SSRI?
9. Co-Q10, Fish-Oil/Omega 3000, Peppermint oil (coated) [for abdo pain]?

Exit Interview

Further Reading

HarperResource

$ 14.95
The mystery of chronic pain [video]  
https://www.youtube.com/watch?v=J6--CMhcCiQ
Clinicians have historically considered most chronic pain to be largely from peripheral nociceptive input (i.e. damage or inflammation), and now data increasingly suggest this is simply not the case.

Many different chronic and recurrent pain syndromes, in both adult and pediatric populations, are now considered manifestations of an underlying vulnerability rather than separate disorders.

Opioids in the absence of tissue injury or inflammation are contraindicated!

Importance of rehabilitative, interdisciplinary team approach

Conclusion

With profound gratitude to our interdisciplinary Pain, Palliative & Integrative Medicine team

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- Kathy Popa, RN, CNS
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- Cyndie Daughtrey
- Jessica Casey

Chaplain: Hal Weiden
Child Life: Margaret Monsoon
Music Therapy: Mark Burtet
Clinic Nurse: Mischelle Nemmar
Massage
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- Jill Mihay
- Lolly Bock

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- Cheryl Fumiko

Social Work
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Music Therapy
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Clinic Nurse
- Blanche Amar

Massage
- Candace Linaris
- Jill Maltrud
- Laura Beck

Admin Assistants
- Katie McQuade
- Cheryl Puumala

Clinic Staff
- Brock Hebert
- Allison McQuade

Manager
- Tracey Crocell
- Lila Leghorn, RN

Thank You
ADDENDUM

Deleted Scenes

(1) Headaches / Migraines
“Bi-modal” Headache Construct

Tension-type headache

- Infrequent episodic
  - At least 10 episodes occurring on <1 day/month on average (<12 days/year)
- Frequent episodic
  - At least 10 episodes occurring on >1 but <15 days/month for ≥3 months (>12 and <180 days/year)
- Chronic

Migraine: No aura / aura

1/2:
- Nausea and/or vomiting
- Photophobia
2/4:
- Unilateral
- Pulsating
- Aggravation by/avoidance of physical activity
- Medium-severe pain

Primary Headache = Severity Continuum?


- High headache frequency (>15 d/mo) and younger age (<24 years old) were associated with unimodal distributions suggestive of dimensional construct of primary headache.
- Lower headache frequency and older age were associated with bimodal distributions characteristic of discrete diagnostic entities.

Headaches

- Warning signals requiring further work-up (incl. neuroimaging):
  - Focal or abnormal neurological signs, ataxia
  - Papilledema (r/o pseudotumor cerebri)
  - Age < 3 years
  - “Worst headache of my life”
  - Progressive worsening headaches
  - VP-shunt
  - Neurocutaneous syndrome
  - Immunocompromized -> CSF? (check with ID)

- Rule out: CO; Obstructive Sleep Apnea
Medication Overuse Headaches (MOH)

International Headache Society (ICHD-II) Criteria, 2006
- headache > 15 days/month > 3 months
- ergotamine, triptans, or combination analgesics on > 10 days
- or, simple analgesics or any combination of ergotamine, triptans, analgesics, and opioids on > 15 days/month
- MOH can be caused by most, if not all acute headache drug therapies
- Treatment duration?
  - Triptans: 1.7 yrs
  - Ergots: 2.7 years

Meta-analyses: Migraine in Kids

  - Placebo were observed in all trials, with pain relief at 2 hours ranging from 53% to 57.5%.

Meta-analyses: Pharmacology Headaches

- Drugs more effective than placebo for episodic migraines: topiramate (difference in headaches per month, -0.71; 95% CI, -1.19 to -0.24); trazodone (-0.60; 95% CI, -1.09 to -0.11).
- Other commonly used drugs have no evidence supporting their use in children and adolescents.

- Ineffective drugs: clonidine, flunarizine, pizotifen, propranolol, and valproate: single trial of fluoxetine for chronic daily headaches
- 10 comparator trials, flunarizine more effective than piracetam, but no better than aspirin, dihydroergotamine, or propranolol. Propranolol compared with valproate, behavioral treatment. 8 & 2 studies compared different doses of topiramate; none showed significant differences.
- Placebo: 5.6 → 2.9 headaches/month [Cochrane Q=8.14]
(2) Dys-Functional Abdominal Pain

Rome III-Criteria (2006)

At least x1/week for > 2 months:
- Episodic or continuous abdominal pain
- Insufficient criteria for other functional GI disorders (cyclic vomiting, functional dyspepsia, IBS, abdominal migraine, functional constipation etc.)
- No evidence of an inflammatory, anatomic, metabolic, or neoplastic process that explains the patient's symptoms

Functional Abdominal Pain

Abdominal Pain

- Constipation most common diagnosis in children presenting with abdominal pain in ED (& no racial difference)  

- Endogenous inhibition of somatic pain is impaired in 7-12 year old girls with irritable bowel syndrome compared with healthy peers.  

- Mothers with children chronic abdominal pain show pain bias when interpreting ambiguous emotional expressions (possibly contributes to maintenance of the condition via specific parenting behavior?)  
Abdominal Pain

Warning signals requiring further work-up:
- Persistent right upper or right lower quadrant pain
- Pain that wakes child from sleep
- Dysphagia
- Arthritis
- Persistent vomiting
- Perirectal disease
- Gastrointestinal blood loss
- Involuntary weight loss
- Nocturnal diarrhea
- Deceleration of linear growth
- Unexplained fever

(3) Chronic Musculoskeletal Pain

Warning signals requiring further work-up:
- Arthralgia: Rubor, Calor, Edema
- Pain, stiffness in the morning
- Abnormal radiographic findings
- Pain at rest, relieved by activity
- Pain at night: Worsened by massage, analgesics ineffective
- Bony tenderness
- Poor growth
- Weight loss
- Abnormal CBC, CRP, ESR
Chronic Musculoskeletal Pain

- Demystifying problem: Pain has lost warning signal
- Often de-conditioned
- Frequently tension at trapezius / paraspinal muscles
- Treatment Goal:
  - (1) Return to function
  - (2) Pain decrease

“Fibromyalgia”

- Diagnostic criteria not (!) validated in children and teenagers
- Animal Model: Rats exposed to unpredictable sound stress develop
  - mechanical hyperalgesia in muscle and skin
  - increased anxiety
  - temporomandibular disorder

Further Links

- Video: Kiran Scardalakis and Horst Rechelbacher Pediatric Pain, Palliative and Integrative Medicine Clinic Tour https://vimeo.com/122654881
- Short Movie: Meet the Interdisciplinary Chronic Pain Clinic Team at Children’s Minnesota: LittleStars TV https://www.youtube.com/watch?v=sl3Jh8UfH4d
- Video Tour of the Kiran Scardalakis and Horst Rechelbacher Pediatric Pain, Palliative and Integrative Medicine Clinic at Children’s Hospitals and Clinics of Minnesota and an overview of the three programs that are offered at Children’s under this clinic: https://vimeo.com/33357296
- Short Movie: LittleStarsFilm ‘Kali’s Story - Beyond the NICU’ This amazing pediatric palliative care short movie (7 min) features 8-year-old Kali’s journey at Children’s Hospitals and Clinics of Minnesota from NICU to today, receiving care by the Pain & Palliative & Integrative Medicine program while inpatient, in the clinic, and at home (Jan 22, 2015) http://www.littlestars.org/littlestarsfilm/beyond-the-nicu
Further Training

10th Annual Pediatric Pain Master Class
- Minneapolis, Minnesota, USA | June 17-23, 2017

Education in Palliative & End-of-life Care [EPEC]: Become an EPEC-Pediatrics Trainer
- Montréal, Québec, Canada | April 28-30, 2017 (Professional Development Workshop: 04/28/17)

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