## *Concepts for Analgesia in Pediatric Patients*

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## *Pain Myths*

- Children do not experience pain because of CNS immaturity
- Because they are up playing (sleeping, not complaining), they must not be experiencing discomfort
- Potent medications are too strong for children, may cause addiction, or may not be available when children really need them

## *General Overview*

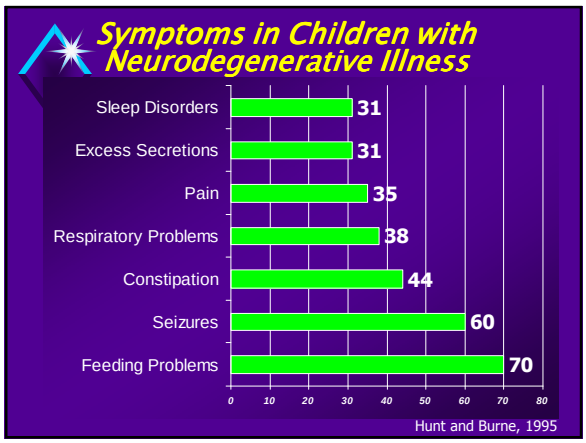
- Huge outpouring of research
- Information in pediatric pain now accessible in most pediatric textbooks
- Myths effectively debunked
- Pain can be experienced by the end of 2nd trimester; Infants may be hyperalgesic
- Addiction is essentially a non-issue in children and adults

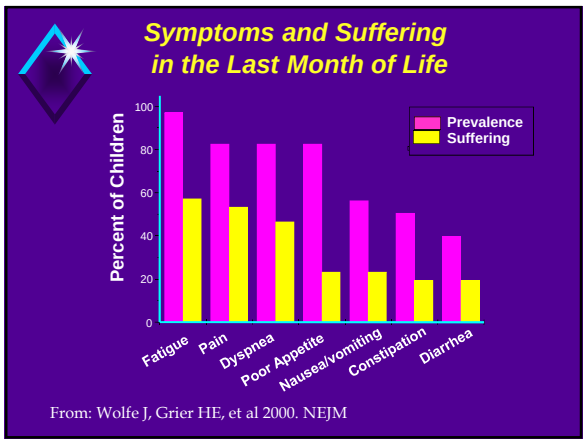
## *Pain Management in Children*

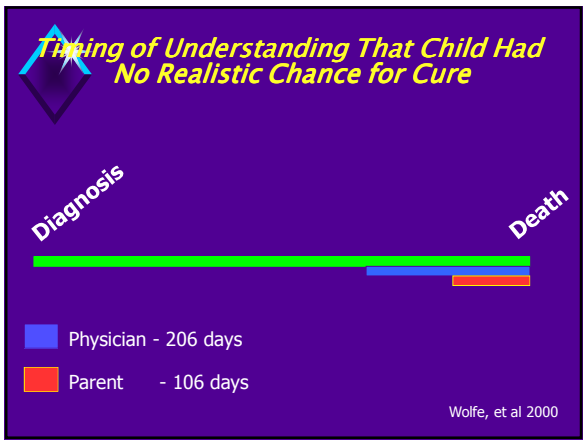
- Limited controlled trials
- Physicians' preferences
- Extrapolated from experience with adults
- Limited empirical data except:
  Cancer, Sickle cell, Rheumatoid Arthritis.

- 1990, Selbst and Clark reported in a retrospective study that 60% of adults but only 28% of children presenting to an emergency department with long bone fractures received adequate analgesia.

- Christopher and Kriwinsky documented a rate of analgesic use for long bone fractures in emergency rooms of 53% in children and 73% in adults.


Symptoms in Children with Neurodegenerative Illness
Sleep Disorders
31
Excess Secretions
31
Pain
35
Respiratory Problems
38
Constipation
44
Seizures
60
Feeding Problems
70
0
10
20
30
40
50
60
70
80
Hunt and Burne, 1995


Symptoms and Suffering in the Last Month of Life
Percent of Children
100
80
60
40
20
0
Prevalence
Suffering
Fatigue
Pain
Dyspnea
Poor Appetite
Nausea/vomiting
Constipation
Diarrhea
From: Wolfe J, Grier HE, et al 2000. NEJM


Timing of Understanding That Child Had No Realistic Chance for Cure
Diagnosis
Death
Physician - 206 days
Parent - 106 days
Wolfe, et al 2000

## Life in the NICU

- 2-10 painful procedures each day
- Estimated up to 488 painful procedures overall
- The more premature the infant, the more painful procedures.
- Analgesia used for less than 10% of painful procedures.

## Memory?

Preterm infants (28-32 GA)

- Observed for 5 heelsticks over 2 weeks
- HR and facial actions
- By 5th test, HR response to picking up foot and holding

Learning to predict painful stimulation?

Goubet et al.: J Dev Behav Pediatr 2001

## Newborns of diabetic mothers

- repeated heel lances in first 24-36 hours
- assessed during a later venipuncture
- increased grimace, cry, VAS compared to normal babies

Taddio et al. JAMA 2002;288(7):857-61

## Neonatal surgery

Full-term newborns requiring major surgery

- Healthy controls
- Medical NICU admissions

National exams. (English, Maths, Science)

- Decreased performance at 11-13 years
- Independent predictor: vent > 3 days; behaviour problems at 3 years

Ludman et al. J Pediatr Surg. 2001;36(6):858-62.

## Peripheral

Behavioural response

- Pain threshold
  - lower at very low gestational age, decreased further with repetitive stimuli (Fitzgerald et al.: Dev Med Child Neurol 1988)
- Recent pain exposure
  - decreased pain threshold (Andrews & Fitzgerald: Pain 1994; Porter et al.: Pediatrics 1998)
  - increased response to procedures (Grunau et al..: Clin J Pain 2000)

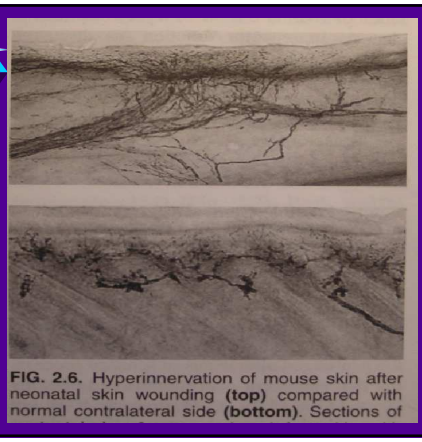


**FIG. 2.6.** Hyperinnervation of mouse skin after neonatal skin wounding **(top)** compared with normal contralateral side **(bottom)**. Sections of

## Systemic

Immune response

- Rats received daily paw pricks (4 paws) P0-P7
- Tested at maturity
- Decreased habituation to open field → i.e. more anxious
- Increased lung tumour retention (decreased NK cell response) — males > females
- Males had increased exacerbation with swim stress

Page et al. Brain Behav Immun 2005;19:78-87.

## What do we need to do?

Assess the pain.
Believe it!
Make pain visible.
Make staff accountable.
Treat the pain.
Measure the outcomes.

## Preventing Procedure Pain

Think of it!

Avoid procedures (reduce number)

Gibbons et al. Expert Opin Pharmacother 2003;4(4):475-83

Sweet taste (sucrose)

Stevens et al. Cochrane Database Syst Rev. 2001;(4):CD001069

Skin-to-skin contact - Kangaroo care

Johnston et al. Arch Pediatr Adolesc Med. 2003;157:1084-88

Non-nutritive sucking

Johnston et al. Biol Neonate. 1999 Aug;76(2):120-4

Local anesthetics

- EMLA/Ametop
- Local infiltration (buffered lidocaine)

## Pain treatment

Oral/rectal

- Acetaminophen/paracetamol
- NSAIDs (little data in neonates)

Intravenous medications

- Opioids (benzodiazepines are not analgesic)
- Tramadol?
- Ketamine?
  - for procedures is a general anesthetic → not a trivial intervention

## Reasons to prevent pain

Humanitarian

Physiological

- Long-term neurophysiological changes

Taddio et al. Lancet 1995, 1997; NEJM 1997

Immunological?

Page et al. Brain Behav Immun 1994;8:241-50/ Pain 2001;90:191-9
Page et al. Brain Behav Immun 2005;19:78-87

Accreditation/policy

Pragmatic

- What happens on the next visit?

## Why isn't pain prevented?

We don't know there's pain (measurement).

We know there is going to be pain, but we don't prevent it…

- "There's no time."
- We think there's no time…

We know there's pain but we don't treat it…

- "It's too dangerous."
- We think it's too dangerous…

## *Reasons for Undertreatment*

- Limited interest in symptoms; focus on cure
- Multi-system symptom; no discipline had "ownership"
- Difficulty of assessment

## *Reasons for Undertreatment*

- Minimal research - lack of financial, ethical problems of research on children
- Societal biases about pain and its treatment
- Persistence of myths

## ***Why Children's pain in undertreated:***

- Fear of addiction
- Fear of tolerance
- Fear of hastening death
- Fear of giving up too soon
- Fear of excessive opioid dosing
- Lack of experience

## Pain in Children

- Pain is understated
- Children do not perceive pain as do adults
- Children do not remember painful occurrences
- Fear that treating pain would mask problems
- Children do not feel pain
- Nociceptive neural pathways are in place by 23-24 weeks of gestation

## Pain in Children – Cont.

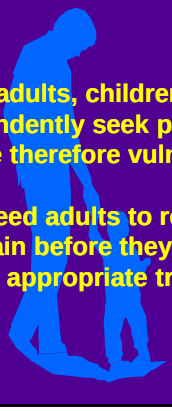
- Term and preterm newborns have fully developed pain transmission pathways
- Term and preterm newborns lack fully developed inhibitory systems
- Fear of serious opioids side effects
- False assumption, children are at increased risk for addiction to narcotics

## Current Status of Pediatric Pain

- Predictable pain problems such as postoperative pain have improved significantly
- Infants and children with chronic disease whose pain is harder to address still are inadequately treated
- Sedation more common but not well standardized
- Though concerned about minor procedure pain, clinicians not attempting interventions

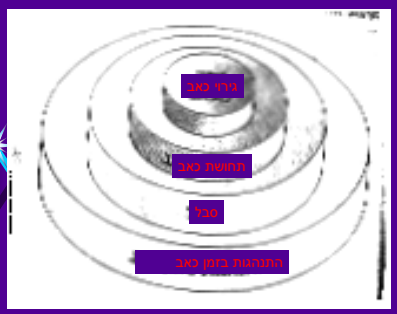
**Unlike adults, children cannot independently seek pain relief and are therefore vulnerable.**

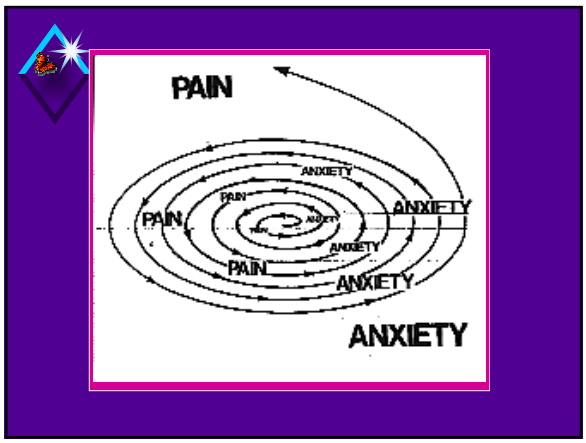
**They need adults to recognize their pain before they can receive appropriate treatment.**

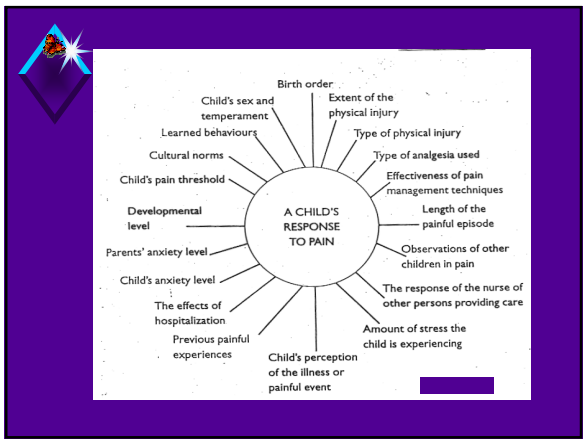


## *Factors in Children's Perception of Pain*

- Children expectations: previous experience, family, culture
- Parental response
- Context






## Physiological measures

Studied in infants

Short, sharp pain only (attenuate)

Clinical practicality?

- Heart rate
- Vagal tone/heart rate variability
- Skin blood flow/palmar sweating
- Blood pressure
- Oxygen saturation/$PO_2$
- Cutaneous flexor response, reflexes

## Biochemical measures

Measures of stress

- Cortisol (Boyer et al. Biol Neonate 2002)
- Glucagon
- Growth hormone, etc.

Slow response, non-specific, not well understood

## Problem Populations

Infants and newborns

Premature newborns

Developmental delay

Cerebral palsy

Intubated patients

Teen-agers!

## Pain assessment

- **Children with brief, strong pain exhibit more obvious physical distress**
- **Children with persistent pain usually exhibit more subtle signs**
- **Absence of behavioural signs does not necessarily mean absence of pain**
- **Parents know their children and can recognize very subtle changes in manner or behaviour**

## Ability to describe pain

- **< 6 years - children can describe only the general amount of pain they feel**
- **> 6 years - children can describe the severity, quality, location, duration, and changes over time**

## *Children Coping with Pain*

- Information seekers
- Information providers
- Focusing attention
- Distracting attention

## *Primary Pain Behaviors*

- Crying
- Distressed Facial Expression
- Motor Disturbances
- Lack of Interest in Surroundings
- Decreased Ability to Concentrate
- Sleeping Difficulties

## *Non Pharmacological Interventions*

- Positive reinforcement
- Providing procedural information, sensory information
- Allow child input
- Distraction: singing, counting, story…
- Hypnotherapy: master control
- Massage and touch
- Relaxation: breathing

## *טיפול התנהגותי בכאב בילדים*

- נדנוד, שיר, מציצה
- נשימה-"בועות קסם"
- הסחת דעת: ספר, קלטת, סיפור
- טכניקות מתקדמות: "כפפת קסם"

היפנוזה,דמיון מודרך

- מעורבות הורים

## *מעורבות הורים*

<u>עוזר</u>

- נשימות
- הומור
- הסבר-בזמן
- דיבור
- הסחת דעת

<u>לא עוזר</u>

- אמפטיה-עודפת
- התנצלות
- התמקחות
- עודף שליטה
- הסבר בזמן פרוצדורה
- הקרנת לחץ

## Non-drug pain relief therapies

- supportive
- cognitive
- behavioural
- physical

## Cognitive methods

### influence a child's thoughts and images

- Active distraction - toys, games, stories, music
- Imagery - storytelling to engage the imagination
- True hypnosis
- Closing pain "switches" or "gates"

## Behavioural methods

- Deep breathing - focuses the attention, reduces muscular tension, relaxes the diaphragm, and oxygenates the body
- Progressive relaxation - often combined with suggestion and deep breathing - can reduce anticipatory anxiety, nausea and vomiting

## Physical methods

- **Touch - stroking, holding and rocking, caressing, massaging, swaddling, vibration, tapping, cuddling, palpation**
- **Cold**
- **Heat**
- **TENS**

## *Pharmacologic Pain Management*

- General Principles:
  - Whenever possible, the oral route is chosen.
  - Subcutaneous infusions, transdermal patches, rectal, or sublingual medications are available when oral or intravenous routes are not available.
  - Permanent intravenous access should be obtained if other routes of drug administration are impossible.
    - Central venous catheters
      - Shiley, Broviac or Hickman catheters
      - Infusaport catheters
      - Percutaneous intravenous central catheter (PICC)

## Opioid analgesics for moderate to severe pain

- **Morphine**
- **Hydromorphone**
- **Methadone**
- **Fentanyl**
- **Oxycodone**

## Guidelines for analgesic drug therapy

- **"By the ladder"**
- **"By the clock"**
- **"By the appropriate route"**
- **"By the patient/family"**

**Morphine is the preferred drug since there is wide experience in children**

## *Morphine Metabolism*

- There is extensive biotransformation in the liver to number of compounds, of which the two most important are morphine 3-glucuronide (M3G) and morphine 6-glucuronide (M6G)

## Morphine Metabolism

The capacity to form both glucuronides is present from early stage in fetal development and there is some evidence that it increases over the first 12 month of life.

## Morphine Metabolism

- Distribution of morphine and M6G seems to be similar in children and adults.
- Better renal clearance and faster glucuronidation in children.
- Clearance of morphine and M6G in children appears to exceed that in adults.
- Clearance of the glucuronides is almost entirely renal and much of the parent compound is also excreted in the urine.

## Morphine Pharmacodynamics

- Volume of distribution per kilogram in children is much the same as adults
- Clearance and half-life are rather shorter.
- The ratio of glucuronides to morphine may be higher in children than in adults.
- A child under 12 months of age have lower clearance particularly in children under 2 weeks old.

## Morphine Pharmacodynamics

- One study that concluded that clearance appeared to reach adults levels by 2 years of age did not address the likelihood that it then improves further before declining to adults levels at puberty.

## Misconception?

- Both morphine and M6G can penetrate into the cerebrospinal fluid of children.
- There is no evidence to suggest that outside infancy this happens more easily in children than in adults.
- Children are not more sensitive to centrally mediated effects of opioids, such as respiratory depression.

## Routine oral dosing

*extended-release preparations*

- Improve compliance, adherence
- Dose q 8, 12, or 24 h (product specific)
  - don't crush or chew tablets
  - may flush time-release granules down feeding tubes
- Adjust dose q 2–4 days (once steady state reached)

## Practical Tips

- In children use a smaller opioid dosage interval particularly in the use of slow-release morphine and fentanyl patches.
- Children require slow-release oral morphine sulfate to be given at 8-hour intervals rather than the recommended 12 hour interval.

## Practical Tips

- Such a difference has not been shown in immediate release preparations of morphine,

## Equianalgesic Opioid Doses

| Name | Equipotent IV Dose (mg/kg) | Equipotent PO Dose (mg/kg) | Parenteral/Oral Ratio |
|---|---|---|---|
| Alfentanil | 0.05 | - | - |
| Butorphanol | 0.01-0.02 | 0.05 | 25% |
| Codeine | 1.2 | 2.0 | 66% |
| Fentanyl | 0.001 | 0.01-0.015 transmucosal | 25-50% transmucosal dose |
| Hydromorphone | 0.015 | 0.02-0.1 | 20-70% |

## *Equianalgesic Opioid Doses-Cont.*

| Name | Equipotent IV Dose (mg/kg) | Equipotent PO Dose (mg/kg) | Parenteral/ Oral Ratio |
|---|---|---|---|
| Meperidine | 1.0 | 1.5-2.0 | 50-60% |
| Methadone | 0.1 | 0.1 | 100% |
| Morphine | 0.1 | 0.3-0.5 | 20-33% |
| Nalbuphine | 0.1 | 0.5 | 20% |
| Oxycodone | - | 0.1 | - |
| Sufentanil | 0.0001 | - | - |

## *Oxycodone*

- Semisynthetic μ-receptor
- Comparable to MOR
- Aged 2-10 higher clearance and shorter mean elimination half life
- Clearance lower at 1-3 months

## *Methadone*

- Long half life (mean 19 h in age >1)
- Analgesic effect comparable to MOR after single dose
- More potent after repeated dose
- Incomplete cross tolerance with opioids.

## . . . Opioid pharmacology

- Steady state after 4–5 half-lives
  - steady state after 1 day (24 hours)
- Duration of effect of "immediate-release" formulations (except methadone)
  - 3–5 hours po / pr
  - shorter with parenteral bolus

## Opioid Analgesic Doses

| Drug | Dose (mg)* i.m. | Dose (mg)* p.o | Potency Ratio (i.m:p.o) | Elimination Half-time (h) | Duration of Action (h) |
|---|---|---|---|---|---|
| Morphine | 10 | 30 | 1:3 | 2 - 3.5 | 3 - 4 |
| | | 60† | 1:6† | | |
| Codeine | 130 | 200 | 1:1.5 | 2 - 3 | 2 - 4 |
| Oxycodone | 15 | 30 | 1:2 | 3 - 4 | 2 - 4 |
| Hydromorphone | 1.5 | 7.5 | 1:5 | 2 - 3 | 2 - 4 |
| Methadone | 10‡ | 20‡ | 1:2 | 15 - 120 | 4 - 8 |
| Meperidine | 75 | 300 | 1:4 | 2 - 3 | 2 - 4 |
| Oxymorphone | 1 | 10 (rectal) | 1:10 | 2 - 3 | 3 - 4 |
| Levorphanol | 2 | 4 | 1:2 | 12 - 16 | 4 - 8 |
| Tramadol | 100 | 120 | 1:1.2 | 3 - 4 | 4 - 6 |
| Fentanyl | 0.1§ | | | 1 - 2† | 1 - 3† |

*Source:* Cherny (1996)

* by convention, relative potency is expressed in comparison to 10mg of i.m. morphine. These doses are approximate and are intended to serve as guidelines only.

† Derived from single-dose study.

‡ Derived from single-dose study. At steady state, potency relative to morphine is probably 1-3:10.

§ Empeirically, transdermal fentanyl 100 µg/h approximately equals i.m. morphine 2-4 mg/h and is prescribed every 48-72 h.

## *Sedation - Confusion: Practical Tips*

- Check metabolic disturbance
- Check and R/O infection
- Cancer related
- Consider opioid rotation
- Consider methylphenidate

## *Opioid induced vomiting/nausea:*

- Ondanestrom 0.1-0.5 mg/kg IV Q 6h.
  Max dose: 4 mg.
- Diphenhydramine 1 mg/kg IV.
  Max dose: 50 mg.
- Metoclopramide 0.1-0.2 mg/kg.
  Max dose: 10mg.

## *NSAIDs*

- These are indicated if there is a significant inflammatory component as well as pain.
- No one drug will suit all patients.
- Evidence that one NSAIDs has superior efficacy to another.
- Only one oral NSAID should be prescribed at a time.
- Regular dosing is required to obtain full anti-inflammatory effect.
- A sustained release preparation taken at the appropriate time can:
  - Relieve night-time pain.
  - Relieve morning stiffness.
  - Aid compliance.

## ***Non-opioid Analgesics***

| | |
|---|---|
| - Acetaminophen | 10-20 mg/kg q 4 |
| - ASA | 10-15 mg/kg q 4 |
| - Choline mg trisalicylate | 25 mg/kg BID |
| - ibuprofen | 10 mg/kg q 6-8 |
| - Diclofenac | 1-1.5 mg/kg 1 12 |
| - Naproxen | 5-7 mg/kg q 8-12 |
| - Ketorolac | 0.5 mg/kg q 6 |
| - Celecoxib | 100 mg BID |
| - Rofecoxib | 25 mg BID |

## NSAIDs Used in Children

| Drug | Age | Oral Dose (mg · kg⁻¹ · d⁻¹) | Frequency per Day | Elimination Half-life (h) | Drug Interaction and Comments |
|---|---|---|---|---|---|
| **Aceta-minophen** | Neonates | 30 | 6 | 3.5 | Phenobarbital, rifampin, phenytoin or ethanol may enhance hepatic toxicity. May accumulate in children with fever and fasting. |
| | Infants and Children | 60 | 6 | 2 | |
| | Infants and Children | 35-45 (rectal) | 1 | | |
| **Ibuprofen** | 3 mo - 12 y | 20-40 | 4 | 2.3 ± 0.5 | Interaction with digoxin, methotrexate probenecid, salicylate. A higher (d-1 kg-1 dose (40 mg is used for rheumatic disorders in children |
| **Naproxen** | >5 y | 10-15 | 2 | 11-15 | Aspirin, aluminum, hydroxide, probenecid. largely renal excretion. |
| **Tolmetin** | >= 2 y | 15-30 | 3 | 4.5-6 | Aspirin |
| **Choline magnesium trisalicylate** | >1 y | 30-60 | 3-4 | ~30 | Other NSAIDs. Monitor salicylate blood level. |
| **Diclofenac** | > 2 y | 1-3 | 3 | 1.2-1.8 | Aspirin, salicylates, lithium, digoxin, and other NSAIDs. |

*Source:* Haapasaari et al ( 1983 ); Watson and Mortensen ( 1989 ); Skeith and Jamali ( 1991 ); Brown et al ( 1992 ); Autret et al (1993); Montgomery et al (1995).

## *Antidepressant as analgetics - practical tips*

- 30% patients > 50% pain relief, 30% minor side effects, 4% major adverse effect.
- No pediatric placebo controlled trials.
- Often used in children: neuropathic pains, cancer or chemotherapy related, phantom pain.
- SSRI less effective than TCA.
- Effective analgesic dose unknown.

## *Antidepressants dosage and effect*

| Drug | Dose | Sedation | Anticholinergic |
|---|---|---|---|
| Amitriptyline | 0.25-2 | High | High |
| Nortriptyline | 0.25-2 | Moderate | Moderate |
| Imipramine | 0.25-2 | Moderate | High |
| Trazodone | 0.25-2 | High | Very Low |
| Desipramine | 0.25-2 | Low | Low |

## Antidepressants - Practical Tips:

- Start low and gradually increase
- Analgesia achieved within few days - week
- One single dose at night
- Pre pubertal and adolescents may need twice daily
- Educate parents and patients
- Clinical response is the best guide.
- Withdrawal reaction??

## Antidepressants - Side Effects Management

- Day time sedation - common
- Lack of energy - common
- Dry mouth, dizziness, tachycardia, hypotension
- Constipation, urinary hesitancy - rare in children.
- Cardiac conduction effect.
- Lower seizure threshold.

## Anticonvulsants

- Are suggested for children with conditions similar to those conditions indicated in adults. We lack controlled clinical trials in children.

## Sedative/hypnotic

- Do not produce analgesia but may potentiate analgesia in painful procedures, allow for the child's cooperation for painless procedures, encourage restorative sleep, or reduce anxiety which amplifies pain

## Sedative/hypnotics

- **Midazolam**
  - **Drug of choice for painful procedures with/without opioid**
  - **Can be antagonized by flumazenil**
  - **Oral, intranasal, intravenous**
- **Chloral hydrate**
  - **Drug of choice for painless procedures (MRI, CT)**
  - **High dose reduces failure rate**

## Sedative/Hypnotic Dosing

- **Midazolam:**
  - 0.05 mg/kg IV
  - 0.5 mg/kg PO
- **Chloral Hydrate**
  - 25-50 mg/kg PO for EEG
  - 50-100 mg/kg PO for CT/MRI
  - Max 1 gm/dose; 2 gms/day


Thank you for your attention