

Treatment of Pain in the Outpatient Setting

See Wan Tham, MBBS

Objectives for Learning Outcomes

After completing this session, you will be better able to:

1. Discuss common acute and chronic pediatric pain conditions.
2. Know the principles of pharmacology applicable to children from birth to adolescence.
3. Describe the current state of opioid prescribing practices.

Treatment of Pain in the Outpatient Setting

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Disclosures

I have no actual or potential conflict of interest in relation to this presentation.



Objectives

1. Common pediatric pain conditions
2. Principles of pharmacology applicable to children from birth to adolescence
3. Current state of opioid prescribing patterns



Common Pediatric Pain Conditions

Pain

An unpleasant sensory and emotional experience associated with **actual or potential** tissue damage, or described in terms of such damage.

International Association of the Study of Pain (IASP)



Prevalence of Pediatric Chronic Pain

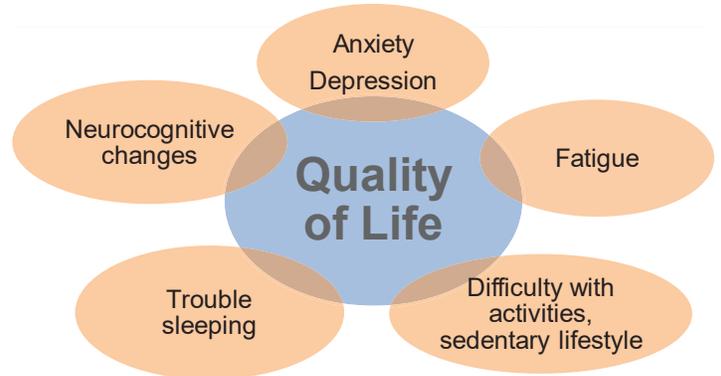
- Chronic pain: Defined as recurrent or persistent pain as lasting greater than 3 months or longer than what would generally be expected for tissue healing.
- In contrast to acute pain:
 - No longer serves as a protective mechanism.
 - Pain is no longer a symptom, but a disease state.
- Prevalence:
 - Affects 20 - 30%.
 - Peak during adolescence.
 - Higher rates in females.
 - 5-15% experience moderate to severe pain related disability.
- Incidence has doubled over the last decade.
King 2011, Perquin 2001, Huguet 2008



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Chronic pain can lead to additional problems...



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Societal Impact of Chronic Pain

- Estimate to cost \$19.5 billion annually:
 - Substantial economic burden to families and society.
 - Primary driver of cost were direct medical cost, and productivity losses.
- Children with chronic pain are at risk of developing chronic pain as adults.

The Institute of Medicine says chronic pain in the U.S....¹



Affects about 100 million adults



Costs \$560-635 billion annually (health care, lost productivity)



A major cause of missed work

Conceptualization of Chronic Pain

- Lack of appropriate classification in the *International Classification of Diseases* 10th Edition:
 - Renders accurate epidemiological investigations difficult.
 - Impedes health policy decisions regarding chronic pain.
- World Health Organization and IASP Working Group developed a classification system.
 - Upcoming 11th edition of *International Classification of Diseases*
 - Improved classification and diagnostic coding
 - Advance the recognition of chronic pain as a health condition in its own right.
 - Will be implemented June 2019.



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International Classification of Diseases 11th Edition

• **Chronic primary pain:**

- Pain can be the sole/leading complaint and requires special treatment and care.
- May be conceived as a disease in its own right, e.g. fibromyalgia or nonspecific low-back pain

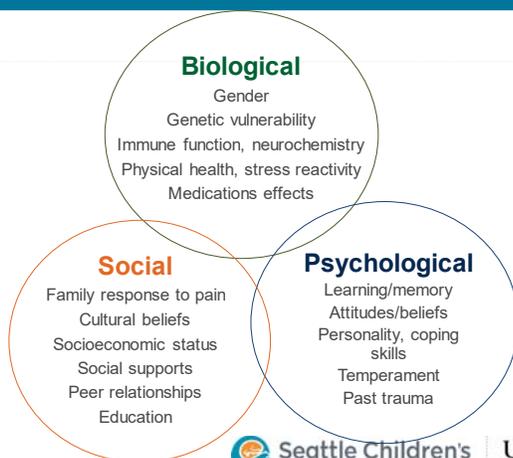
• **Chronic secondary pain**

- Pain is secondary to an underlying disease where pain may at least initially be conceived as a symptom.
 1. Chronic cancer-related pain
 2. Chronic neuropathic pain
 3. Chronic secondary visceral pain
 4. Chronic posttraumatic and postsurgical pain
 5. Chronic secondary headache and orofacial pain
 6. Chronic secondary musculoskeletal pain

Context of Persistent/Chronic Pain in Children and Adolescents

- A major source of suffering for the child:
 - Interferes with daily functioning.
 - Often accompanied by distress.
 - Delay in developmental milestones e.g. school, peer relationships, skills towards independence.
- Family functioning:
 - Parental distress.
 - Family conflict.
 - Utilization of resources and time
- Lack of clarity of long term prognosis:
 - Fear of undiagnosed disease condition.
 - Uncertainty of the future.

Biopsychosocial Approach to the Treatment of Pain



Interdisciplinary Approach

- Interdisciplinary approach better than any single stand-alone therapy
 - Neuroscience education
 - Reassurance that pain is REAL
 - Dysregulation in pain neural signalling
 - Physical and occupational therapy
 - Pain psychology
 - Medication management
 - Lifestyle factors (e.g. sleep, nutrition)
 - Complementary therapies
 - Treatment of comorbid conditions e.g. physical, psychological
- Primary goal: improved all domains of functioning and quality of life.

Headaches and Migraines

- Most headaches are benign
- Classification:
 - Migraine with/without aura
 - Tension headaches
 - Cluster (rare)
 - Chronic daily headache
 - Secondary: trauma, infection, brain tumor, toxins/drugs
- Migraines:
 - 10% of school aged children and adolescents; up to 1/4 women
 - Familial - 70% have positive family history in 1st degree relative
 - Episodic, not daily
 - Variable symptoms (frequency, severity, location, duration, associated symptoms)



International Classification of Headache Disorders 3rd Edition

Migraine without aura:

- At least 5 attacks
- Last 4 – 72 hours
- 2/4 characteristics – unilateral location (can be bilateral in children), pulsating quality, moderate/severe intensity, aggravated by routine activity.
- During the headaches, have at least one or the following:
 - nausea and/or vomiting,
 - photophobia and phonophobia.
- Not attributed by another disorder.

Cephalalgia 2018, 38 (1) 1 - 211

International Classification of Headache Disorders 3rd Edition

Migraine with aura:

- Criteria same as migraine without aura.
- Also have focal symptoms over 5 - 20 minutes and lasts less than 60 minutes (Visual, sensory, speech and/or language, motor, brainstem, retinal).
- At least 2 attacks.
- Headaches begins during or after aura.



Chronic migraine:

- Headache occurring on 15 or more days per month for >3 months, and has features of migraine on at least 8 days/month.

Cephalalgia 2018, 38 (1) 1 - 211

International Classification of Headache Disorders 3rd Edition

Tension-Type Headache:

- At least 10 episodes (more than once but less than 15 days/month).
- Headaches lasting 30 minutes to 7 days
- At least 2 of the following:
 - Pressing/tightening (non-pulsating)
 - Mild or moderate intensity
 - Bilateral location
 - Not aggravation by activity
 - Both of the following:
 - NO nausea/vomiting,
 - photophobia OR phonophobia



Headache and Migraine Abortives

Over-the-counter medication:

- **Ibuprofen** most effective in children
 - Inhibit cyclooxygenase (COX) and reduce prostaglandin production at the site of tissue injury and diminish the inflammatory cascade.
 - **Boxed warning:** Associated with adverse cardiovascular thrombotic events, may increase with duration of use or cardiovascular risk factors or disease.
 - Dosing 10mg/kg.
 - Side effects: epigastric pain, heartburn, nausea, dyspepsia, skin rash, renal dysfunction.
- **Naproxen** may be substituted for ibuprofen.
- Aspirin and Excedrin (>16 years) are other options.



Headache and Migraine Abortives: **Triptans**

- Selective 5-hydroxytryptamine (5-HT) agonists:
 - Block actions of 5-HT e.g. dilation of cranial arteries/AV anastomoses, neurogenic dural plasma extravasation.
- Triptans:
 - Faster onset: Rizatriptan, sumatriptan, zolmitriptan.
 - Slower onset: Naratriptan.
- Use early, more effective in mild/moderate pain.
- Caution about rebound headaches.
- Side effects: chest pressures/heaviness, jaw tightness, dizziness, somnolence, fatigue, nausea, paresthesia.
- Relative contraindications: complicated migraine, cardiovascular disease, smoker, +oral contraceptive, severe hypertension.



Medication-Overuse and Rebound Headaches

- Consider if:
 - Analgesics at least 15 days/month for > 3 months.
 - Triptans at least 10 days/month for 3 > months.
 - Headache developed or markedly worsened during medication overuse e.g. NSAIDs, acetaminophen, aspirin, caffeine, triptans.
 - Headache resolves or reverts to previous pattern within 2 months after stopping analgesics.
- Daily low dose use worse than high dose use once a week.
- Treatment:
 - Withdraw offending agent.
 - Limit analgesic use to 2 -3 days per week.
 - Triptan use limited to 6 headaches a month.
 - Limit: no more than 2 doses of medication per headache.



Evidence for prescription **preventive medications** therapy

- Often recommended and prescribed by headache specialists as first line treatment for recurrent headache and migraine (twice a week or more).
 - Findings inferred from adult migraine trials to children.
- Common classes:
 - Seizure medications: topiramate, valproate, gabapentin, zonisamide.
 - Blood pressure medications: propranolol, nadolol, verapamil.
 - Antidepressants: tricyclics, combinations e.g. venlafaxine.
- Only FDA approved medication for headache prevention is topiramate in adolescents 12 -17 years of age; no medicine are approved for use under age 12.



Topiramate

- Antiepileptic agent.
- For prophylaxis of migraines:
 - Initial dose: 25mg/day at night for one week, can be increased weekly by increments of 25mg.
 - Recommended dose: 100mg/day in two divided doses.
- Precautions: **cognitive dysfunction**, **weight decrease**, **fatigue**, **dizziness**, **somnolence**, psychomotor slowing, difficulty with memory/concentration, mood problems, paresthesia, taste perversion, increase risk of suicidal thoughts or behavior

www.accessdata.fda.gov



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Amitriptyline

- Tricyclic antidepressants
 - Noradrenergic and serotonergic pathways; antimuscarinic and antihistaminic properties.
 - Anticholinergic effects of slowing transit.
- Recommended dose:
 - Starting dose 0.2mg/kg
 - Increased to therapeutic dose of 0.5mg/kg.
- Precautions: potential for inducing cardiac arrhythmias, evaluate for prolonged QT syndrome, sedative side effects, increased suicidal thoughts and/or behavior, especially with the FDA black box warning (2004).
- Obtain EKG prior to starting amitriptyline.



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Childhood and Adolescent Migraine Prevention (CHAMP)

- Trial: Tested effects of amitriptyline and topiramate in comparison with each other and with placebo in pediatric migraine.
 - Medications chosen as the most commonly used medications.
 - Clinically meaningful endpoint is reduction of 50% or more days
- Trial stopped early due to futility as results showed that neither of the two medications were more effective to placebo; and had more adverse events.
- Results:
 - **High placebo response rates of 50 to 60%** with reduction of 50% or more in the number of headache days.
 - No significant differences in reduction in headache frequency or disability over 24 weeks.
 - Active drugs were associated with higher rates of adverse events.

Powers et al 2017



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Interdisciplinary and Multimodal Therapy for Headaches

- Lifestyle: reduce triggers, hydration, exercise, sleep and stress management.
- Psychology:
 - Cognitive behavioral therapy.
 - Biofeedback.
- Physical therapies.
- Naturaceuticals: Coenzyme Q10, magnesium, riboflavin, Butterbur/feverfew/skullcap.
- Complementary therapies: acupuncture, yoga/meditation.

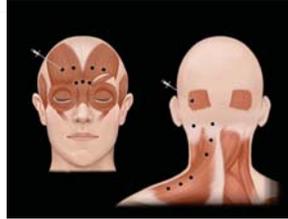


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Other Therapies

- **Onabotulinumtoxin A (Botox)**
 - FDA approved in adults for chronic migraine
 - Injected directly into muscles to reduce contractions and relaxation. Administered every 12 weeks
- New class of migraine preventive agents: **Anti-CGRP drugs**
 - In the planning stages for initial efficacy clinical trials in youth.
 - Studies are designed with the notable placebo effects.
 - Results will be available in the coming few years.



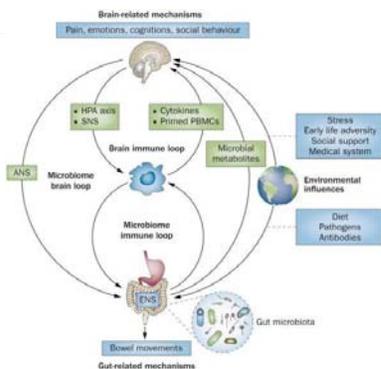
Abdominal Pain

- Prevalence:
 - 13 -38% of children with pain weekly.
 - Up to 24% with symptoms >8 weeks.
- Clinical presentation:
 - Gastrointestinal symptoms.
 - Disturbances in defecation.
- The majority of patients with mild symptoms improve with reassurance and time.
- For children with more severe and disabling illness, effective treatment remains challenging.



Gut Brain Axis

Altered brain inputs via the ANS and HPA influence motility, secretion, permeability, immune function and gut microbial composition.



Peripheral and environmental factors provide feedback to the brain setting up circular regulatory loops.

Reviews

- Evidence is low, few placebo-controlled randomized controlled trials.
 - “The true efficacy of drugs for FGIDs in children remains to be elucidated” (Cochrane review).
 - “Limited evidence to justify the use of drugs or herbal preparations for chronic abdominal pain in children” (Technical review by American Academy of Pediatric and North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition)
- Role of placebo:
 - Strong placebo response in uncontrolled studies.
 - Placebo effect due to high level of expectancy, frequency of contact between doctors and patients; or variation in natural course of disease.
 - Can contribute to 50% chance of improvement.

Management Strategies

- Interdisciplinary approach
- Major therapeutic approaches:
 - Dietary therapy.
 - Cognitive behavioral therapy & psychosocial interventions.
 - Pharmacotherapy.
 - Complementary and alternative therapies
 - 36 - 41% use complementary and alternative medicine annually

Antispasmodic Agents: Peppermint Oil

- Mechanisms:
 - Menthol component of peppermint is known to **block calcium channels** which might lead to reduction of colonic spasms.
 - Decrease smooth muscle spasms of gastrointestinal tract.
- Peppermint oil:
 - Shown to be effective in adults with irritable bowel syndrome compared to placebo.
 - Kline et al: After 2 weeks, 76% of children receiving peppermint oil report improvement in 19% of children.
 - Well tolerated.



Antispasmodic Agents: Hyoscyamine

- Anticholinergic, antispasmodic.
- Mechanism:
 - Non selective competitive antagonist of muscarinic receptors,
 - Inhibit the parasympathetic activities of acetylcholine on salivary, bronchial, sweat, eye, heart, bladder, gastrointestinal tract.
 - Prevents bladder contraction and decrease motility.
- Side effects: dizziness, drowsiness, nervousness, blurred vision, headache, trouble sleeping, dry mouth, urinary retention.
- No studies in pediatrics, in adults was found to have consistent evidence of efficacy.

Antidepressants: Amitriptyline in Pediatric Trials

Double-blind Placebo-Controlled Trial of Amitriptyline for the Treatment of Irritable Bowel Syndrome in Adolescents

ROH J. BAIER, MD, BENJI S. COLLINS, MD, BAILEY STRANDEZ, MD, AND MARVIN E. ARINI, MD

- N = 33 randomized to amitriptyline (weight based 10/20/30mg) versus placebo.
- Compared to placebo, patients with amitriptyline were more likely to have improvement in quality of life; improvement of pain in some but not all areas of abdomen.

Multicenter, Randomized, Placebo-Controlled Trial of Amitriptyline in Children With Functional Gastrointestinal Disorders

MIGUEL SARRS,¹ NADER YOUSSEF,² ADRIAN MIRANDA,³ SAMUEL NURKO,⁴ PAUL HYMAN,⁵ JOSE COCJIN,⁶ and CARLO DI LORENZO^{7*}

- N = 83 randomized to 4 weeks of placebo or amitriptyline.
- Both groups reported excellent therapeutic response, 63% (amitriptyline) and 57.5% (placebo).
- Patients in the amitriptyline group had reduced anxiety scores, but no difference in pain, disability, depression, or somatization score.

Selective Serotonin Reuptake Inhibitors

- Block uptake of 5-HT, increasing its concentration at presynaptic nerve endings.
 - Central nervous system effects on mood and anxiety
 - May be beneficial for gastrointestinal complaints, since serotonin is an important neurotransmitter in the GI tract, and greater than 80% of the body's stores are located in enterochromaffin cells of the gut.
 - Exact role in the GI tract has not been elucidated, but implicated in the modulation of colonic motility and visceral pain in the gut.
- Prospective open label flexible dose study of **citalopram** (10/20mg to 40mg/day) for 25 children.
 - At the end of 12 weeks, 84% were classified as responders on a global illness improvement scale (Campo et al).
- In a recent randomized placebo controlled trial in adults, there was not significant benefit after 8 weeks of treatment

Acid suppressants agents

- Mechanisms:
 - H2 receptor antagonist
 - Proton pump inhibitors
- Study (See et al.)
 - N = 25 children in randomized double blind placebo controlled crossover trial for dyspepsia.
 - Famotidine 0.5mg/kg twice a day for 14 days.
 - Self report improvements in the famotidine group (68%) versus placebo (12%).
 - No significant difference on quantitative measures of symptom frequency and severity.
- No controlled studies on proton pump inhibitors

Cyproheptadine

- Mechanisms:
 - Antihistaminic
 - Anticholinergic
 - Antiserotonergic
 - Calcium channel blockade effects
- Used in appetite stimulation, abdominal pain, cyclic vomiting syndrome.
- Single study (Sadeghian et al)
 - N = 29 children and adolescents (age 4.5 – 12 years) in 2 week double blind placebo controlled trial.
 - 86% in cyproheptadine group had improvement compared to 35.7% in the placebo group.

Musculoskeletal Pain: Back Pain

- Begin around school age, rise until age 18 years.
 - 1% age 7 years, 6% 10 years, 18% 14-16 years,
 - By 18 years estimated prevalence of 20% yearly, lifetime prevalence of 75%.
 - > 7% seek medical attention.
- History and physical examination are the foundation of evaluation
- Indication of imaging vary depending on the etiology.
- Treatment:
 - Rehabilitation
 - Pharmacologic treatment is used, but brief course.
 - Referrals: orthopedic, rheumatologic



Medication Options

- No specific evidenced based studies for medication in low back pain (LBP).
- Inflammatory conditions; general musculoskeletal pain:
 - NSAIDs are effective for short term symptomatic pain relief for both acute and chronic low back pain
- Muscular contraction conditions:
 - Muscle relaxants in nonspecific LBP found that they can be effective in the treatment of pain
- Limited or no benefit for systemic glucocorticoid therapy

Cochrane review



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Muscle relaxants

- **Baclofen**
 - Gamma-aminobutyric acid B receptor agonist used to treat spasticity, and may be used to treat muscle spasm pain.
 - Showed benefit in acute low back pain
- **Cyclobenzaprine**
 - Works supraspinally, has anticholinergic effects.
 - Improve in global function, ameliorate sleep disturbances.
- **Tizanidine**
 - Alpha 2 agonist with antispasmodic properties
 - Very sedating
 - Risk of hepatocellular damage and liver enzymes should be followed for 6 months
- Choice may be guided by side effect profile, sedation most commonly reported.

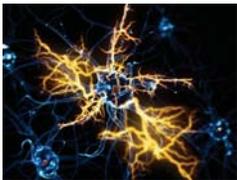


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Back Pain with Neuropathy

- Key elements:
 - Descriptors of pain e.g., burning, sharp needle-like, pain on non-nociceptive stimuli.
 - Allodynia, hyperesthesia, hyperpathia, hypoesthesia.
 - May follow a dermatomal distribution.
- Multidisciplinary approach
 - Physical and occupational therapy
 - Pharmacologic treatment with anticonvulsants.



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Anticonvulsants: Gabapentin and Pregabalin

- Limited evidence in pediatric population.
 - FDA approval for neuropathic pain with diabetic peripheral neuropathy, postherpetic neuralgia, seizures, fibromyalgia
 - Off label use in pediatric population
- **Mechanism of action:**
 - Lipophilic structural analogue of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA).
 - Binds to the alpha 2 gamma subunit 1 and 2.
 - Hypothesized to work via modulation of voltage gated calcium channels.
- **Dose recommendations:**
 - Gabapentin: 5 mg/kg/day once a day, increase to 3 times/day weekly; Max of 35 mg/kg/day.
 - Pregabalin: 150 mg daily in divided dose (75 mg twice a day).



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Gabapentin & Pregabalin

- Dose adjustment
 - Check baseline BUN and serum creatinine
 - Increased half life with decreased renal function
 - Titration required
- Adverse reactions
 - Increased risks of suicidal ideation
 - Central nervous system: somnolence, dizziness, fatigue, emotional lability and hostility, depression.
 - Gastrointestinal: nausea and vomiting, diarrhea,
 - Ocular: nystagmus, diplopia and blurred vision
 - Peripheral edema

Juvenile Fibromyalgia: Controversial diagnostic criteria

Yunus and Masi criteria:

Major criteria

- Generalized musculoskeletal pain at ≥ 3 sites for at least 3 months
- Absence of underlying condition
- Normal test results
- 5 tender points

Minor criteria

1. Chronic anxiety of tension
2. Fatigue
3. Poor sleep
4. Chronic headaches
5. Irritable bowel syndrome
6. Subjective soft tissue swelling
7. Numbness
8. Pain modulation of physical activity
9. Pain modulation by weather factors
10. Pain modulation by anxiety or stress

Juvenile Fibromyalgia: Controversial diagnostic criteria

American College of Rheumatology

- 1990: Widespread pain for at least 3 months and at least 11 of 18 tender points.
- 2010: Generalized widespread pain for at least 3 months, and a scale based upon nonrestorative sleep, and/or cognitive symptoms and somatic symptoms.
 - Validated in one small study for female adolescents.
 - Reduced number of somatic symptoms in pediatric populations e.g. chest pain, hair loss.
- 2016: Generalized pain in at least 4 or 5 regions, for at least 3 months, widespread pain index ≥ 7 and symptom severity score of ≥ 5 OR WPI of 4-6 and SSS score ≥ 9 .

Duloxetine

- Serotonin and norepinephrine reuptake inhibitor.
- Some evidence supporting its use in diabetic neuropathic pain, fibromyalgia.
 - Some data point to addressing psychological symptoms, and other suggest improvement in somatic pain.
- Adverse effects: nausea, sleep disturbance
- Titrated towards efficacy
- Some data for fluoxetine – due to risks of suicidal ideation has led to warning regarding antidepressants in the pediatric age range.

Complex Regional Pain Syndrome

- Aberrant inflammatory mechanisms, vasomotor dysfunction, Maladaptive neuroplasticity.
- Moderate to severe pain localized to an extremity, not distribution of a specific nerve
- Hyperalgesia, allodynia, edema, color, temperature changes in the affected limb.
- Early aggressive **multidisciplinary** treatment associated improved outcomes (intensive physical and occupational therapy, medication management, pain psychology)
- Refer to SCH Pain Clinic for triage and expedited treatment for intensive rehabilitation.



Principles of Pharmacology

Practice of pediatric pain management has made great progress in the last decade:

- Development and validation of assessment tools.
- Multimodal and interdisciplinary approach.
- Inclusion of pediatric analgesic trials to provide evidenced based pain management guidelines.
- Decision making:
 - Match mechanisms of action of medication with the best known pathophysiology of pain condition.
 - Choose medication “based on all available data, thoughtful consideration, presumed mechanisms, pharmacology, and expert consensus”.
 - Extrapolation from adult data and practice can be useful in young adults and older children when the problem under treatment can be reasonably assumed to have a similar mechanism.

Understanding etiology to guide treatment

- **Types of pain:**
 1. **Nociceptive** – stimulation of nociceptors
 - Somatic – skin, soft tissue, skeletal muscle, bone
 - Visceral – internal organs involvement e.g., kidney, gastrointestinal tract
 2. **Neuropathic**
 - Damage to nerves in peripheral or central nervous system
 - Caused by compression, transection, infiltration, ischemia
 - Descriptors of burning, shooting, electric, tingling
 3. **Chronic** – central sensitization, altered conditioned pain modulation
- **Source**
 - Related to disease process e.g., cancer, sickle cell disease

Pharmacology of Opioids

Caution in the use of opioids in neonates and young infants

- Increased susceptibility to **apnea** due to the imbalance of mu 1 and mu 2 receptors.
- Increased susceptibility to hypoventilation due to **decreased ventilation response to hypoxia and hypercapnia**.
- **Immature** liver conjugation and renal filtration.
- **Metabolism and excretion of opioids** and metabolites are markedly decreased.
- Higher concentration of drug in brain due to **immature blood brain barrier**.
- Increase free fraction of drug in the blood because of **decrease plasma protein binding**.

Washington Medical Commission adopted opioid prescribing rules, effective January 2019.

What you need to know:

- These rules will be effective January 1, 2019.
- Prescriptions must not be written for more than is needed for effective pain control. The rules provide specific timelines for each phase of pain, you must document the justification for such a quantity.
- [PMP](#) checks are required at first refill/renewal, during a pain phase transition and periodically based on the patient's risk level.
- Prescribing opioids must be based on clear documentation of unrelieved pain.

What you need to do to prescribe opioids:

- Give the patient resources regarding the risks associated with opioids as well as the safe storage and disposal of opioids, at the first issuance of an opioid prescription and when the patient transitions to another pain phase.
- Complete 1 hour of opioid prescribing CME by the end of your next full CME reporting period after January 1, 2019.

Washington Medical Commission adopted opioid prescribing rules, effective January 2019.

Important Terms:

For the purpose of these rules:

- Inappropriate treatment of pain includes non-treatment, under treatment, overtreatment and the continued use of ineffective treatments.
- Pain includes: acute, perioperative, subacute and chronic. These rules do not apply to palliative, in-patient hospital care, procedural medications and cancer related treatments.
- Children and adolescent patients should be treated based on weight of the patient and adjust the dosage accordingly.

Washington State Health Care Authority

Prescription limits

The policy limits the quantity of opioids that can be prescribed to opiate naïve patients for noncancer pain. The ~~limits for new opioid prescriptions will be:~~

- No more than 18 doses (approximately a 3-day supply) for patients age 20 or younger.
- No more than 42 doses (approximately a 7-day supply) for patients age 21 or older.

You can ~~override these limits~~ if you feel this is medically necessary, by typing "Exempt" in the text of the prescription.

At the point of transition from acute to chronic opioid treatment, defined as six weeks of therapy, the policy requires you attest that you are following best practices for opioid prescribing. These are listed on the HCA [Chronic Opioid Attestation form](#) and include actions such as checking the [Prescription Monitoring Program](#) ¹, informing the patient about the risks of opioid use, and using a pain contract. Documentation of these practices should be in the chart, but you are not required to submit supporting materials.

Is there a role for opioid therapy?

- Post surgical/procedural pain
- Acute trauma
- Sickle cell disease and crisis
- Acute nociceptive pain
 - Burns, dressing changes
 - Recurrent ulceration
- Cancer plan
- Avascular necrosis

Opioids

- Derived from poppy plant:
 - Natural alkaloids (e.g., morphine)
 - Synthetic derivative (e.g., heroin, fentanyl, hydromorphone, methadone, buprenorphine)
- Exert effects on opioid receptors in the brain, spinal cord, and peripheral nerve cells, decrease release of excitatory neurotransmitters.
- Opiate receptors:
 - μ 1: supraspinal analgesia, bradycardia, sedation, dependence
 - μ 2: respiratory depression, euphoria, dependence, gastrointestinal dysmotility
 - δ : spinal analgesia, respiratory depression
 - κ : spinal analgesia, not significant respiratory depression, sedation
- Reversal by antagonist naloxone

Opioids

- Children **vary greatly in dose requirements and response**
 - Recommended starting doses may need to be adjusted
 - Titrate dose and interval
 - Offer rescue doses for breakthrough or poorly controlled pain
- Most opioids have **similar effects and side effects**
 - Narrow therapeutic index
 - Pharmacokinetic differences, tissue distribution and receptor type specificity probably account for the variation in effects
- Tolerance and physiologic dependence are unusual** in short-term postoperative opiate-naïve patients

Opioids: Morphine

- Natural alkaloid
- Prototype opiate
- Predominantly μ receptor agonist
- Pharmacodynamics and pharmacokinetics:**
 - Onset: Oral: 30 minutes
 - Peak: Oral: 1 hour
 - Duration 3 - 5 hours
 - Half-life elimination:

Age	Half-life
Preterm	10 - 20 hours
Neonates	7.6 (4.5 - 13.3) hours
1 - 3 months	6.2 (5 - 10) hours
3-6 months	4.5 (3.8 - 7.3) hours
6 months to 2.5 years	2.5 (1.4 - 7.8) hours
Preschool	1 - 2 hours
6-19 years	1.3 hours

Opioids: Morphine

- Dosing recommendations:

Route	Age	Dose/weight
Oral	<6 months	0.08 - 0.1mg/kg/dose every 3 - 4 hours
	>6 months and < 50kg	0.2 - 0.5mg/kg/dose every 4 - 6 hours
	>50kg	15 - 20mg every 4 hours

- Hepatic metabolism
 - Metabolites morphine 6-glucuronide (active) and morphine 3-glucuronide (inactive)
 - Renally excreted
 - Dosage adjustment based on creatinine clearance
 - E.g. CrCl 10 to 50ml/min, administer at 75% of normal dose; CrCl <10ml/min administer at 50% of normal dose.
 - Associated with neuroexcitatory effects.

Opioids: Hydromorphone

- Semi-synthetic derivative of morphine
 - Differs at position 6 of the benzol ring with a keto-group instead of hydroxy group from morphine
 - **5 to 10 times more potent than morphine**
 - μ receptor agonist
- Pharmacokinetics and pharmacokinetics:
 - Onset: Oral: 30 minutes
 - Peak: Oral: 30 – 90 minutes
 - Half-life: 1 - 3 hours
- Dose recommendations:
 - Oral: 0.03 to 0.08mg/kg/dose every 4 - 6 hours, maximum 5mg
- **Metabolism:** Hepatic metabolism to hydromorphone-3-glucuronide

Morphine versus Hydromorphone

- National trend shows increasing use of hydromorphone
 - 261.5% increase in hydromorphone compared to 190.1% increase in morphine (2003-13)
 - Parallel increase in diversion, misuse and addiction disorders to prescription opioids
- Studies have shown that morphine and hydromorphone at equianalgesic doses are similar, with no difference in side effects
- Hydromorphone compared to morphine:
 - Shorter half life
 - Crosses blood brain barrier faster, quick onset and peak of analgesia
 - Unclear advantage of improved analgesia
 - Greater risk for sedation
 - May be better tolerated in patients with renal failure

Opioids: Oxycodone

- Semi-synthetic opioid
 - Potency is **1.5 - 2 times greater** than morphine
 - No clinically significant active metabolites
 - Most commonly prescribed opioid in children
- Mechanism of action:
 - Targets μ and κ receptors
- Pharmacodynamics and pharmacokinetics:
 - Onset 30 minutes, half-life 2 – 3 hours, duration 4 - 5 hours
- Metabolism:
 - By hepatic cytochrome P450 enzyme system
- Dosing recommendations:
 - 0.1mg/kg/dose every 4 hours as needed
 - **Caution <6 months for respiratory depression**
 - > 50kg, 5 – 10 mg every 3-4 hours as needed

Opioids: Side effects and Treatment

- Gastrointestinal: **Constipation** (9 - 48%) tolerance may not develop, nausea (7 - 28%) tolerance usually develops.
- Dermatologic: **Pruritis** (>10%) may be related to central and peripheral mechanisms.
- Genitourinary: **Urinary retention** (16%)
- Central nervous system (>10%): **Drowsiness** (9-48%) tolerance develops, dizziness (6 – 20%)
- Respiratory: Reduce respiratory rate, increased carbon dioxide retention and reduce ventilatory response to hypoxia and/or hypercarbia, **desaturations**.
- Cardiovascular: Bradycardia, hypotension

Opioids: Codeine

- National guidelines **recommended against codeine use in children**
 - American Academy of Pediatrics
 - American College of Chest Physicians
 - WHO removed codeine from its analgesic ladder
 - FDA issued a black box alert against use post-tonsillectomy and/or adenoidectomy
- “**Prodrug**” metabolized to morphine by cytochrome P450 CYP2D6
 - Up to 33% are **poor metabolizers**, leading to inadequate pain relief.
 - 2 – 40% are **ultra-rapid metabolizers**, convert 5 – 30 times greater than typical, leading to fatal toxicity.
- National patterns of codeine prescription
 - Prescription decreased from 3.7% to 2.9% between 2001 – 2010
 - But there was no decline in codeine prescriptions for cough or URI ER visits

Kaiser, 2014



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Opioids: Tramadol

- Synthetic 4-phenyl-piperidine analogue of codeine
- **Mechanism of action:**
 - Weak affinity to u-opiate receptors
 - Inhibits serotonin and norepinephrine reuptake in the spinal cord
- **Pharmacokinetics and pharmacodynamics:**
 - Rapidly absorbed, bioavailability 65 to 70% extensive first pass metabolism
 - Onset 1 hour, maximum effect 2 to 4 hours
- **Metabolism**
 - Via cytochrome P450 enzyme CYP2D6 to O-desmethytramadol, providing 40% of analgesic action.
 - Plasma time-concentration might be different in infant due to immature metabolite elimination via kidneys, therefore high adverse events rates might be possible

Boskurt 2005; Scott 2000; Hennes
1988; Lintz 1998; Allegaert 2011



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Tramadol: FDA

- Warning against use in children <18 years to treat pain after tonsillectomy or adenoidectomy.
- Recommend against use in adolescents between 12 to 18 years who are obese or have conditions e.g. obstructive sleep apnea or severe lung disease.
- Warning: Mothers who are breastfeeding and taking codeine/ tramadol.
- Concerns:
 - **Genetic** variances (cytochrome P450 enzyme (CYP2D6) deficiency influence analgesic efficacy vs. ultra-metabolizers)
 - Risk of respiratory depression
 - Decrease **seizure** threshold
 - **Serotonin syndrome**
 - Opioid like and atypical **withdrawal** following downward titration and/or cessation

Bosenberg 1998, Scott 2000; Tarkkila
1998; Vickers 1992; Oliaguet 2015



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Resources

- Washington State Department of Health:
<https://www.doh.wa.gov/ForPublicHealthandHealthcareProviders/HealthcareProfessionalsandFacilities/OpioidPrescribing>
www.hca.wa.gov/assets/billers-and-providers/opioid_policy_webinar.pdf
- Washington Medical Commission
<https://wmc.wa.gov/resources/pain-management-resources>
- Agency Medical Directors Group
<http://www.agencymeddirectors.wa.gov/CMEActivities.asp>
- Washington State Prescription Monitoring Program
<https://www.doh.wa.gov/ForPublicHealthandHealthcareProviders/HealthcareProfessionalsandFacilities/PrescriptionMonitoringProgramPMP><https://>



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Pain Management Resources

Professional Pain Management Resources

- AMDS Homepage
- AMDS Opioid Dosing CME
- Emergency Room Prescription
- FDA Report from Sudden Discontinuation of Opioids
- Suboxone Treatment

Patient Resources

Washington Physicians Health Program & HDAL WA

- Opioid Dosage Calculator
- Pain Management Interpretive Statement
- Seattle Pain Center Practitioner Alert
- SCOPE of Pain-free CME

Frequently Asked Questions (FAQ)

MD and PA Demographics

- UW Provider Toolkit
- UW Telepain
- UW Triplex Brand

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Referring to Pediatric Pain Clinic

- Risk factors:
 - Multiple presentations to emergency department due to pain symptoms.
 - History of multiple inpatient hospitalizations due to pain symptoms.
 - Multiple outpatient providers and specialist visits in order to obtain a diagnosis of symptoms of pain.
 - Disability due to pain symptoms (e.g. school absenteeism, reduce normative roles, impacting psychological functioning).
 - Failure of outpatient therapies.
 - Complex regional pain syndrome.



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Questions?



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