Management of Refractory Pain: Practical Issues and Challenges

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Learning Objectives

- Review the causes of and pathophysiologic processes associated with refractory pain in children with blood disorders and cancer
- Discuss strategies for evaluating children with pain refractory to standard treatment
- Better understand available treatment strategies for refractory pain, including integrative ("non-pharmacologic") approaches, use of newer pharmacologic agents and incorporation of daily opioids

Refractory Pain

- Pain related to conditions such as cancer or SCD or its treatment, remaining beyond expected time of healing, that has not responded to standard treatment with opioids and co- analgesics Modified after: Currow DC, Spruyt O, Hardy J (2012) Defining refractory pain in cancer for clinicians and researchers. J Palliat Med 15(1):5–6
- Usually "Refractory" = "Really Difficult"
- Very rarely "Refractory" = "Refractory" (→ palliative sedation?)

What are we measuring...?

(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

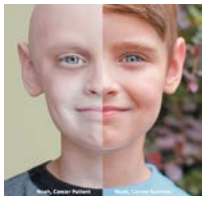
(3) Psycho-social-spiritual-emotional Pain / Total Pain

(4) Chronic Pain

- Pain beyond expected time of healing

Pediatric Cancer Survivors

- Prevalence of pain **during treatment**: Outpatient 9-26%, inpatient 39-54% (1) Elliott SC, Miser AW, Dose AM, Betcher DL, O'Fallon JR, Ducos RS, et al. Epidemiologic features of pain in pediatric cancer patients: a co-operative community-based study. North Central Cancer Treatment Group and Mayo Clinic). The Clinical journal of pain. 1991 Dec;7(4):263-8. (2) Forgeron PA, Finley GA, Arnaout M. Pediatric pain prevalence and parents' attitudes at a cancer hospital in Jordan. Journal of Pain and Symptom Management. 2006 May;31(5):440-8. (3) Miser AW, Doshage JA, Wesley RA, Miser JS. The prevalence of pain in a pediatric and young adult cancer population. Pain. 1987 Apr;29(1):73-83.
- **Survivors**: Prevalence of pain conditions (12% pain/abnormal sensation; 15.5% migraines; 20.5% other headaches) and using prescription analgesics higher among survivors than siblings Lu Q, Krull KR, Leisenring W, Owen JE, Kawashima T, Tsao JC, et al. Pain in long-term adult survivors of childhood cancers and their siblings: a report from the Childhood Cancer Survivor Study. Pain. 2011 Nov;152(11):2616-24.
- Pediatric brain tumor survivors experience many symptoms after treatment. lack of energy (52%), difficulty with sleep (38%), lack of concentration (36%), and **headaches** (36%). Macartney G, VanDenKerkhof E, Harrison MB, Stacey D. Symptom experience and quality of life in pediatric brain tumor survivors: a cross-sectional study. J Pain Symptom Manage. Nov 2014;48(5):957-967.



http://www.popsugar.com/moms/Childhood-Cancer-Survivor-Photos-34819602

Chronic-on-acute pain

- Limited longitudinal and cross-sectional data suggest that **Sickle Cell Pain** is Dampier C.Treatment of Chronic Sickle Pain: Lessons from Fibromyalgia and Other Musculoskeletal Disorders. APS Annual Conference 2013
  - 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 of 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

Neurobiology of Sickle-Cell Pain

- Sickle cell pain goes beyond mechanical vaso-occlusion as sole explanation for pain
  - neuroplasticity
  - peripheral/central nervous system sensitization
  - chronic inflammation
- Research suggests that sickle cell disease (SCD) pain has neuropathic component whereas in past pain has been thought to be only nociceptive
- Data support existence of nervous system abnormalities that could contribute to sickle cell pain
- Murine model and humans reveals congruent findings of both heat and cold hypersensitivity in SCD supporting potential abnormalities in the central and / or peripheral nervous system that could explain neurobiology of SCD pain
- Brandow AM, Farley RA, Panepinto JA: Early insights Into the Neurobiology of Pain in Sickle Cell Disease: A Systematic Review of the Literature. Pediatr Blood Cancer 2015;62:1501–1511

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?

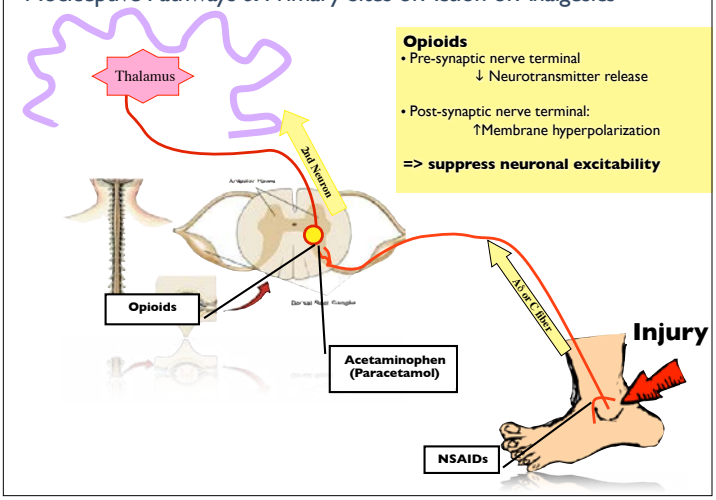
Inappropriate Analgesia: Why Bother...?

- Children with persistent pain suffer more physical symptoms in adult life, more anxiety and more depression 1946 Medical Research Council and 1958 National Child Development Study
- Inadequate analgesia for initial procedures in children diminishes effect of adequate analgesia in subsequent procedures Weisman SJ, Bernstein B, Schechter NL: Consequences of inadequate analgesia during painful procedures in children. Arch Pediatr Adolesc Med 1998, 152:147-9
- NICU: increased morbidity & mortality Anand KJ, Barton BA, McIntosh N, Lagercrantz H, Pelausa E, Young TE, et al. Analgesia and sedation in preterm neonates who require ventilatory support: results from the NOPAIN trial. Neonatal Outcome and Prolonged Analgesia in Neonates. Arch Pediatr Adolesc Med. 1999 Apr;153(4):331-

How Do We Manage Acute Pain in Children?

Multimodal (Opioid-sparing) Analgesia

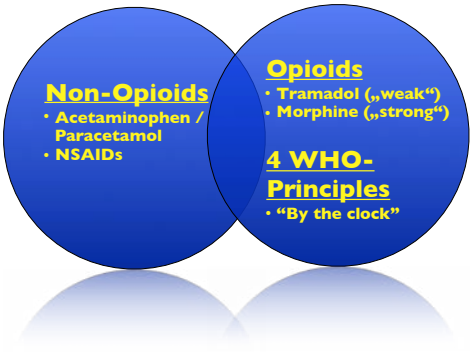
Nociceptive Pathways & Primary Sites of Action of Analgesics



Opioids
- Pre-synaptic nerve terminal
  ↓ Neurotransmitter release
- Post-synaptic nerve terminal:
  ↑Membrane hyperpolarization

=> suppress neuronal excitability

Multimodal (Opioid-sparing) Analgesia



WHO Principle 1: Dosing at Regular Intervals

- PRN = Patient Receives Nothing
- When pain is constantly present, analgesics should be administered, while monitoring side-effects, at regular intervals
- “By the clock” and NOT as an “as needed” (or pro re nata “PRN”) basis

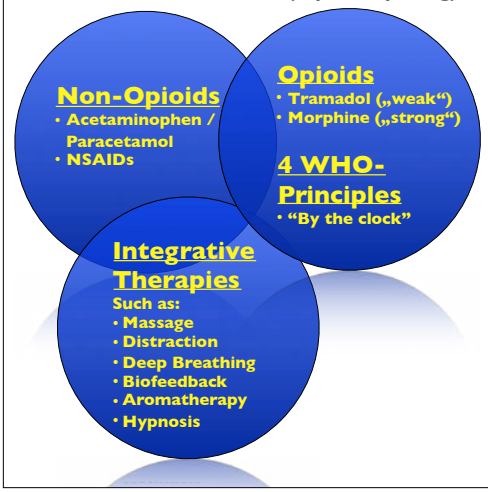
- Regular scheduling ensures a steady blood level, reducing the peaks and troughs of PRN (“as needed”) dosing
- PRN (as needed) only:
  - May take several hours & higher opioid doses to relieve pain
  - Results in cycle of undermedication and pain, alternating with periods of overmedication and drug toxicity

American Pain Society: Principles of Analgesic Use in the Treatment of Acute Pain and Cancer Pain 2008; 24-27

WHO Principle 2: Adapting Treatment to the Individual Child

- Treatment should be tailored to the individual child and opioid analgesics should be titrated on an individual basis
- **At analgesic dosing: no sedation expected**
- The effective dose is what relieves the pain
  - Different children may respond differently to same dose
  - Effective dose must be adjusted to child's needs
  - Dose of strong opioids: only the sky is the limit
- Assess response frequently
  - Pain Scales
  - Look for opioid-induced side effects and toxicity

Multimodal (Opioid-sparing) Analgesia



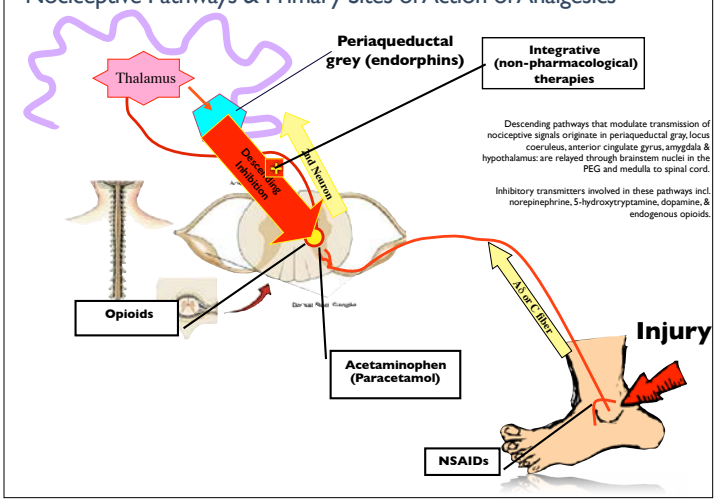
Integrative Pain Management

- **State of the art pain management in the 21st century demands that pharmacological management must be combined with supportive and integrative, non-pharmacological therapies to manage a child's pain.**
- **Physical methods** (e.g. cuddle/hug, massage, comfort positioning, heat, cold, TENS)
- **Cognitive behavioral techniques** (e.g. guided imagery, hypnosis, abdominal breathing, distraction, biofeedback)
- Acupuncture, acupressure, aromatherapy

Integrative Pain & Symptom Management

A Pediatrician's Top 10 Apps for Distraction & Pain Management http://NoNeedlessPain.org

Nociceptive Pathways & Primary Sites of Action of Analgesics



Multimodal (Opioid-sparing) Analgesia

Friedrichsdorf S: 8th Annual Pediatric Pain Master Class, Minneapolis, MN, June 20-26, 2015

Non-Opioids
- Acetaminophen / Paracetamol
- NSAIDs

Opioids
Such as:
- Tramadol („weak")
- Morphine („strong")

4 WHO-Principles
- "By the clock"

Invasive Approaches
- Regional anesthesia
- Neuraxial anesthesia
  - Epidural or intrathecal
  - Nerve blocks
  - Neurolytic blocks
- *Intraventricular opioids?*
- *Percutaneous cervical cordotomy?*

Integrative Therapies
Such as:
- Massage
- Distraction
- Deep Breathing
- Biofeedback
- Aromatherapy
- Hypnosis

Psychology
- CBT

Rehabilitation
- Exercise
- Physical Therapy
- Sleep Hygiene
- Occupational Therapy
- Child Life

Adjuvants
Such as:
- Alpha-Agonist
- Gabapentinoids
- TCA/Antidepressants
- NMDA-Antagonists
- Na-channel blockers
- Antispasmodics
- Benzodiazepines
- Corticosteroids
- Muscle relaxants
- Radiopharmaceuticals
- Bisphosphonates

Multimodal Analgesia

- (Adults): Multimodal analgesia therapy (versus PCA only) reduces length of hospitalization in patients undergoing surgery Michelson, J.D., R.A. Addams, and M.D. Charlson, Multimodal analgesia therapy reduces length of hospitalization in patients undergoing fusions of the ankle and hindfoot. Foot Ankle Int, 2013. 34(11): p. 1526-34.

Multimodal
=
Awesome!

Case Report: Clark

- 15-year-old, relapsed T-cell lymphoma, weight: 72 kgs
- Onset of chemotherapy-induced bi-pedal neuropathy VAS 9/10
- Abdominal pain (hemorrhagic cystitis)
- Unresponsiveness versus over sedation
- Autonomic changes at feet

Neuropathic Pain

- Population prevalence of pain with neuropathic characteristics is likely 6.9% - 10% van Hecke, O., et al., Neuropathic pain in the general population: a systematic review of epidemiological studies. Pain, 2014. 155(4): p. 654-62.
- Prevalence of neuropathic pain in children unclear
  - Cancer pain > 12 years: Metaanalysis (n=22): Conservative 19%; liberal estimate: 39% Bennett MI, Rayment C, Hjermstad M, Aass N, Caraceni A, Kaasa S. Prevalence and aetiology of neuropathic pain in cancer patients: a systematic review. Pain. 2012 Feb;153(2):359-65.

Potential Causes Include

- **Tumor related:** direct tissue and nerve injury; advanced unresectable solid tumors
- **Phantom limb pain:** 60 - 80% of adult patients with amputation experience phantom sensations in their amputated limb, majority are painful Sherman RA., Sherman CJ, Parker L. Chronic phantom and stump pain among American veterans: Results of a survey". Pain. 1984;18: 83–95.
- **Cancer-directed chemotherapy**, including
  - Vincristine: 50% painful peripheral neuropathy, muscle camps, numbness, tingling (hand, feet)
  - Cisplatin: Paresthesias in extremities
- **Spinal cord injury:** "pain arising as a direct consequence of affecting the somatosensory

Pharmacotherapy for neuropathic pain in adults

Finnerup NB, Attal N, Haroutounian S, et al. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. The Lancet. Neurology. Feb 2015;14(2):162-173.

Medication (# of placebo controlled studies)	# of participants	Pain Relief	Placebo	NNT	NNH
Botox A (4)	137	60%	6%	1.9	ns
TCAs (15)	948	45.9%	17.9%	3.6	13.4
Strong Opioids (7)	838	51. 9 %	26.2%	4.3	11.7
Tramadol (6)	741	46.3%	26.6%	4.7	12.6
Gabapentin (14)	3503	34.7%	20.3%	6.3*	25.6
Serotonine-noradrenaline reuptake inhibitor (10)	2541	43.4%	28.3%	6.4	11.8
Pregabalin (25)	5940	38.5%	24%	7.7	13.9
Capsaicin 8% (6)	2073	35.9%	27.4%	10.6	ns

* extended release gabapentin NNT: 8.; NNH 31.9
ns=non significant

Management of Neuropathic Pain in Pediatrics Suggested "Non-Evidence-based" Step-by-Step Approach

Case Report: Clark at Home

Methadone: 10 mg PO Q8h

Hydromorphone: 10 mg PO Q1h PRN (0-3/day)

Pregabalin: 300 mg BID

Amitriptyline: 25 mg QHS

Ketamine: (1-5 mcg/kg/min IV) 40 mg PO PRN Q1h (discontinued after 2 weeks)

Lidocaine Patches: Discontinued after 3 weeks

Chronic Pain in Children

- 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**

Turk DC, Okifuji A. Pain terms and taxonomies of pain. In: Bonica JJ, Loeser JD, Chapman CR, Turk DC, Butler SH. Bonica's management of pain. Hagerstwon, MD: Lippincott Williams & Wilkins; 2001; Treede RD, Rief W, Barke A, et al. A classification of chronic pain for ICD-11. Pain. Jun 2015;156(6):1003-1007.

Pain versus Disability

- Chronic pain is a significant problem in the pediatric population, conservatively estimated to affect 15% to 20% of children Goodman, J.E., & McGrath, P.J. (1991). The epidemiology of pain in children and adolescents: A review. Pain, 46, 247-264
- Chronic Pain: 15-25% of children, approximately 3% in need of intensive pain rehabilitation Hechler T, Dobe M, Zernikow B. Commentary: A worldwide call for multimodal inpatient treatment for children and adolescents suffering from chronic pain and pain-related disability. Journal of pediatric psychology. 2010 Mar;35(2):138-40.
- However, majority of Children reporting chronic pain are not greatly disabled by them Huguet A, Miro J. The severity of chronic pediatric pain: an epidemiological study. The journal of pain : official journal of the American Pain Society. 2008 Mar;9(3):226-36.
- 12% of pediatric inpatients possibly suffer from chronic pain Friedrichsdorf SJ, Postier AC, Eull D, Foster L, Weidner C, Campbell F: Pain outcomes in a US children's hospital: a prospective cross-sectional survey. Hospital Pediatrics 2015. 5(1):18-26

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.
- Significant link between child and parent catastrophizing Lynch-Jordan A, Kashikar-Zuck S, Flowers S, Harding K, Wolf D, Paulford-Lecher N, Desai A, Szabova A, Goldschneider K: The relationship between adolescent pain behaviors and and catastrophizing about their adolescents' pain. (Poster) 29th Annual Scientific Meeting of the American Pain Society, Baltimore, May 6-8, 2010
- Catastrophizing delays analgesic effect of distraction Campbell CM, Witmer K, Simango M, Carteret A, Loggia ML, Campbell JN, et al. Catastrophizing delays the analgesic effect of distraction. Pain. 2010 May;149(2):202-7.
- Assessment Tool: Pain Catastrophizing Scale-child version Parkerson, H.A., et al., Factorial validity of the English-language version of the Pain Catastrophizing Scale--child version. J Pain, 2013. 14(11): p. 1383-9.

Fear of Pain

- Plays a significant role in relation to functional disability and depressive symptoms in the context of pediatric chronic pain Simons LE, Kaczynski KJ, Conroy C, Logan DE. Fear of pain in the context of intensive pain rehabilitation among children and adolescents with neuropathic pain: associations with treatment response. J Pain 2012 Dec;13(12):1151-61.

- 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** von Baeyer CL, Champion GD. Commentary: Multiple pains as functional pain syndromes. Journal of pediatric psychology. [Comment]. 2011 May; 36(4):433-7.
- Considerable evidence, especially from twin studies, points to a role of **shared biological sensitivity**: "pain vulnerability", "pain sensitivity", or "central sensitivity syndrome" (1) von Baeyer CL, Champion GD. Commentary: Multiple pains as functional pain syndromes. Journal of pediatric psychology. [Comment]. 2011 May; 36(4):433-7. (2) Kindler LL, Bennett RM, Jones KD. Central sensitivity syndromes: mounting pathophysiologic evidence to link fibromyalgia with other common chronic pain disorders. Pain Manag Nurs. 2011 Mar;12(1):15-24. (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. (4) Mayer EA, Bushnell Mc: Functional pain syndromes: presentation and pathophysiology. Seattle: IASP Press, 2009



Chronic-on-acute Pain

- Approximately 5% of children and teenagers in general population have significant pain related dysfunction King S, Chambers CT, Huguet A, MacNevin RC, McGrath PJ, Parker L, et al. The epidemiology of chronic pain in children and adolescents revisited: a systematic review. Pain. 2011 Dec;152(12):2729-38.
- In USA: > 3.7 million children
  - USA - Age 0-17: 74.3 million children (2014): http://www.childstats.gov/americaschildren/tables/pop1.asp
- 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 episode

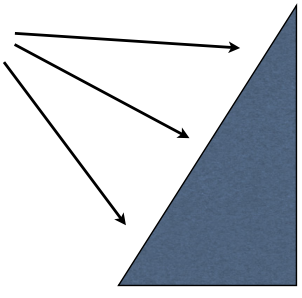
Communication with Patient / Family

- Pain is real!
- First "function" gets better, then "pain" (not other way around)
- Positive Expectation = Self-fulfilling prophecy

Communication with Patient / Family

What is the Hard Work...and non-negotiable...?

- **Physical Therapy**
  - Daily home exercise



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What is the Hard Work...and non-negotiable...?

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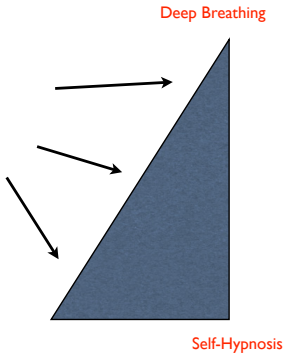
  - Self-Hypnosis
  - Biofeedback
  - Progressive Muscle relaxation, etc.
  - Daily home exercise
    - Passive: Massage, Acupuncture



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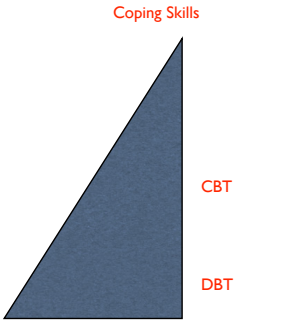
- **Psychology**
  (...if missing school, anxiety, depression...)



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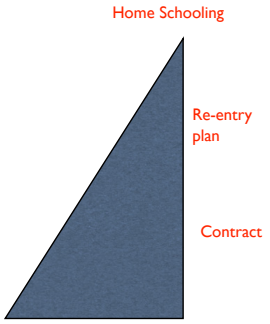
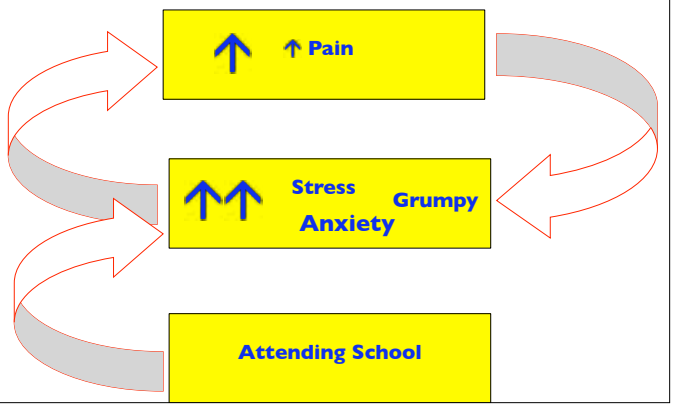
- **Psychology** (...if missing school)
- **Normalize Life**
  - Sports/Exercise
  - Sleep-hygiene
  - Social: Having daily fun
  - School: Attending full-time (or school-re-entry plan)





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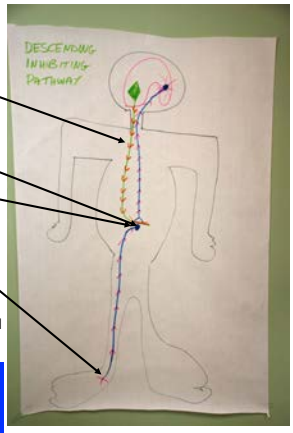
  - School: Attending full-time (or school-re-entry plan)
- **Family Coaching**
- **Medications...???**

Medications ???

Exit Interview

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]?



Opioids in the absence of tissue injury or inflammation not indicated!

Conclusions Acute (!) Pain

- Pain is, when the child says so
- Use multimodal (opioid-sparing) analgesia
  - incl. combination of integrative methods, rehabilitation and analgesic medications
- Include 4 WHO Principles
- Patients/Parents do NOT have to choose between poor pain control or over sedation
- Opioids should NOT be administered long-term

Conclusion chronic-on-acute pain

- Many clinicians have historically considered most chronic pain to be largely from peripheral nociceptive input (i.e. damage or inflammation), and 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
- Close collaboration with specialist of underlying acute condition to ensure no injury will be caused by pain rehab treatment
- **Opioids in the absence of tissue injury or inflammation are contraindicated!**
- Importance of rehabilitative, interdisciplinary team approach

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

Physician
- Kaci Osenga, MD
- Kris Catrine, MD
- Kathleen Farah, MD
- Stefan Friedrichsdorf, MD
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Nurse Practitioner
- Barb Symalla, RN, CNS
- Nancy Jaworski, RN, CNS
- Kathy Popp, RN, CNS
- Sarah Thu, RN, CNS
- Anna Hoffman, RN, CNS
- Maura Fitzgerald, RN, CNP
- Jennifer Worley, RN, CNS

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- Jessica Convey

- **Chaplain:** Hal Weiden
- **Child Life:** Margaret Monsoon
- **Music Therapy:** Mark Burnet
- **Clinic nurse:** Blanche Amar

Massage
- Candace Linaris
- Jill Maltrud
- Laura Beck

Admin Assistants
- Katie McQuire
- Cheryl Puumala

Clinic staff
- Brock Hebert
- Allison McQuade

Manager
- Tracey Crocoll
- Liz Leighton, RN

Children's MINNESOTA

Further Training:
CIPPC@ChildrensMN.org

9th Annual Pediatric Pain Master Class
- Minneapolis, MN | June 11-17, 2016

Education in Palliative & End-of-life Care [EPEC]: Become an EPEC-Pediatric Trainer
- 9th Conference: Chicago, IL | March 12-13, 2016 http://tinyurl.com/EPEC2016

Twitter: @NoNeedlessPain
LinkedIn
Blog: http://NoNeedlessPain.org

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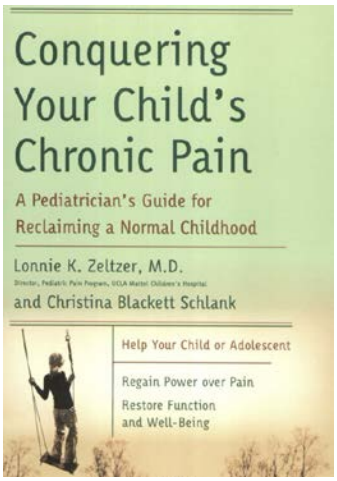
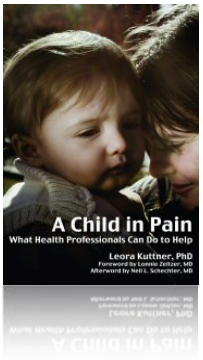
ADDENDUM

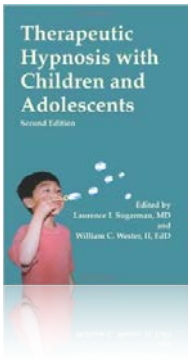
Further Reading

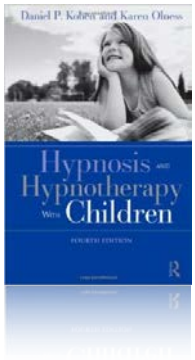
HarperResource
$ 14.95



Recommended Reading





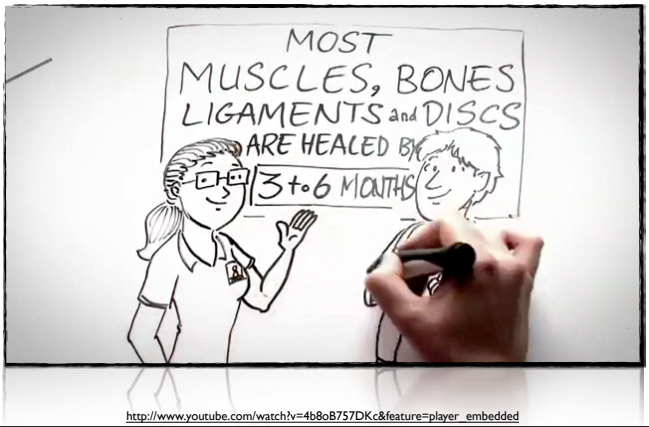


PainBytes

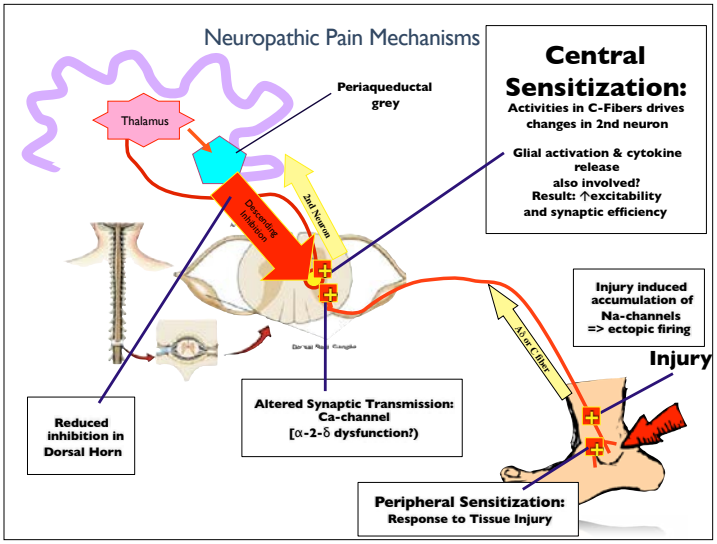
http://www.aci.health.nsw.gov.au/chronic-pain/painbytes

- The mystery of chronic pain https://www.youtube.com/watch?v=J6--CMhcCfQ

Persistent (Chronic Pain)



http://www.youtube.com/watch?v=4b8oB757DKc&feature=player_embedded



Interaction between autonomic and somatosensory systems

- Clinically, sympathetically maintained pain may manifest as temperature or color changes (or both) in affected extremity, swelling or atrophy, and pain worsened by cold weather or stress, which enhances sympathetic outflow Cohen, S.P. and J. Mao, Neuropathic pain: mechanisms and their clinical implications. BMJ, 2014. 348: p. f7656
- Sympathetically maintained pain most commonly linked to CRPS, but same principles apply to other pain conditions, such as postherpetic neuralgia. Cohen, S.P., S.G. Kapoor, and J.P. Rathmell, Intravenous infusion tests have limited utility for selecting long-term drug therapy in patients with chronic pain: a systematic review. Anesthesiology, 2009. 111(2): p. 416-31.
- Interaction between anatomically distinct autonomic and somatosensory systems is complex but probably includes: Nickel, F.T., et al., Mechanisms of neuropathic pain. Eur Neuropsychopharmacol, 2012. 22(2): p. 81-91.
- expression of α adrenoceptors on primary afferent sensory fibers
- sympathetic sprouting into dorsal root ganglia
- impaired oxygenation and nutrition in response to sympathetically mediated vasoconstriction.

Integrative, rehabilitative & supportive therapies

- Expected part of treatment protocol; Age-appropriate modalities include
- **Physical** (massage, TENS, comfort positioning, allowing family for close contact/touch)
- **Rehabilitation** (physical therapy, occupational therapy)
- **Behavioral** (deep breathing, imagery, hypnosis, smart-phone/ tablet "apps")
- Acupressure, acupuncture, aromatherapy

In other words...

- Adult data: Despite best of care and sequential trials of pharmacological therapies: 40-60% of patients remain unrelieved or inadequately relieved Dwokin et al. Pain 2007, 132:237-51
- In the treatment of medium to severe neuropathic pain in children **medications alone are <u>not</u> sufficient**
- Management likely inefficient without:
  - PT/OT
- Integrative Therapies
- Psychological therapies (patient or parents)

Interventional management of neuropathic pain in adults

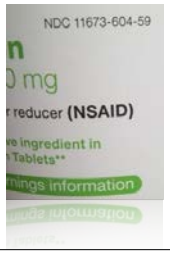
- NeuPSIG recommendations 2013: Due to the paucity of high-quality clinical trials, **no strong recommendations can be made**. Dworkin, R.H., et al., Interventional management of neuropathic pain: NeuPSIG recommendations. Pain, 2013. 154(11): p. 2249-61.
- **4 <u>weak</u> recommendations** based on the amount and consistency of evidence, including degree of efficacy and safety, are:
- (1) epidural injections for herpes zoster
- (2) steroid injections for radiculopathy
- (3) spinal cord stimulation (SCS) for failed back surgery syndrome
- (4) SCS for CRPS type I (*who do not respond adequately to noninvasive treatments and sympathetic nerve blocks*)
- Based on the available data, we recommend not to use sympathetic blocks for PHN nor radiofrequency lesions for radiculopathy

Regional anesthesia approaches to pain management in PC

- **Regional anesthesia:** pediatric knowledge limited to case reports and case series: Rork, J.F., C.B. Barde, and R.D. Goldstein, Regional anesthesia approaches to pain management in pediatric palliative care: a review of current knowledge. J Pain Symptom Manage, 2013. 46(6): p. 859-73.
  - central neuraxial infusions
  - peripheral nerve and plexus blocks or infusions
  - neurolytic blocks
  - implanted intrathecal ports & pumps for baclofen, opioids, local anesthetics, and other adjuvants
- **Neurolytic Sympathectomy:** Amr YM, Mokhtaris MY. Neurolytic sympathectomy in the management of cancer pain-time effect: a prospective, randomized multicenter study. J Pain Symptom Manage. Nov 2014;48(5):944-956 e942.
  - RCT (n=109) inoperable abdominal or pelvic cancer: better pain control, less opioid consumption, and better quality of life

NSAIDs for Neuropathic Pain

- No RCTs Finnerup NB, Attal N, Haroutounian S, et al. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. The Lancet. Neurology. Feb 2015;14(2):162-173.
- NSAIDs are so widely viewed as being ineffective for neuropathic pain that no major guidelines even mention them in their algorithm. Attal N, Cruccu G, Baron R, Haanpää M, Hansson P, Jensen TS, et al. EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. Eur J Neurol 2010;17:1113-e88.
- Preclinical and clinical studies have demonstrated efficacy for NSAIDs in neuropathic pain states Vo T, Rice AS, Dworkin RH. Non-steroidal anti-inflammatory drugs for neuropathic pain: how do we explain continued widespread use? Pain 2009;143:169-71.; Cohen KL, Harris S. Efficacy and safety of nonsteroidal anti-inflammatory drugs
- NSAIDs are commonly prescribed for neuropathic pain Dieleman JP, Kerklaan J, Huygen FJ, Bouma PA, Sturkenboom CJ. Incidence rates and treatment of neuropathic pain conditions in the general population. Pain 2008;137:681-8.



Diclofenac-Patch

- NSAID
- Analgesic action of topical diclofenac: peripheral NMDA receptor antagonism? Dong XD, Svensson P, Cairns BE. The analgesic action of topical diclofenac may be mediated through peripheral NMDA receptor antagonism. Pain. 2009 Dec 15;147(1-3):36-45.

Opioids for Neuropathic Pain

<u>"Weak" opioids</u> (= multimechanism)

- **Tramadol** NNT 4.7; NNH 6.3 Finnerup NB, Attal N, Haroutounian S, et al. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. The Lancet. Neurology. Feb 2015;14(2):162-173.
- **Tapentadol**? Bias; NNT 10.2

- **Morphine, oxycodone** NNT 4.3; NNH 11.7 Finnerup NB, Attal N, Haroutounian S, et al. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. The Lancet. Neurology. Feb 2015;14(2):162-173.
- No additional benefit > 180 mg morphine equivalent
- Cochrane analysis: Oxycodone NOT effective as a pain medicine in diabetic neuropathy or postherpetic neuralgia Gaskell H, Moore RA, Derry S, Stannard C. Oxycodone for neuropathic pain and fibromyalgia in adults. Cochrane Database Syst Rev. 2014;6:CD010692.

Amitriptyline

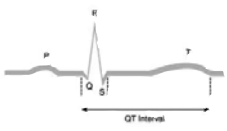
- NNT: 3.6; NNH: 13.4 Finnerup NB, Attal N, Haroutounian S, et al. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. The Lancet. Neurology. Feb 2015;14(2):162-173.
- No dose-response effect
- Nortriptyline: only 1 study
- Efficacy of TCA in central pain Rintala DH, Holmes SA, Courtade D, Fiess RN, Tastard LV, Loubser PG. Comparison of the effectiveness of amitriptyline and gabapentin on chronic neuropathic pain in persons with spinal cord injury. Archives of physical medicine and rehabilitation.. 2007 Dec;88(12):1547-60.
- 2 studies (high effect size): no effect of amitriptyline in HIV neuropathy Kieburtz K, Simpson D, Yiannoutsos C, Max MB, Hall CD, Ellis RJ, et al. A randomized trial of amitriptyline and mexiletine for painful neuropathy in HIV infection. AIDS Clinical Trial Group 242 Protocol Team. Neurology. 1998 Dec;51(6):1682-8. Shlay JC, Chaloner K, Max MB, Flaws B, Reichelderfer P, Wentworth D, et al. Acupuncture and amitriptyline for pain due to HIV-related peripheral neuropathy: a randomized controlled trial. Terry Beirn Community Programs for Clinical Research on AIDS. JAMA. 1998 Nov 11;280(18):1590-5.

Tricyclic antidepressants (TCA)

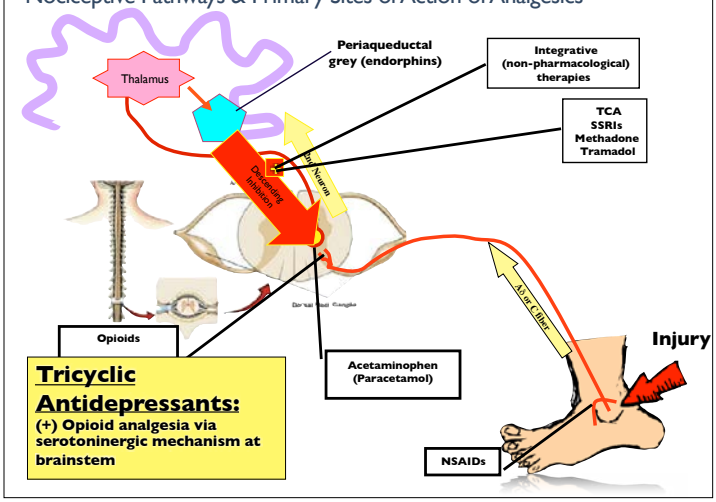
- Relieve various neuropathic pain 2 studies: no effect of amitriptyline & nortriptyline in chemotherapy-induced neuropathy (pain not primary outcome) Hammack JE, Michalak JC, Loprinzi CL, Sloan JA, Novotny PJ, Soori GS, et al. Phase III evaluation of nortriptyline for alleviation of symptoms of cis-platinum-induced peripheral neuropathy. Pain. 2002 Jul;98(1-2):195-203. Kautio AL, Haanpaa M, Saarto T, Kalso E. Amitriptyline in the treatment of chemotherapy-induced neuropathic symptoms. Journal of Pain and Symptom Management. 2008 Jan;35(1):31-9.
- Secondary amine TCAs (nortriptyline and desipramine) better tolerated than tertiary amine TCAs (amitriptyline and imipramine) with comparable analgesic efficacy Max, N Eng J Med 1992,326:1250-6; Rowbotham, J Pain 2005,6:741-6; Watson, Neurology 1998,51:1166-71

Amitriptyline (or Nortriptyline)

- Dosage: initial 0.1 mg /kg -> titrate to 0.4 mg/kg p.o., [max. 20-25 mg] (usually not up to 1-2 mg/kg/day) once at night -
  - wean: decrease gradually!
- Effect: days - weeks; depends on length of symptoms
- Adverse effects: arrhythmia: EKG (QTc, WPW?), anticholinergic / antihistamine (dry mouth, constipation, blurred vision, sedation)
- Desipramine: anecdotal evidence of sudden death in children Amitai Y, Frischer H: Excess fatality from desipramine in children and adolescents. J Am Acad Child Adolesc Psychiatry 2006. 45(1):54-60



Nociceptive Pathways & Primary Sites of Action of Analgesics



Gabapentin

- **Gabapentin**: NNT: 6.3; NNH: 25.6
- **Extended-release gabapentin**: NNT 8.3; NNH 31.9 Finnerup NB, Attal N, Haroutounian S, et al. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. The Lancet. Neurology. Feb 2015;14(2):162-173.
- No dose-response effect
- 15 studies (1468 participants) (post-herpetic neuralgia, diabetic neuropathy, cancer related neuropathic pain, phantom limb pain, Guillain Barré syndrome, spinal chord injury pain, various neuropathic pains) Wiffen PJ, McQuay HJ, Edwards JE, Moore RA. Gabapentin for acute and chronic pain. Cochrane Database Syst Rev. 2005 Jul 20;(3):CD005452.
- 42% improved compared to 19% on placebo
- NNT for effective pain relief in diabetic neuropathy 2.9; post herpetic neuralgia 3.9

Pregabaline

- Efficacy worse than gabapentin
- NNT: 7.7; NNH: 13.9 Finnerup NB, Attal N, Haroutounian S, et al. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. The Lancet. Neurology. Feb 2015;14(2):162-173.
- Dose-response (600mg/day more effective than 300 mg/day)
- Linear (pregabalin) versus non-linear (gabapentin) bioavailability: Clinical relevance unclear.
- Negative RCTs: HIV neuropathy; central post-stroke pain (1) Simpson DM, Schifitto G, Clifford DB, Murphy TK, Durso-De Cruz E, Glue P, et al. Pregabalin for painful HIV neuropathy: a randomized, double-blind, placebo-controlled trial. Neurology. 2010 Feb 2;74(5):413-20.; (2) Kim JS, Bashford G, Murphy TK, Martin A, Dror V, Cheung R. Safety and efficacy of pregabalin in patients with central post-stroke pain. Pain. 2011 May;152(5):1018-23.
- Adverse effects include: Weight increase, dizziness, somnolence, blurred vision, life-threatening angioedema (face, mouth, larynx) - careful concurrent administration with ACE inhibitors

Children with impairment of CNS

- Gabapentin appears to be an effective treatment for children with severe impairment of the CNS and recurrent pain behaviors, including intermittent changes in muscle tone. Hauer JM, Solodiuk JC. Gabapentin for management of recurrent pain in 22 nonverbal children with severe neurological impairment: a retrospective analysis. J Palliat Med. May 2015;18(5):453-456.

	Less than 6 years (n=11)	Greater than 6 years (n=11)
Age range	5 months – 5 years	11 – 27 years
Average daily dose	50 mg/kg/day (42-72 mg/kg/day)	36 mg/kg/day (32-40 mg/kg/day)
Suggested guidelines: •Initial trial 35-40 mg/kg/day •Increase up to 50-70 mg/kg/day in those <6 years		

Gabapentin

Example: 10-year-old girl, 30 kg

Day 1:	100 mg once daily
Day 2:	100 mg BID
Day 3:	100 mg TID
Day 4:	100-100-200 mg
…	
Day 9:	300 mg TID

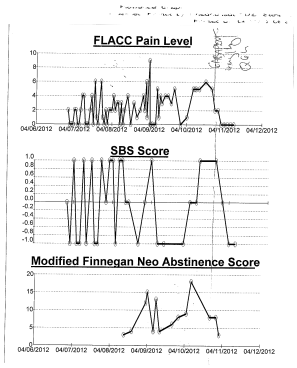
- **Pediatric Dosage**: gradually increasing from 3-5 mg/kg/dose TID to 10-20mg/kg/dose TID, max. 1,200 mg/dose TID
- **Infants**: 4.5 mg PO Q6h (titrated to max. 15 mg Q6h)
- [Extended release: 300 -> 1800 mg Qday: No pediatric data; NNT worse]
- wean: decrease gradually x 1-2 weeks!
- Effect: days - weeks
- Adverse effects include: ataxia, nystagmus, myalgia, hallucination, dizziness, somnolence, aggressive behaviors, hyperactivity, thought disorder, (peripheral edema)

Gabapentin for Acute Pain?

- Total knee replacement: Decreased post-op opioid use, improved functional recovery Clarke H, Pereira S, Kennedy D, Gilron I, Katz J, Gollish J, et al. Gabapentin decreases morphine consumption and improves functional recovery following total knee arthroplasty. Pain research & management. 2009 May-Jun;14(3):217-22.
- Hip arthroplasty: did not result in better analgesia, less opioid use, nor improved functional recovery Clarke H, Pereira S, Kennedy D, Andrion J, Mitsakakis N, Gollish J, et al. Adding gabapentin to a multimodal regimen does not reduce acute pain, opioid consumption or chronic pain after total hip arthroplasty. Acta Anaesthesiol Scand. 2009 Sep;53(8):1073-83.
- Laparoscopic cholecystectomy: combination with meloxicam did not result in enhanced pain relief Gilron I, Orr E, Tu D, Mercer CD, Bond D. A randomized, double-blind, controlled trial of perioperative administration of gabapentin, meloxicam and their combination for spontaneous and movement-evoked pain after ambulatory laparoscopic cholecystectomy. Anesthesia and analgesia. 2009 Feb;108(2):623-30.
- Type of clinical condition may influence effectiveness of combination drug therapy Mao J, Gold MS, Backonja MM. Combination drug therapy for chronic pain: a call for more clinical studies. The Journal of Pain. 2011 Feb;12(2):157-66.

Gabapentin postoperatively?

- 17-day, term infant, 3kg, TGA (post OP day #15), day 10 post ECMO; max. fentanyl 8 mcg/hr, episodes of severe irritability (pain? withdrawal?) unrelieved by opioids, dexmedetomidine:
- 04/10/2012: Gabapentin 4 mg/kg Q6h



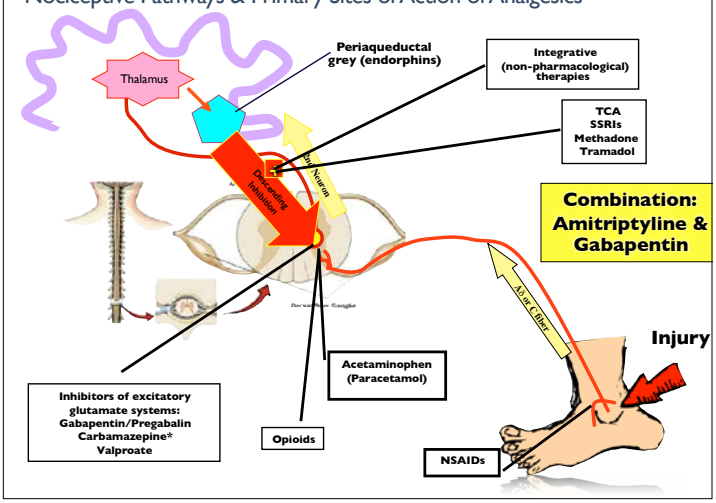
Gabapentinoids & TCAs?

- Non-placebo controlled study: Nortriptyline & gabapentin (at maximum tolerated doses) provided greater analgesia (plus improved sleep & mood) than when each drug was administered alone Gilron I, Bailey JM, Tu D, Holden RR, Jackson AC, Houlden RL. Nortriptyline and gabapentin, alone and in combination for neuropathic pain: a double-blind, randomised controlled crossover trial. Lancet. 2009 Oct 10;374(9697):1252-61.
- **Comparative Drug Trials**
- **Metaanalysis:** 6 RCTs - TCA vs gabapentin/ Pregabalin: No difference Finnerup NB, Sindrup SH, Jensen TS. The evidence for pharmacological treatment of neuropathic pain. Pain. 2010 Sep;150(3):573-81.

Other Antiepileptic Drugs

- Most studies negative Finnerup NB, Attal N, Haroutounian S, et al. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. The Lancet. Neurology. Feb 2015;14(2): 162-173.
- **Poorest safety profile:**
  - **Topiramate** NNT 6; NNH 6.3
  - **zonisamide** NNH 2.0
- **oxcarbazepine / carbamazepine** NNH 5.5

Nociceptive Pathways & Primary Sites of Action of Analgesics



Glucocorticosteroids

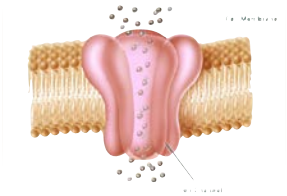
- **Possibly helpful:**
  - Nerve root / nerve trunk compression (e.g. tumor infiltration brachial plexus / lumbosacral plexus)
  - Spinal cord compression
  - Bone metastasis
  - Bowel obstruction
  - Lymphedema
- **Effect:**
  - Antiedematous (ameliorate painful nerve or spinal cord compression)
  - Antiinflammatory
  - Directly lyse some tumors (e.g. lymphoma)
  - Prostaglandin inhibition ➡ direct analgesic effect? Paulsen, O., et al., Do corticosteroids provide analgesic effects in cancer patients? A systematic literature review. J Pain Symptom Manage, 2013. 46(1): p. 96-105.

Glucocorticosteroids

- **Adverse effects:** Mood swings, Cushing's syndrome, pituitary-adrenal axis suppression, peptic ulcer, immunosuppression
- Psychosis - consider steroid switching Okishiro N, Tanimukai H, Tsuneto S, Ito N: Can "Steroid Switching" Improve Steroid-Induced Psychosis in a Patient with Advanced Cancer? J Palliative Med 2009. 12(5): 487-90
- Concurrent administration with NSAIDs: Risk of life-threatening GI bleeding x 5-fold Piper JM, Ray WA, Daugherty JR, Griffin MR: Corticosteroid use and peptic ulcer disease: role of nonsteroidal anti-inflammatory drugs. Ann Intern Med 1991. 1;114(9):735-40
- Dosage iv/po: Dexamethason (glucocorticoid): 0.1 -1.5 mg/kg (max. 10mg) starting dose, then 0.1 - 0.25 mg/kg x2/day (for < 14 days)
- Malignant spinal cord compression (adult dose): Dexamethason 16-96 mg/day or equivalent American Pain Society: Principles of Analgesic Use in the Treatment of Acute Pain and Cancer Pain 2008. 69-70 Mehta RS, Arnold RM. Management of spinal cord compression #238. Journal of Palliative Medicine. 2011 Mar; 14(3):362-3.
- Use gastroprotective agent (!)

Sodium channels are involved in pain...

- After nerve injury, expression of some Na+ channels increases de novo, the expression of others diminishes, and some translocate into different cellular compartments Levinson, S.R., S. Luo, and M.A. Henry, The role of sodium channels in chronic pain. Muscle Nerve, 2012. 46(2): p. 155-65.
- The proliferation of heterotopic sodium channels, such as Nav1.3, Nav1.7, and Nav1.8, may lower the stimulation threshold and provoke ectopic discharge, resulting in spontaneous pain. Cohen, S.P. and J. Mao, Neuropathic pain: mechanisms and their clinical implications. BMJ, 2014. 348: p. f7656.



Topical Lidocaine

- > 3 weeks: 3 studies (1 positive, 2 negative) Finnerup NB, Attal N, Haroutounian S, et al. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. The Lancet. Neurology. Feb 2015;14(2):162-173.
- Cochrane analysis: Small, short-term trials indicate topical lidocaine may be effective in treating neuropathic pain; safety & tolerability were good in all cases Derry S, Wiffen PJ, Moore RA, Quinlan J. Topical lidocaine for neuropathic pain in adults. Cochrane Database Syst Rev. 2014;7:CD010958.
- Produces selective, but incomplete block of A-delta and C fibers Krumova EK, Zeller M, Westermann A, Maier C. Lidocaine patch (5%) produces a selective, but incomplete block of Adelta and C fibers. Pain. 2012 Feb;153(2):273-80.

Topical Lidocaine 5% patch

- RCT (n=87) effective adjunct in post-operative (knee replacement) pain management Nafissi A: Lidoderm's effectiveness in reducing pain in post-operative unilateral knee replacements patients. 30th Annual Scientific Meeting of the American Pain Society May 2011 (Poster)
- For localized pain only
- Patch can be cut to fit
- 12 hours on/12 hours off [possibly longer?]
- Not with severe hepatic dysfunction
- Side effects include skin problems (such as irritation and redness)

IV Lidocaine - Pediatric Experience

- Nausea after 4 days? Neuropathic Pain: 1mg/kg over 5 min, then 1mg/hr - target: 2-5 mcg/mL Krane E, Leong M, Golianu B, Leong Y. Treatment of Pediatric Pain with Nonconventional Analgesics. In: Schechter N, Berde C, Yaster M, editors. Pain in infants, children, and adolescents. Philadelphia: Lippincott Williams & Wilkins; 2003. p. 225-40
- Side Effects: Allergic reaction (serious, but rare), dose related: numbness around mouth, dizziness, slurring of speech, hallucinations, muscle twitches, seizures R, Paice JA. How to initiate and monitor infusional lidocaine for severe and/or neuropathic pain. The journal of supportive oncology. 2004 Jan-Feb;2(1):90-4.
- **Case Series (n=5) after anti-GD2 antibody therapy in children with neuroblastoma: 1mg/kg/hr** Wallace MS, Lee J, Sorkin L, Dunn JS, Yaksh T, Yu A. Intravenous lidocaine: effects on controlling pain after anti-GD2 antibody therapy in children with neuroblastoma--a report of a series. Anesthesia and analgesia. 1997 Oct;85(4):794-6.
- **Case report; end-of-life cancer care: 2.1-3 mg/kg/hr** Massey GV, Pedigo S, Dunn NL, Grossman NJ, Russell EC. Continuous lidocaine infusion for the relief of refractory malignant pain in a terminally ill pediatric cancer patient. Journal of pediatric hematology/oncology. 2002 Oct;24(7):566-8.
- **Case report 5-year-old girl, meningitis caused by malignant T-cell lymphoma with difficult to treat neuropathic pain; IV lidocaine (9.3–14 mcg/kg/min)** J Palliat Med. 2012 Jun;15(6):719-22. doi: 10.1089/jpm.2011.0097. Epub 2012 Mar 8. Continuous intravenous infusion of ketamine and lidocaine as adjuvant analgesics in a 5-year-old patient with neuropathic cancer pain. Kajiume T, et al.

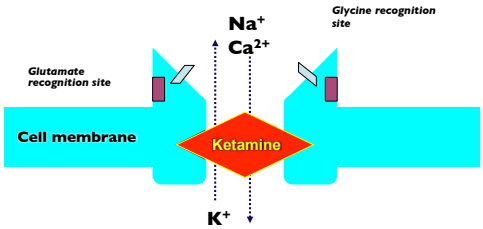
Other Sodium Channel Blocker

- **IV Lidocaine** for cancer pain: n=51 adult patients: without ECG monitoring: 5 mg/kg infused over 1 hour, option for subsequent doses increased if necessary, maximum of 10 mg/kg; effective analgesia in 49% Peixoto RD, Hawley P. Intravenous lidocaine for cancer pain without electrocardiographic monitoring: a retrospective review. J Palliat Med. Apr 2015;18(4):373-377.
- **Oral mexiletine, tocainide, flecainide**: High side effect liability from oral drugs: Not recmmended
- How about local **lidocaine** and **novocaine**...?

Magnesium as Analgesic?

- 2007: systematic review, no analgesic evidence (postoperative, adjuvant) Lysakowski C, Dumont L, Czarnetzki C, Tramer MR. Magnesium as an adjuvant to postoperative analgesia: a systematic review of randomized trials. Anesthesia and analgesia. 2007 Jun;104(6):1532-9.
- Therapeutic Review 2013 Crosby V, Elin RJ, Twycross R, Mihalyo M, Wilcock A. Magnesium. Journal of Pain and Symptom Management. 2013 Jan;45(1):137-44.
  - 13 RCTs, all but 2 reported reduced postop pain & analgesic requirements
- 8 RCTs spinal Mg: lower pain scores & analgesic requirements
- Administration: IV (severe hypo-Mg), PO (mild)

NMDA-Receptor Channel Blocker



3. Phencyclidin (PCP) - binding sites [uncompetitive NMDA receptor antagonists with moderate affinity]
   - Ketamine
   - Methadone
   - Levorphanol
   - (Dextrometorphane?)

NMDA-Receptor Channel Blocker

- **Central NMDA receptors**
  - NMDA receptors in supraspinal facilitatory sites (such as rostral ventromedial medulla, nucleus gigantocellularis) maintain non-inflammatory muscle pain in animal model Da Silva LF, Desantana JM, Sluka KA. Activation of NMDA receptors in the brainstem, rostral ventromedial medulla, and nucleus reticularis gigantocellularis mediates mechanical hyperalgesia produced by repeated intramuscular injections of acidic saline in rats. J Pain. 2010 Apr; 11(4):378-87.
- **Peripheral NMDA receptors**
  - topical 10% ketamine (compounded in pluronic lecithin organogel) reduced allodynia in CRPS. Adult RCT (n=20) Finch PM, Knudsen L, Drummond PD. Reduction of allodynia in patients with complex regional pain syndrome: A double-blind placebo-controlled trial of topical ketamine. Pain. 2009 Nov;146(1-2):18-25.
- Evidence: **Dextromethorphan** (6), **Memantine** (5), **Mg** (1): NNT 5.0; NNH 9.4 Finnerup NB, Attal N, Haroutounian S, et al. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. The Lancet. Neurology. Feb 2015;14(2):162-173.
- No **ketamine**

Ketamine

- Dissociative anesthetic which has analgesic properties in sub-anesthetic doses.
- Racemic mixture [S(+)-enantiomer (Analgesia, GA); R(-)-enantiomer (bronchodilatation, nightmares)]
- **Sedative-Hypnotic-Dissociative Dosing**: 1-2 mg/kg/dose IV
- **Analgesic (subanesthetic) Dosing**: IV: 1-5 mcg/kg/min [=0.06-0.3 mg/kg/hr]
- PO: 0.2-0.5 mg/kg TID-QID and PRN (sc, sl, intranasal, pr, spinally)
- Adverse effects: intracranial hypertension, tachycardia, psychotomimetic phenomena (euphoria, dsyphoria, vivid hallucinations) -> at low-dose??

Low-dose Ketamine

- Action which may contribute to analgesic effect: Meller S, Pain 1996. 68:435-6
  - Cholinergic transmission
  - Noradrenergic / serotinergic re-uptake inhibition
  - μ, δ, κ - opioid-like effect
  - Interactions with other Na-/Ca-channels

Low-dose Ketamine - Adult Evidence

- 37 RCTs (n=2240): subanesthetic Ketamine effective in reducing morphine requirements in first 24 hours after surgery, reduces postoperative nausea and vomiting; Adverse effects are mild or absent. Bell RF, et al. Perioperative ketamine for acute postoperative pain. Cochrane Database Syst Rev. 2006 Jan 25; (1):CD004603.
- RCT (n=60): Adult CRPS patients - 4 day low-dose (1.2-7 mcg/kg/min) infusion reduced pain scores week 1-11 (not 12) without functional improvement Sigtermans MJ, et al. Ketamine produces effective and long-term pain relief in patients with Complex Regional Pain Syndrome Type 1. Pain. 2009 Oct;145(3): 304-11.
- Metaanalysis: NMDA antagonists (& mexiletine) have no consistent clinical relevant efficacy in neuropathic pain Finnerup NB, Sindrup SH, Jensen TS. The evidence for pharmacological treatment of neuropathic pain. Pain. 2010 Sep;150(3):573-81.
- RCT (n=20) adults; opioid-refractory cancer pain: only 4/11 effective Salas S, et al. Ketamine analgesic effect by continuous intravenous infusion in refractory cancer pain: considerations about the clinical research in palliative care. Journal of Palliative Medicine.. 2012 Mar; 15(3):287-93.
- Increased risk for ketamine induced liver injury? Noppers IM, et al. Drug-induced liver injury following a repeated course of ketamine treatment for chronic pain in CRPS type 1 patients: a report of 3 cases. Pain. 2011 Sep;152(9):2173-8.

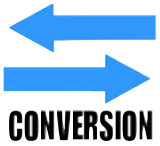
Low-dose Ketamine - Pediatric Evidence

- no RCT's, few case reports Finkel JC. J Pain 2007; 8(6):515-21
- n = 11, terminal cancer, age 3-17
  - Starting dose: 0.1-0.2 mg/kg/hr (max 1 mg/kg/hr)
  - Lorazepam 0.025 mg/kg BID
  - n = 8/11: ↓ Pain; ↓ Opioid requirements (28-100%)
  - No psychotropic side effects, no hallucinations
- 5-year-old girl, meningitis caused by malignant T-cell lymphoma with difficult to treat neuropathic pain. IV lidocaine (9.3–14 mcg/kg/min) and later ketamine (2 mcg/kg/min) in combination with fentanyl (0.8-1.2 mcg/kg/hr) provided good analgesia without significant side effects for the last 20 days of her life. J Palliat Med. 2012 Jun;15(6):719-22. doi: 10.1089/jpm.2011.0097. Epub 2012 Mar 8. Continuous intravenous infusion of ketamine and lidocaine as adjuvant analgesics in a 5-year-old patient with neuropathic cancer pain. Kajiume T, Sera Y, Nakanuno R, Ogura T, Karakawa S, Kobayakawa M, Taguchi S, Oshita K, Kawaguchi H, Sato T, Kobayashi M.

Ketamine

- Short-term 'burst' treatment with ketamine may have long-term benefit Jackson K, J Pain Sympt Managem 2001; 22: 834-42; Mitchell A, Pain Society Annual Scientific Meeting 2001, Poster 42: 50.
- Prevents analgesic tolerance to TENS (in rats) Priyanka MH, J Pain 2008, 9(3):217-25
- Low-dose: Effective rapid acting anti-depressant? Thangathurai D, Roby J, Roffey P. Treatment of resistant depression in patients with cancer with low doses of ketamine and desipramine. J Palliat Med. 2010 Mar;13(3):235. Stefanczyk-Sapieha L, Oneschuk D, Demas M. Intravenous ketamine "burst" for refractory depression in a patient with advanced cancer. J Palliat Med. 2008 Nov;11(9):1268-71. . Kollmar R, Markovic K, Thurauf N, Schmitt H, Kornhuber J. Ketamine followed by memantine for the treatment of major depression. Aust N Z J Psychiatry. 2008 Feb;42(2):170.
- Anti-depressant mechanism: up-regulation of mammalian target of rapamycin (mTOR). Li N, Lee B, Liu RJ, Banasr M, Dwyer JM, Iwata M, et al. mTOR-dependent synapse formation underlies the rapid antidepressant effects of NMDA antagonists. Science. 2010 Aug 20;329(5994):959-64. May cause acceleration of tumor growth? Shor B, Gibbons JJ, Abraham RT, Yu K. Targeting mTOR globally in cancer: thinking beyond rapamycin. Cell Cycle. [Review]. 2009 Dec;8(23):3831-7.

Ketamine



- Steady-state oral/parenteral ratio unclear
- Bio-availibilty 93% IM/IV; 20% PO
- Ketamine -> norketamine
- Potency ketamine: norketamine 3:1 (anesthetic); 1:1 (analgesic)
- Plasma half-life: ketamine 1-3 hrs; norketamine 12 hrs
- Maximum blood concentration of norketamine: oral > IV
  - Domino E, Clinical Pharm Therapeut 1984, 36:645-53; Clements JA, J Pharm Scienc 1982,71:539-42
- **Estimated at 1:1- 1:3** (i.e. 1mg IV = 1-3 mg PO) Benitez-Rosario MA, Salinas-Martin A, Gonzalez-Guillermo T, Feria M. A strategy for conversion from subcutaneous to oral ketamine in cancer pain patients: effect of a 1:1 ratio. Journal of Pain and Symptom Management. 2011 Jun;41(6):1098-105.

Other Adjuvant Analgesics / Co-analgesics

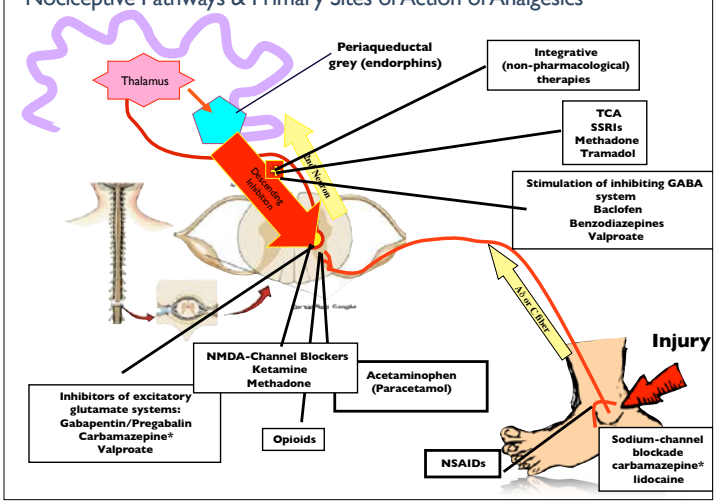
Benzodiazepines (incl. diazepam, lorazepam, midazolam)

- **Mechanisms of action**: gamma-aminobutyric acid (GABA) receptors
  - Potentiation of GABA-mediated transmission: sedative, anxiolytic, and anticonvulsant actions
  - GABA-agonist activity in the limbic cortex: amnestic property Cohen, I., Gallagher, TJ, Pohlman, AS, et al., Management of the agitated intensive care unit patient. Critical Care Medicine, 2002. 30(1): p. S97-S123.
  - **Flumazenil**, a competitive antagonist, can rapidly reverse (some of) the effects of benzodiazepines.

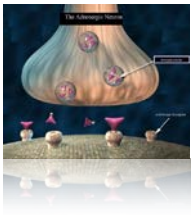
SNRI

- NNT: 6.4; NNH: 11.8 Finnerup NB, Attal N, Haroutounian S, et al. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. The Lancet. Neurology. Feb 2015;14(2):162-173.
- Duloxetine, venlafaxine

Nociceptive Pathways & Primary Sites of Action of Analgesics



α-Adrenergic Agonists



Analgesic effect?

- Postsynaptic alpha-2-adrenergic & mu-opioid receptors activate the same K-channel via inhibitory $G_{i/0}$ -proteins
- Presynaptic alpha-2-adrenoreceptors reduce neurotransmitter release by inhibiting calcium influx Ruffolo, R.R., Jr., et al., Structure and function of alpha-adrenoceptors. Pharmacol Rev, 1991. 43(4): p. 475-505.
- Systemic alpha-2-adrenoceptor stimulation may facilitate inhibitory synaptic responses in the superficial dorsal horn to produce analgesia mediated by activation of the pontospinal noradrenergic inhibitory system Funai, Y., et al., Systemic dexmedetomidine augments inhibitory synaptic transmission in the superficial dorsal horn through activation of descending noradrenergic control: an in vivo patch-clamp analysis of analgesic mechanisms. Pain, 2014. 155(3): p. 617-28.

α-2-Adrenergic Agonists: Clonidine vs Dexmedetomidine

- **Dexmedetomidine** has greater α2- versus α1- selectivity than **clonidine**
- **Postoperative neuropathic pain crisis** O'Neil T, Rodgers PE, Shultz C. Dexmedetomidine as adjuvant therapy for acute postoperative neuropathic pain crisis. J Palliat Med. Oct 2014;17(10):1164-1166.
- **Metaanalysis**: Perioperative systemic alpha-2 agonists (clonidine or dexmedetomidine) decrease postoperative opioid consumption, pain intensity, and nausea. Recovery times are not prolonged. Common adverse effects are bradycardia and arterial hypotension. Clonidine increased risk of intraoperative (NNH 9) & postoperative hypotension (NNH 20). Dexmedetomidine increased the risk of postoperative bradycardia (NNH 3) Blaudszun G, Lysakowski C, Elia N, Tramer MR. Effect of Perioperative Systemic alpha2 Agonists on Postoperative Morphine Consumption and Pain Intensity: Systematic Review and Meta-analysis of Randomized Controlled Trials. Anesthesiology. 2012 Jun;116(6):1312-22.

Clonidine

- PO: 1-3 mcg/kg Q6h
- Transdermal patch 4-12 mcg/kg/day [patches: 0.1, 0.2 or 0.3 mg/day - occluding smallest patch by 50%?]
- IV : not FDA approved
  - 1mcg/kg Q6-8 hourly given over 15-20mins to reduce some of dramatic blood pressure swings, obviously we like to swap to orals ASAP, the other [Sydney Children's Hospital, LISTSERV@LISTS.DAL.CA on 5/15/14]
  - 1 mcg/kg/hr titrated to effect up to 3 mcg/kg / hr [Athens, Greece 5/16/2014];
- Adult NHS Wolverhampton Guidelines: starting dose 1 mcg/kg/h [up to 4 mcg/kg/hr]

Dexmedetomidine

- Used in palliative care Roberts SB, Wozencraft CP, Coyne PJ, Smith TJ. Dexmedetomidine as an adjuvant analgesic for intractable cancer pain. Journal of Palliative Medicine. 2011 Mar;14(3):371-3. Soares LG, Naylor C, Martins MA, Peixoto G. Dexmedetomidine: a new option for intractable distress in the dying. Journal of Pain and Symptom Management. 2002 Jul;24(1):6-8.
- **Children's of MN: Dose** 0.2-2 mcg/kg/hr IV
- **Rotation to clonidine:**
  - 0.1-0.6 mcg/kg/hr DEX = 1 mcg/kg/dose Q (4-) 6h CLONIDINE
  - 0.7-1.4 mcg/kg/hr DEX = 2 mcg/kg/dose Q (4-) 6h CLONIDINE
  - 1.5-2.0 mcg/kg/hr DEX = 3 mcg/kg/dose Q (4-) 6h CLONIDINE

Dexmedetomidine

- n=107 patients, age 3 days-17 years, retrospective review
  - Dexmedetomidine, as part of multi-modal management, appears to be safe and efficacious; providing analgesia and sedation throughout all pediatric age groups following cardiac surgery.
  - Overall well tolerated and safe with higher doses than previously noted [0.8 µg/kg/hr to 2.17 µg/kg/hr]
  - Also well tolerated by neonates, infants, and patients with Trisomy 21
  - Withdrawal effects were noted in patients following prolonged infusion. Horvath, R (1) Halbrooks, EF, Zielinski, EE, Lin, CW (2), Overman, DM (1), Friedrichsdorf, SJ (3), (4):Efficacy and safety of postoperative dexmedetomidine administration in infants and children undergoing cardiac surgery: A retrospective cohort study. in Print 2015 J Ped Intensive Care

Dexmedetomidine in Neonates

- Pharmacokinetics, safety, and efficacy of dexmedetomidine in preterm and term neonates at three dose levels between 0.2 µg/kg/hr and 0.5 µg/kg/hr: overall effective for sedating this population and it was well tolerated, different overall PK profile compared to older patients Chrysostomou, C, Schulman, SR, Castellanos, MH, et al. (2013). A Phase II/III, multicenter, safety, efficacy, and pharmacokinetic study of dexmedetomidine in preterm and term neonates. Journal of Pediatrics. Pii:S0022-3476(13)01230-4.
- Efficacy of fentanyl vs dexmedetomidine in patients less than 36 weeks gestational age at birth who were less than 2 weeks old at the study start and mechanically ventilated. mean duration 12.4 days, 0.3 - 1.2 µg /kg/hour (mean 0.6), O'Mara, K, Gal, P, Wimmer, J, et al. (2012). Dexmedetomidine versus standard therapy with fentanyl for sedation in mechanically ventilated premature neonates. J Pediatr Pharmacol Ther. 17(3): 252-262

Cannabis

> 60 active compounds extracted from cannabis

- Activation of endocannabinoid system suppresses behavioral responses to acute and persistent noxious stimulation
  - Central and peripheral mechanisms Walker JM, Hohmann AG: Cannabinoid mechanisms of pain surpression. Handb Exp Pharmacol 2005. 509-54; Johanek LM, Simone DA: Activation of peripheral cannabinoid receptors attenuates cutaneous hyperalgesia produced by heat injury. PAIN 2004. 109:432-42
  - Cannabinoid receptors: periaqueductal gray (PAG), rostral ventro-medial medulla, dorsal horn of spinal cord
  - Animal experiments: Cannabinoids produce analgesia and potentiate opioids, particularly in neuropathic pain Cichewicz DL: Synergistic interactions between cannabis and opioid analgesics. Lie Sci 2004. 74:1317-24; Vaughan CW, Christie MJ: An analgesic role for cannabinoids. Med J Aust 2000. 173:270-2; Herzberg U, Herzberg U, Eliav E, Bennett GJ, Kopin IJ: The analgesic effects of R(+)-WIN 55,212-2 mesylate, a high affinity cannabinoid agonist, in a rat model of neuropathic pain. Neurosci Lett 1997. 221(2-3):157-60

Cerebral Cortex: Cannabis

- Medical Cannabis program currently (2014) in 22 US states plus Washington, D.C.
- State adult population registered for medical marijuana: Bowles DW. Persons registered for medical marijuana in the United States. Journal of Palliative Medicine. [Letter]. 2012 Jan;15(1):9-11.
  - Montana: 4.1 %
  - Vermont: 0.07 %

Cannabis

- Cannabinoids: NNT: ns; NNH 12.1 . Only 2 out of 9 trials positive
  Finnerup NB, Attal N, Haroutounian S, et al. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. The Lancet. Neurology. Feb 2015;14(2):162-173.
- Nabiximol (Sativex) oromucosal pump spray: D-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) in 1:1 ratio
  - Effective for MS patients with neuropathic pain Rog DJ, Nurmikko TJ, Friede T, Young CA: Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis. Neurology 2005. 65(6):812-9
- RCT Cancer pain: not effective
  Portenoy RK, Ganae-Motan ED, Allende S, Yanagihara R, Shaiova L, Weinstein S, et al. Nabiximols for opioid-treated cancer patients with poorly-controlled chronic pain: a randomized, placebo-controlled, graded-dose trial. J Pain 2012 May;13(5):438-49

Cannabis

- Correlation with **mental illness**
  Casadio, P, et al., Cannabis use in young people: the risk for schizophrenia. Neurosci Biobehav Rev, 2011. 35(8): p. 1779-87.; Hermens, D.F., et al., Frequent alcohol, nicotine or cannabis use is common in young persons presenting for mental healthcare: a cross-sectional study. BMJ Open, 2013. 3(2).; Lev-Ran, S., et al., Exploring the association between lifetime prevalence of mental illness and transition from substance use to substance use disorders: results from the National Epidemiologic Survey of Alcohol and Related Conditions (NESARC). Am J Addict, 2013. 22(2): p. 93-8.; Lev-Ran, S., et al., Cannabis use and cannabis use disorders among individuals with mental illness. Compr Psychiatry, 2013. 54(6): p. 589-98. Smith, M.J., et al., Prevalence of psychotic symptoms in substance users: a comparison across substances. Compr Psychiatry, 2009. 50(3): p. 245-50.
- Also, Stacey, B.R. and J.L. Moller, Marijuana for pain relief: don't jump to conclusions. J Pain, 2013. 14(10): p. 1250-1.
  - Impairment of driving ability
  - Associated with drugs of abuse
  - Impacts on work
  - Health issues associated with cannabis
- 3 studies show positive correlation between marijuana use and **testicular cancer** (1) Lacson JC, Carroll JD, Tuazon E, Castelao EJ, Bernstein L, Cortessis VK. Population-based case-control study of recreational drug use and testis cancer risk confirms an association between marijuana use and nonseminoma risk. Cancer. Nov 1 2012;118(21):5374-5383. (2) Trabert B, Sigurdson AJ, Sweeney AM, Strom SS, McGlynn KA. Marijuana use and testicular germ cell tumors. Cancer. Feb 15 2011;117(4):848-853. (3) Daling JR, Doody DR, Sun X, et al. Association of marijuana use and the incidence of testicular germ cell tumors. Cancer. Mar 15 2009;115(6):1215-1223.

Early-Onset, Regular Cannabis Use Is Linked to IQ Decline

- Study participants who initiated weekly cannabis use before age 18 **dropped IQ points in proportion to how long they persisted in using the drug,** while nonusers gained a fraction of a point. Meier, M.H.; Caspi, A.; Ambler, A.; Harrington, H.; Houts, R.; Keefe, R.S.E.; McDonald, K.; Ward, A.; Poulton, R.; and Moffitt, T. Persistent cannabis users show neuropsychological decline from childhood to midlife. Proceedings of the National Academy of Sciences 109(40):E2657–E2664, 2012. Moffitt, T.E.; Meier, M.H.; Caspi, A.; and Poulton, R. Reply to Rogeberg and Daly: No evidence that socioeconomic status or personality differences confound the association between cannabis use and IQ decline. Proceeding of the National Academy of Sciences 110(11):E980-E982, 2013.

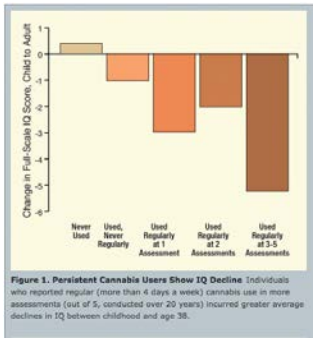


Figure 1. Persistent Cannabis Users Show IQ Decline Individuals who reported regular (more than 4 days a week) cannabis use in more assessments (out of 5, conducted over 20 years) incurred greater average declines in IQ between childhood and age 38.

Positive Effects

Cannabinoids

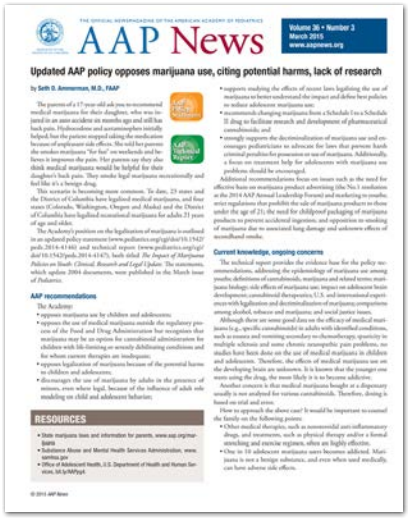
- May result in reduction of pain and inflammation
- May work as an antiepileptic

Negative Effects

noids

- Youthful exposure leads to earlier onset & more severe psychosis, incl. schizophrenia
- 9% of adults (17% teens) who experiment with marijuana become dependent
- Samples from household marijuana grew up to 10,000,000/ gram organisms **Salmonella** muenchen (incl. 85 cases of acquired **enteritis** in Georgia, Alabama, Ohio, Michigan)

- **AAP Handout for parents "Despite relaxed regulations, marijuana harms developing brain":** http://aapnews.aappublications.org/content/36/3/4.full.pdf+html
- **Updated AAP policy opposes marijuana use, citing potential harms, lack of research** http://aapnews.aappublications.org/content/early/2015/01/26/aapnews.20150126-1



AAP News

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Updated AAP policy opposes marijuana use, citing potential harms, lack of research

by Seth D. Ammerman, M.D., FAAP

RESOURCES

Other Adjuvant Analgesic / Co-analgesics

- **Muscle relaxants:** Baclofen; Cyclobenzaprine (Flexaril®)
- **Bisphosphonates**: Osteoclast inhibitors -> metastatic bone pain
  Weinstein E, Arnold RM. Bisphosphonates for bone pain #113. Journal of Palliative Medicine. 2010 Jul;13(7):893-4.
- **Antispasmodics**: Hyoscine butyl bromide (Buscopan®) [not in USA], hyoscyamine (Levsin®); oxybutynin (Ditropan®), glycopyrrolate (Robinul®)
- β-ray emitting osteotrope **radio pharmaceutical**: e.g. Samarium-153-EDTMP
- **Anti-TNF α agent** [treatment of rheumatoid arthritis (RA) and spondyloarthropathies (SpAs)] adalimumab (Humira), certolizumab (Cimzia), etanercept (Enbrel), infliximab (Remicade), golimumab (Simponi).
  - Back Pain Kivitz, A.J., et al., Efficacy and safety of tanezumab versus naproxen in the treatment of chronic low back pain. Pain, 2013. 154(7): p. 1009-21.
  - Osteoarthritis Spierings, E.L., et al., A phase III placebo- and oxycodone-controlled study of tanezumab in adults with osteoarthritis pain of the hip or knee. Pain, 2013. 154(9): p. 1603-12.
- **Statins**? Mouse: simvastatin, rosuvastatin prevented injury induced neuropathiv pain Shi XQ, Lim TK, Lee S, Zhao YQ, Zhang J. Statins alleviate experimental nerve injury-induced neuropathic pain. Pain. 2011 May;152(5):1033-43.

Botulinum toxin A

- Peripheral neuropathic pain
- 6 RCTs: 50-200 units s.c. in the region of pain
- Low placebo effect
- NNT: 1.9 [95% CI 1.5-2.5 for 4 studies]; one large (unpublished) study negative

Finnerup NB, Attal N, Haroutounian S, et al. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. The Lancet. Neurology. Feb 2015;14(2):162-173.

Adult Evidence Based Recommendations Neuropathic Pain

First Line

- Tricyclic antidepressants
- Gabapentin, pregabaline
- Serotonin/norepinephrine reuptake inhibitors

Second Line

- Tramadol
- Capsaicin 8%
- Lidocaine patch

Third Line

- Strong opioids
- Botolinum toxin A

Finnerup NB, Attal N, Haroutounian S, et al. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. The Lancet. Neurology. Feb 2015;14(2):162-173.

Children's MINNESOTA

Further Training:
CIPPC@ChildrensMN.org

9th Annual Pediatric Pain Master Class
• Minneapolis, MN | June 11-17, 2016

Education in Palliative & End-of-life Care [EPEC]: Become an EPEC-Pediatrics Trainer
• 9th Conference: Chicago, IL | March 12-13, 2016 http://tinyurl.com/EPEC2016

Twitter: @NoNeedlessPain
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Blog: http://NoNeedlessPain.org

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http://www.childrensmn.org/services/painpalliativeintegrativemed