Management of Distressing Non-Pain Symptoms in Pediatric End-of-Life Care

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Disclosure

Neither I nor any member of my immediate family has a financial relationship or interest with any proprietary entity producing health care goods or services related to the content of this CME activity.

I do intend to discuss unapproved or investigative use of commercial products or devices (= off-label).

Lecture Overview
• Dyspnea
• Noisy Breathing
• Nausea & Vomiting

Pediatric Symptoms during the last week of life

Pain 84 %
Loss of Appetite 73 %
Fatigue 63 %
Nausea/Vomiting 58 %
Dyspnea 55 %
Constipation 47 %

Dyspnea

T. Dangel (Poland)
R. Drake (Australia)
A. Goldman (UK)
T. Hongo (Japan)
J. Wolfe (USA)

SUBJECTIVE
sensation
breathing has become
unpleasant (= uncomfortable awareness)

OBJECTIVE
observation
breathing has become fast or difficult

Treat!

Investigate!
**Respiratory Distress Observation Scale**

- Non-communicative adult
- Ordinal level scale (0, 1, or 2)
- Heart rate
- Respiratory rate
- Accessory muscle use
- Paradoxical breathing pattern
- End-expiratory grunting
- Nasal flaring
- Fearful facial display

0 = no distress, 16 = most severe distress


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**Step 1: Evaluation**

History & clinical exam

- Pain
- Fatigue
- Anxiety
- Sleep disorders
- Fluid intake

**Step 2: Treat underlying causes** (when possible & feasible):

- Anemia
- Ascites
- Infection
- Obstruction
- Pericardial / pleural effusion
- Pulmonary emboli
- Thick secretions
- Volume overload

**Step 3: Integrative therapies**

- 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

**Principles of Pediatric Symptom Management**

- State of the art pain & symptom management in the 21st century demands that pharmacological management must be combined with supportive and integrative, non-pharmacological therapies to manage a child’s distressing symptoms.

- 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
Step 3: Implement Integrative/Supportive Therapies

**Adult Data**

- **High-level evidence**
  - Neuromuscular electrical stimulation
  - Chest wall vibration
- **Moderate-level evidence**
  - Breathing training
  - Walking aids
- **Low-level evidence**
  - Acupuncture
  - Acupressure


Step 3: Implement Integrative/Supportive Therapies

- Find most comfortable position
- Improve air circulation, fan
- Use a humidifier
- Lower room temperature
- Stop smoking
- Provide background information about dyspnea
- Management of anxiety
- Counseling
- Relaxation
- Breathing techniques
- Occupational & music therapy
- Guided imagery, hypnosis
- Cuddle / hug


Step 3: Implement Integrative/Supportive Therapies

- Adult RCT: Handheld fan directed to face significantly reduces sensation of breathlessness (malignant and non-malignant causes)


Step 4: Implement Drug Therapy

**Oxygen**

- Controversial
- No correlation with oxygen saturation, blood gases (ABG's) or lung function tests
- Oxygen does not improve dyspnea in patients with cancer.
- Oxygen provides no additional symptomatic benefit for relief of refractory dyspnea in patients with life-limiting illness compared with room air.


Step 4: Implement Drug Therapy

**Opioid therapy**

- Main therapy
- Exact mode of action unclear: Many brain regions that process perception of pain and dyspnea (e.g., anterior insula & other cortical structures) can be pharmacologically modulated by opioids
- Endogenous opioids lessen dyspnea in COPD

Opioid therapy

- Mu-receptors in brain (incl. brainstem, spinal cord, lung)
  - Perception of breathlessness
  - Ventilatory drive by responsiveness to hypercapnia and hypoxia
  - \( O_2 \) consumption
  - Morphine: vasodilatory (beneficial heart failure, PHT ?)

Concerns about respiratory depression?

- Systematic reviews in adults confirm low-dose opioids are effective in relieving breathlessness and do NOT compromise respiration
- Erroneous assumption: evidence from acute care setting, where opioids are used for analgesia in postoperative care also applies in palliative care setting. This is not the case!
- Opioid studies for dyspnea: oxygenation and \( CO_2 \)-levels do not change with introduction of opioids

- Whether opioid naïve or already on opioids: careful titration of morphine or hydromorphone for dyspnea or pain does not result in respiratory depression (measured by respiratory rate, \( O_2 \)-saturation, \( CO_2 \)-levels)

American College of Physicians Recommendation:

In patients with serious illness at the end of life, clinicians should use therapies of proven effectiveness to manage dyspnea, which include opioids in patients with unrelieved dyspnea... (Grade: strong recommendation...)

Advanced lung disease, terminal cancer

Current body of evidence supports ineffectiveness of nebulized opioids for the dyspnea management
**Routes of Administration**

- **oral**
- **i.v. / s.c.**
- **intranasal**
- **nabulization?**
- **buccal**
- **transdermal**
- **suppository**

**Opioids (50% of analgesic dose)**

- **intravenous**
- **intramuscular**
- **sublingual**
- **buccal**
- **nasal**

**Benzodiazepines:**

- Pharmacology unclear (enhance action of neurotransmitter GABA & reduce anxiety)
- Many brain regions that process perception of pain and dyspnea (incl. anterior insula & other cortical structures) can be pharmacologically modulated by benzodiazepines.


- Little evidence for dyspnea sensation modification, but improves mood (CNS side effects: delirium, falls, sedation)

**Dyspnea**

- Addition of midazolam to morphine in cancer dyspnea treatment beneficial

  - Midazolam:
    - buccal: 0.1-0.3 mg/kg Q15min
    - IV: 60 mcg/kg/hr plus 60 mcg/kg bolus Q15min
  - Diazepam, Lorazepam

**Noisy Breathing / Death Rattle**

Common during last hours of life:

- Prepare family in advance
- Explain pathophysiology
- Evaluate fluid intake
- Treatment only, if distressing for the child
- Positioning
- Reduction of fluid intake
- (suction)

**Anticholinergics:**

- **Quaternary amines** (do not cross blood/brain barrier):
  - Glycopyrrolate (Robinul) 5-10 mcg/kg iv/sec TID; 20-40 (1-100) mcg/kg oral TID
- **Tertiary amines** (cross blood/brain barrier):
  - Scopolamine (Hyoscine Hydrobromide) 0.5-5 mcg/kg iv/sec TID; children > 11years: 1mg patch Q24h
  - Atropine (eye drops) 1-2 (0.5%) Q4-6h
  - Hyoscyamine (Levsin)

- No evidence (just eminence-based)

- Salivary glands: Botulinum toxin A
MORPHINE IV: Starting dose: 7 mcg/kg/hr = 0.028 mg/hr 
(plus PCA bolus 0.028 mg)

- DOSE ESCALATION: Titrated to effect in increments:
  - If receiving > than 2 PCA boluses/hr for > 4 hours in a row, increase by 50% 
    (background and bolus, respectively)
  - FINAL DOSE: 4.5 mg/hr plus 4.5 mg nurse-administered PCA bolus every 10 
    minutes as needed (≈ 1150 mcg/kg/hr)

MIDAZOLAM IV: Starting dose: 0.5 mcg/kg/min = 0.012 mg/hr (plus PCA 
bolus 0.012 mg)

- FINAL DOSE: 8 mg/hr plus 8 mg nurse-administered PCA bolus every 10 
  minutes as needed (≈ 33 mcg/kg/min)

Hi Dr. Friedrichsdorf! 
[...] We are so thankful that we had you to help us get her to where she is now. 
If we hadn't found a drug combination that helped her to stay comfortable until 
she was able to get her transplant, I do believe that she wouldn't have made it. 
Yes it was scary having her on so much drugs but it kept her alive and look at her now. 
We just had trust in you and we knew you knew exactly what you were doing! Thank you so much. 
(Kali's mother)

Nausea & Vomiting

- Step 1: Evaluation
- Step 2: Treat underlying causes
- Step 3: Integrative therapies
- Step 4: Drug therapy

- Correlation with eating
- Correlation with other distressing symptoms
- Drug administration
- Raised intracranial pressure?
- Bowel sounds?
- Constipation?
Nausea Assessment Tools For Children with Cancer

Memorial Symptom Assessment Scale 7-12

7. Did you feel like you were going to vomit (or going to throw up) yesterday or today? [Yes or No]

If Yes: How much of the time did you feel like you could vomit (or could throw up)?

- A very short time
- A medium amount
- Almost all the time

How much did this feeling bother you or trouble you?

- Not at all
- A little
- A medium amount
- Very much

Memorial Symptom Assessment Scale 10-18

7. Nausea or Feeling like you could vomit? [Yes or No]

If Yes: How often did you have it?

- Almost never
- Sometimes
- A lot
- Almost always

How severe was it usually?

- Slight
- Moderately
- Severe
- Very Severe

How much did this bother you or distress you?

- Not at all
- A little bit
- Somewhat
- Quite a bit
- Very much

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Nausea Assessment Tools For Children

PeNAT


- Parents may not accurately assess their child’s nausea.

- Nausea more significant than previously appreciated.

- Parents may not accurately assess their child’s nausea.

Nausea & Vomiting

Step 2: Treat underlying causes

- GI: constipation, reflux, ileus
- Drug adverse effects
- Antibiotics
- Anticholinergics
- Antihistamines
- Corticosteroids
- Disopyramide
- Ileus
- NADs
- Opioids
- Palliative chemotherapy
- Tricyclic antidepressants
- Infections (e.g. gastroenteritis)
- Metabolic disorders (e.g. Ca^2+, renal failure)
- Anxiety
- Seizure

Step 3: Integrative & Supportive Therapies

- Provide small meals, chosen by child (hypogeusia? dysgeusia?)
- Frequent provision of favorite drinks
- Management of anxiety
- Counseling
- Relaxation
- Breathing techniques
- Occupational & music therapy
- Hypnosis
- Good oral care
- Avoid discomforting smells
- Aromatherapy (lemon, peppermint)

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**Acupressure, Acupuncture**

- P6 point (or “inner gate”): 2 or 3 finger widths down from the top crease in the wrist, centered in the groove between the two large tendons.

- Take thumb and index (or middle finger) and press firmly on the points on both sides of the wrist when nauseous; relief in 10-30 seconds (may take up to five minutes).

**Step 4: Drug Therapy**

- According to assumed pathophysiology
- RCT’s only in children with cancer and postoperative nausea.

**Dopaminergic**

- Chemoreceptor trigger zone
  - Area postrema
  - Blood Brain Barrier
  - Emetic pattern generator (Vomiting center)

**Peripheral**

- **Central**

**Serotonin (5-HT3) - Receptor Antagonists**

- 5-hydroxytryptamine-3 (5-HT3) Antagonists: Good results in children with cancer after application of chemotherapy
  - Ondansetron (Zofran®)
  - 0.1-0.2 mg/kg (max. 8mg) TDS-QID po/iv (sublingual!)
  - Granisetron (Kytric®)
  - 0.01-0.05 mg/kg Q8h; max. 3 mg/dose IV/PO/patch
  - Adverse effect: constipation
  - Nauseating in higher doses

**Based on Twycross 2002**

**Basic**

- Morphine / digoxin
- Ca / uremia
- Gastric irriants

**Based on Twycross 2002**

**Thoracic and abdominal muscle contractions**
• Metoclopramide & Haloperidol (phenotiazine) extrapyramidal reactions!
• Dyskinetic syndrome: 1:5,000 (treated with either centrally acting antihistamine (diphenhydramine) or anticholinergic (benztropine))
• Domperidon does not cross the blood-brain barrier NO extrapyramidal reactions!

• Metoclopramide (Reglan®) - short half-life
  0.15-0.3 mg/kg QID PO/IV/SC/PR
• Haloperidol (Haldol®)
  0.01-0.1 mg/kg Q12h (slowly titrated to max. of 1-2 mg/kg, max. 100mg/dose) IV/PO
  Haloperidol (Adult uncontrolled study, n=42): N/V with cancer not related to chemotherapy: 61% complete/partial control
  1.5 mg PO Qday - 2.5 mg PO BID (or 5 mg s.c. Qday)

• Stress, anxiety and nausea via peripheral dopaminergic receptors at plexus myentericus may cause a slowing of gastrointestinal passage ("Dopamine Break") antagonized by metoclopramide and domperidon
• Concurrent administration with anticholinergics: Block the final common pathways of prokinetics
• Concurrent IV administration with 5-HT3-Receptor Antagonists: Risk of cardiac arrhythmia

• Diphenhydramine (Benadryl®)
  0.5-1 mg/kg Q6h (max. 50mg) PO/IV
• Dimenhydrinate (Dramamine®, TripTone®)
  1-2 mg/kg Q8h IV; 2-5 mg/kg Q6-12h PO/IV/PR
• Cyclizine
  1mg/kg TBS PO/W/V/C
• Promethazine (Phenergan®) [phenotiazine, no dopaminergic activity]
  0.2-0.5 mg/kg Q6h PO/IV
• Scopolamine: AChm (but not H1)
  0.61 mg/kg IV 8h IV; Patch: 6.33mg/24h or 0.5mg/24h: > 16 years G/Eh

Phenotiazine Derivates (Psychotropics)
• Prochlorperazine (Compazine®)
  0.1-0.2 mg/kg Q6h PO
• Chlorpromazine (Thorazine®)
  PO, PR: 0.5-2 mg/kg IV: 0.25-1 mg/kg slow infusion
• Levomepromazine = Methotrimeprazine (also H1/2 and to VRA)
• Extrapyramidal and anticholinergic side effects, agranulocytosis
D-9-tetrahydrocannabinol (THC) has been shown to have an antiemetic effect.

CB1 receptors are found in the central nervous system, (e.g., periaqueductal gray, rostral ventro-medial medulla, peripheral neurons) - activation produces a suppression in neurotransmitter release in intestine.

Metaanalysis (30 RCTs, 1368 adult patients): Cannabinoids effective antiemetics for controlling chemotherapy related sickness. Adverse effects included dizziness, dysphoria or depression, hallucinations, paranoia, and arterial hypotension.

• THC can stimulate appetite in addition to minimizing nausea.

• Medical Cannabis program currently in 13 US states.
• Dronabinol and Nabilone do not fully replicate effect of total cannabis preparation.

Corticosteroid
- Raised intracranial pressure due to a brain tumor may show dramatic short-medium term improvement due to reduction of surrounding tumor edema.
- Inhibit prostaglandine synthesis, which also may play a role in its antiemetic (not analgesic?) effect.
- Due to its significant side effect profile, including mood swings and excessive weight gain, the administration in PPC is somewhat controversial.

Benzodiazepines
- Clinical experience: Often very effective in PPC nausea management.
- Midazolam, lorazepam, diazepam...
- RCTs showing effectiveness for postoperative nausea or chemotherapy induced nausea.
- Adult dose: 1-2 mg BID.

Thoracic and abdominal muscle contractions

Dronabinol (Marinol®) or Nabilone (Cesamet®) superior to placebo, domperidone, prochlorperazine.
- Not superior: metoclopramide, chlorpromazine.
- Dronabinol (Marinol®) or Nabilone (Cesamet®) more effective than placebo in controlling chemotherapy induced nausea and vomiting. Systematic review. BMJ. 1996 Sep 21;313(7065):923-7.
- Metaanalysis (30 RCTs, 1368 adult patients): Cannabinoids effective antiemetics for controlling chemotherapy related sickness. Adverse effects included dizziness, dysphoria or depression, hallucinations, paranoia, and arterial hypotension.

Midazolam, lorazepam, diazepam...

Low-dose midazolam infusions (1mg bolus plus 1mg/hour) effective in prevention of nausea/vomiting and pruritus following epidural morphine (0.06, abdominal total hysterectomy) study by Mack et al. J Pain Symptom Manage. 2006;31(3):216-23.
Add benzodiazepine:
Add corticosteroid:

**Second Line Therapy**
- **Scheduled dosing**
  - Add corticosteroid:
  - Dexamethasone (Decadron®)
  - Methylprednisolone (Solu-Medrol®)
  - Prednisone (Delta-Beef®)
- Add benzodiazepine:
  - Midazolam (Versed®)
- Substitute 1st line drugs of same class:
  - 5-HT<sub>3</sub>-Receptor Antagonist:
  - Granisetron (Kyrtec®)
  - Ondansetron [Zofran®, Zophan®]
  - Metoclopramide (Reglan®, Domperidone®)
  - Haloperidol (Haldol®, Thorazine®)
  - Diphenhydramine (Benadryl®, Dimenhydrinate®)

**Third Line Therapy**
- **Scheduled dosing**
  - Consider substituting phenothiazine derivatives for 1st/2nd line drugs of same class:
  - D<sub>2</sub>-Receptor Antagonist:
  - Chlorpromazine (Thorazine®, Thorazine®, Thorazine®)
  - Thioridazine (Mellaril®, Mellaril®, Mellaril®)
  - H<sub>3</sub>, & ACh<sub>3</sub>-Receptor Antagonist:
  - Aprepitant (Emend®)
  - Dimenhydrinate (Dramamine®, Dramamine®)
  - Metoclopramide (Reglan®, Reglan®, Reglan®)
  - Haloperidol (Haldol®, Haldol®, Haldol®)
  - Granisetron (Kyrtec®, Kyrtec®, Kyrtec®)
  - Ondansetron [Zofran®, Zofran®, Zofran®]
  - Dexamethasone (Decadron®, Decadron®, Decadron®)
  - Diphenhydramine (Benadryl®, Benadryl®, Benadryl®)
  - Dimenhydrinate (Dramamine®, Dramamine®, Dramamine®)
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Titration (Anesthesia !): IV infusion - increments of 5 - 10 mcg/kg/min (0.3 - 0.6 mg/kg/hour) over 5 to 10 minutes.

General anesthetic; short-acting hypnotic.

Mechanism of action not well-defined.

Potentiation of GABA-A receptor activity → slowing the channel closing time.

Sodium channel blocker.

Endocannabinoid system may contribute to its unique properties.

No analgesic activity (?).

Postoperative pain is less after propofol compared to inhalation agents for anesthesia.

Ventilatory depressant effects of propofol may be counteracted by painful surgical stimulation.

Antiemetic properties.

Opioid induced Pruritus: Adults at subhypnotic doses (0.3 mcg/kg/min). Possible inhibition of ventral and dorsal spinal routes.

PEDIATRIC HYPNOSIS WORKSHOPS
MINNEAPOLIS
Pediatric Clinical Hypnosis Training
Introductory - Intermediate - Advanced Levels
National Pediatric Hypnosis Training Institute
(formerly associated with the SDBP)

www.nphti.org
Guidelines
Symptom Management in Palliative Care:
Step 1: Evaluation (history & clinical exam)
Step 2: Treat underlying causes
Step 3: Integrative therapies
Step 4: Drug therapy (according to assumed pathophysiology)
Step 5: Focus on the child’s quality of life
P.S.: Morphine & Midazolam do not shorten a child’s life
„The goal is to add life to the child’s days; not simply days to the child’s life.“ (AAP)