Pharmacologic Treatment of Pain in Special Populations

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Objectives

- Identify classes of medications utilized for pain
- Discuss benefits and side effects of meds for geriatric, pediatric, and obstetric patients
- Integrate the role of medication assisted treatment into special populations
Pediatric Pain

Common Pain Conditions in Children

Complex Regional Pain Syndrome

Headaches

Abdominal Pain

Cancer Pain

Complex Regional Pain Syndrome

Typically extremity pain—non-dermatomal

Allodynia, hyperalgesia, sudomotor dysfunction, neurovascular degeneration, loss of motor function, hair/nail growth changes, osteoporosis

Type I—No definable nerve injury

Type II—Evidence of nerve dysfunction
Budapest Criteria

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuing regional pain</td>
<td>Disproportionate to inciting event</td>
</tr>
<tr>
<td>Sensory</td>
<td>Hyperalgesia, Allodynia</td>
</tr>
<tr>
<td>Vasomotor</td>
<td>Temperature asymmetry, Skin color changes, Skin color asymmetry</td>
</tr>
<tr>
<td>Sudomotor/edema</td>
<td>Swelling due to edema, Sweating changes, Sweating asymmetry</td>
</tr>
<tr>
<td>Motor/trophic</td>
<td>Decreased range of motion, Motor dysfunction, Changes in hair, skin, nail, bone</td>
</tr>
</tbody>
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Non-pharmacologic Options

Physical therapy—TENS units, active/passive modalities, desensitization, warm/cold baths, massage

Behavioral therapy—biofeedback, visual guided imagery, structured counseling with/without family members

Multidisciplinary Pain Programs
Pharmacologic Options

Antidepressants
Anticonvulsants
Systemic vasodilators—significant orthostatic hypotension
Regional anesthesia and sympathetic blocks
Opioids are typically not helpful

Antidepressants

Tricyclics
- Amitriptyline anticholinergic effects
- Nortriptyline has fewer
- Both for neuropathic pain, cause QT prolongation

Serotonin/norepinephrine reuptake inhibitors—treat neuropathic pain and psychological comorbidities

Serotonin reuptake inhibitors—can treat pain-induced psychological issues
Anticonvulsants

Gabapentin and pregabalin

somnolence and weight gain—especially pregabalin

RCT of amitriptyline vs. gabapentin for pediatric CRPS I
decreased pain, increased sleep, equally safe


Low Dose Naltrexone

Competitive inhibitor of mu and kappa receptors at high doses

Low dose—1-5 mg qd

Inhibits microglial activation

Decreases downstream activity leading to inflammation

Transient opioid receptor blockade leading to upregulation of endogenous opioids

Used for autoimmune diseases—MS, infl bowel dz

Trofimovitch-D, et al. Pharmacology Update: Low-Dose Naltrexone as possible nonopioid modality for some chronic, nonmalignant pain syndromes
High-Dose Ketamine Infusion

Young female adult, <21 years

Refractory CRPS, 7/10

Admitted to PICU, lumbar epidural with lidocaine/ropivicaine
Ketamine titrated from 10-110 mg/h over 11 days

PT starting day 1, epidural weaned at day 9

Hallucinations controlled with midazolam

Pasek TA, et al. Case study of high-dose ketamine for treatment of complex regional pain syndrome in the pediatric intensive care unit

Goals of Therapy

<table>
<thead>
<tr>
<th>Before Hospitalization</th>
<th>At Discharge from Hospital to Rehabilitation Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total restriction to bed for 3 y</td>
<td>Transferring to and from cardiac chair independently; assistance required to protect intravenous tubing connections only</td>
</tr>
<tr>
<td>Hands in a fist position from dystonia</td>
<td>Hands almost fully open and extended</td>
</tr>
<tr>
<td>Unable to give/receive hugs owing to severe pain and syncope</td>
<td>Able to give/receive hugs without severe pain and syncope</td>
</tr>
<tr>
<td>Needed assistance with position changes in bed</td>
<td>Independently changes position in bed using the side rails for support</td>
</tr>
<tr>
<td>Limited endurance for activity</td>
<td>Improved endurance for activity; able to sit in cardiac chair for a minimum of 3 h</td>
</tr>
<tr>
<td>Arms propped with pillows to eat, brush teeth owing to limited shoulder function</td>
<td>Improved shoulder function; able to lift arms to eat, brush teeth; propping with pillows unnecessary</td>
</tr>
</tbody>
</table>
Headaches

Migraines—3.9% under age 12
Non-migraine—6.8%
Psychiatric disorders
CV disease and ischemic stroke

https://www.neworleansmomsblog.com/2017/03/07/headache-clinic-childrens-hospital/

Tension-type Therapies

Non-pharmacologic—physical therapy, biofeedback, complementary and alternative medicine
Pharmacologic—NSAIDS, regional blocks
Migraine Therapies

Non-pharmacologic—physical therapy, biofeedback, complementary and alternative medicine

Pharmacologic—Abortives—nsaids, triptans, injections
  Preventives—antidepressants, antiseizures, calcium channel/beta blockers, botox injections

Rebound Headaches

Overuse of NSAIDS, triptans cause transition from episodic to chronic daily headache

Treatment
1. Educate patient on medication overuse headache
2. Some patients benefit from medication withdrawal
3. Preventive drug therapy and non-pharmacologic therapy
Abdominal Pain

Functional abdominal pain—a abdominal pain not relatable to a specific diagnosis

Cognitive behavioral therapy, family centered therapy

Regional blocks for post-surgical abdominal pain

https://www.navicenthealth.org/service-center/page/pediatric-gastroenterology/abdominal-pain

Pediatric Cancer Pain

Strategies to decrease tolerance:

Avoid synthetic opioids—morphine or hydromorphone, avoid fentanyl

Rotate opioids

Use adjuvant drugs—clonidine, ketamine infusions, magnesium, regional anesthesia
Obstetrics

Teratogenesis of drugs determined through surveys

Reporting bias

Lack of control—environmental exposure, other drugs (ETOH, tobacco), disease

Case reports of association more likely to be published

http://cameronshorter.blogspot.com/2016/05/government-ask-nine-open-source.html

Changes in Drug Metabolism

Increased renal elimination

Hepatic function

Increase in total body water

Decreased protein binding
Drug Transfer Across the Placenta

Maternal
- CO, placental binding, placental metabolism

Maternal plasma levels
- Site of administration
- Total dose
- Dosing interval
- Co-administered drugs

Fetal
- CO and distribution of this output to fetal organs, metabolism, protein binding

Teratogenicity

Structural malformations

Intrauterine fetal death

Altered fetal growth

Neurobehavioral teratogenicity

Acute neonatal intoxication

Neonatal abstinence syndrome
Organogenesis

31-71 days after first day of LMP

Before 31 days—all or none

CNS development continues after 71 days

Old FDA Classification

<table>
<thead>
<tr>
<th>Category</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>None</td>
</tr>
<tr>
<td>B</td>
<td>Acetaminophen; butorphanol, nalbuphine; caffeine; oxycodone IR; ibuprofen, naproxen, indomethacin; prednisone, prednisolone</td>
</tr>
<tr>
<td>C</td>
<td>Amisulpride; aspirin, ketorolac; betamethasone; cortisone; codeine; fentanyl; hydrocodone; hydromorphone, meperidine; levomepromazine, 5-methyl-6-methoxy-3-piperidinomethyl-4-aminohydroquinoline; oxycodone E, oxymorphone, tramadol; gallopentin, pregabalin; lidocaine; propranolol, sumatriptan, sertraline, fluvitoxin; bupropion</td>
</tr>
<tr>
<td>D</td>
<td>Imipramine; carbamazepine; diazepam; paroxetine; phenobarbital; phenytoin, valproic acid</td>
</tr>
<tr>
<td>X</td>
<td>Ergotamine</td>
</tr>
</tbody>
</table>

*Opioid agonists and agonist-antagonists are considered risk category D when used at high doses over term.*

New Classification

<table>
<thead>
<tr>
<th>Category</th>
<th>Risk Summary</th>
<th>Clinical Considerations</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy</td>
<td>Risk of adverse developmental outcomes</td>
<td>• Drug-associated maternal and/or embryo/fetal risk&lt;br&gt;• Dose adjustments during pregnancy and post-partum&lt;br&gt;• Maternal adverse reactions&lt;br&gt;• Fetal/neonatal adverse reaction&lt;br&gt;• Labor and delivery</td>
<td>Human or animal data providing the scientific basis for the risk summary and clinical considerations</td>
</tr>
<tr>
<td>Lactation</td>
<td>Summary of information on drug and/or active metabolite(s):&lt;br&gt;• Presence in human milk&lt;br&gt;• Effects on the breast-fed infant&lt;br&gt;• Effects on milk production</td>
<td>Information for prescribing and risk/benefit analysis to limited exposure and monitor child for adverse reactions</td>
<td>Human or animal data providing the scientific basis for the risk summary and clinical considerations</td>
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Known Drug Effects

ASA—gastroschisis, decreased amniotic fluid, narrowing of ductus arteriosis, fetal intracranial hemorrhage

Opioids—neonatal abstinence, not teratogenic

Local anesthetics—lidocaine/bupivacaine have no known negative effects, mepipvacine increases fetal anomalies by 50%

Steroids—orofacial clefts?
Antidepressants

TCA's not teratogenic

SSRI in 1st trimester—no assoc., 3rd increased neonatal withdrawal

Paroxetine—increased congenital heart abnormalities

Duloxetine—increased spontaneous abortion rate

Venlafaxine/mirtazapine—no abnormalities, but these drugs are newer

Bupropion—increased cardiac malformations

Anticonvulsants

1. Fetal growth restrictions

2. Congenital malformations

3. Higher risk of developmental delay and cognitive impairment

Carbamazepine, lamotrigine, oxcarbazepine, gabapentin, and pregabalins

Low malformation rates

Topiramate—increased fetal growth restrictions, microcephaly

Valproic acid—increased hypospadias and septal heart defects

Valproic acid and phenytoin—highest risk

Lamotrigine and carbamazepine—lowest risk
Treatment of Pain in Pregnancy

Aspirin associated with gastroschisis (>150 mg qd)

Ibuprofen/naproxen—not appear teratogenic (ok until 3rd trimester)

Acetaminophen—relatively safe, associated with ADHD

Opioid Use

Opioids—neonatal abstinence syndrome (NAS)
  CNS hyperirritability
  autonomic NS dysfunction
  gastrointestinal disturbances

No teratogenesis with opioids or agonist/antagonist
Opioid Use Disorder

Medication assisted treatment (MAT) outweighs the risk of unmedicated mother

- More compliant prenatal care
- Improved nutrition and weight gain
- Fewer children in foster care
- Improved enrollment in treatment

Buprenorphine without naloxone
unknown effects
withdrawal in infant
hormonal changes

Buprenorphine has better infant outcomes than methadone
- milder NAS
- 11% of morphine use
- shorter taper

https://www.contemporaryobgyn.net/modern-medicine-feature-articles/when-opiate-abuse-complicates-pregnancy/page/0/1

Drugs During Lactation

Acetaminophen—safest

ASA—controversial, intermittent use probably ok

NSAIDS—considered compatible

Opioid agonist and agonist/antagonists cross freely
- Achieve >10% TD—oxycodone, pentazocine, meperidine, codeine

Other drugs—buproprion, citalopram, fluoxetine, venlafaxine
- lamotrigine, NSAIDS, opioids, steroids, sumatriptan

Safer options—sertraline, duloxetine, paroxetine, although carbamazepine, phenytoin, valproic acid may be used
Common in Pregnancy

Back/pelvic girdle pain
Carpal tunnel—due to hormonal changes
Migraine is rare—other causes should be sought

Physiologic Changes of Aging

Increase in painful conditions
Decrease in number and speed of neurons
Decrease in muscle mass
Decrease in hearing/vision
Changes in drug metabolism
Red Flags

New onset weakness/sensory deficit
Pain after a trauma
Pain that awakens patient from sleep
Fever
Jaw claudication
New headaches
Bone pain in h/o malignancy
Weight loss
Bowel/bladder dysfunction

Sudden pain in an extremity with pulselessness, pallor

http://docinthed.com/2012/03/

Changes in Drug Metabolism

Pharmacokinetics—describes absorption, distribution, metabolism and elimination of a drug

Pharmacodynamics—response of the body to the drug concentration, the degree and length of response and adverse effects
Pharmacokinetics

Absorption—increased gastric pH, decreased capacity and GI blood flow

Distribution—decreased albumin, protein affinity, total body water
increased expression of P-glycoprotein in liver

Metabolism—decreased liver volume and blood flow, decreased first pass
effect, decreased metabolism

Elimination—decline in renal function with age, decreased glomerular
filtration rate and renal plasma flow

Pharmacodynamics

Body Composition—increased body fat, decreased lean and total body muscle
mass

Cardiovascular function—decreased resting heart rate, stroke volume, cardiac
output

CNS—decreased blood supply to the brain and baroreceptor activity

Renin/Angiotensin/Aldosterone—decreased renin and aldosterone
Aging Pharmacokinetics

Hepatic
Meperidine and morphine—high extraction-ratio analgesics
Long half life NSAIDS—celecoxib, diflunisal, naproxen, oxaprozin, piroxicam, salsalate, sulindac
Opioids—levorphanol and methadone

Renal
Codeine, duloxetine, gabapentin, meperidine, pregabalin, propoxyphene, salicylate, tramadol
Opioids—morphine, oxycodone, hydromorphone, fentanyl and methadone

Pharmacodynamic Changes

Opioid receptor density

Opioid affinity
Topical Medications

Topical lidocaine
Capsaicin cream
NSAIDS—diclofenac
Compounded cream

Oral Analgesics

NSAIDS/acetaminophen—initiate at low doses metabolized by glucuronidation
Consider salsalate at 500-750 mg per day
Ibuprofen/naproxen—diuretics/antihypertensives
Anticonvulsants

Gabapentin—100 mg qhs

Pregabalin—25-50 mg qhs

Carbamazepine—50 mg qhs (target 200-600 mg qd)

Antidepressants

TCA's nortriptyline, desipramine—10 mg qhs
  Unfavorable SE profile of CV, seizures, increased glaucoma/BPH, dementia, falls

SNRI's
  venlafaxine—37.5 mg qd, mania in BP 1, htn, glaucoma
duloxetine—30mg qd, same SE plus seizures
Muscle Relaxants

Baclofen—5 mg qhs
  ataxia, renal dz, dementia, seizures
Cyclobenzaprine—very similar to amitriptyline
Tizanidine—hepatotoxicity, decreased HR/BP,
Magnesium—abdominal cramps, diarrhea, respiratory depression

Beers Criteria

Syncope—tertiary TCA’s
Epilepsy—tramadol
Delirium—corticosteroids, meperidine
Falls/fractures—anticonvulsants, TCA’s, opioids
Ulcers—ASA>325 mg qd, non-COX-2 NSAIDS
CKD/Heart failure—NSAIDS
Initiating Medications

Consider acetaminophen first

NSAIDs

Opioids

Gabapentin, pregabalin

SNRIs

Carbamazepine, oxcarbazepine

Corticosteroids (short term)

Injections—steroid for joints or LA +/- steroid for trigger point injections

NSAIDS

Cox Selective—More cox selective= meloxicam, nimesulid

Coxibs—1st celecoxib

etorcoxbib

Non-Selective—by class

Acetates—diclofenac, indomethacin, sulindac

Fenamates—mefenamic acid

Oxicams—piroxicam

Propionates—ibuprofen, ketoprofen, naproxen

Pyrazolones—phenylbutazone

Salicylates—salsalate, difunisal

NSAIDS

Cardiotoxic, nephrotoxic, gastrointestinal toxic

Lesser known SE:
- Decreases depression—not in geriatric patients
- Increased fall risk
- Improves bladder function and decreases nocturia
- Increased hallucinations
- Decreases incidence of cancer—endometrial, prostate, esophageal, H/N
- Increases well-being in end stage cancer
- Increased stroke with diclofenac and aciclofenac—no assoc with naproxen/ibuprofen

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5772852/

Interactions

GI Bleed—ASA, coumadin/anticoags, SSRI, steroids

Hypertension—attenuates ACE inhibitors, calcium antagonists, beta blockers, diuretics

Increases drug concentration—digitalis, methotrexate
Summary

Non-pharmacologic means to control pain should be utilized first

NSAIDs, antidepressants, and anticonvulsants can be used to manage pain in many populations

Opioids can be used for acute pain

With any medication, use the lowest effective dose

References
