Original Article

PALLIATIVE MEDICINE

The 'surprise' question in paediatric palliative care: A prospective cohort study

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Aim:

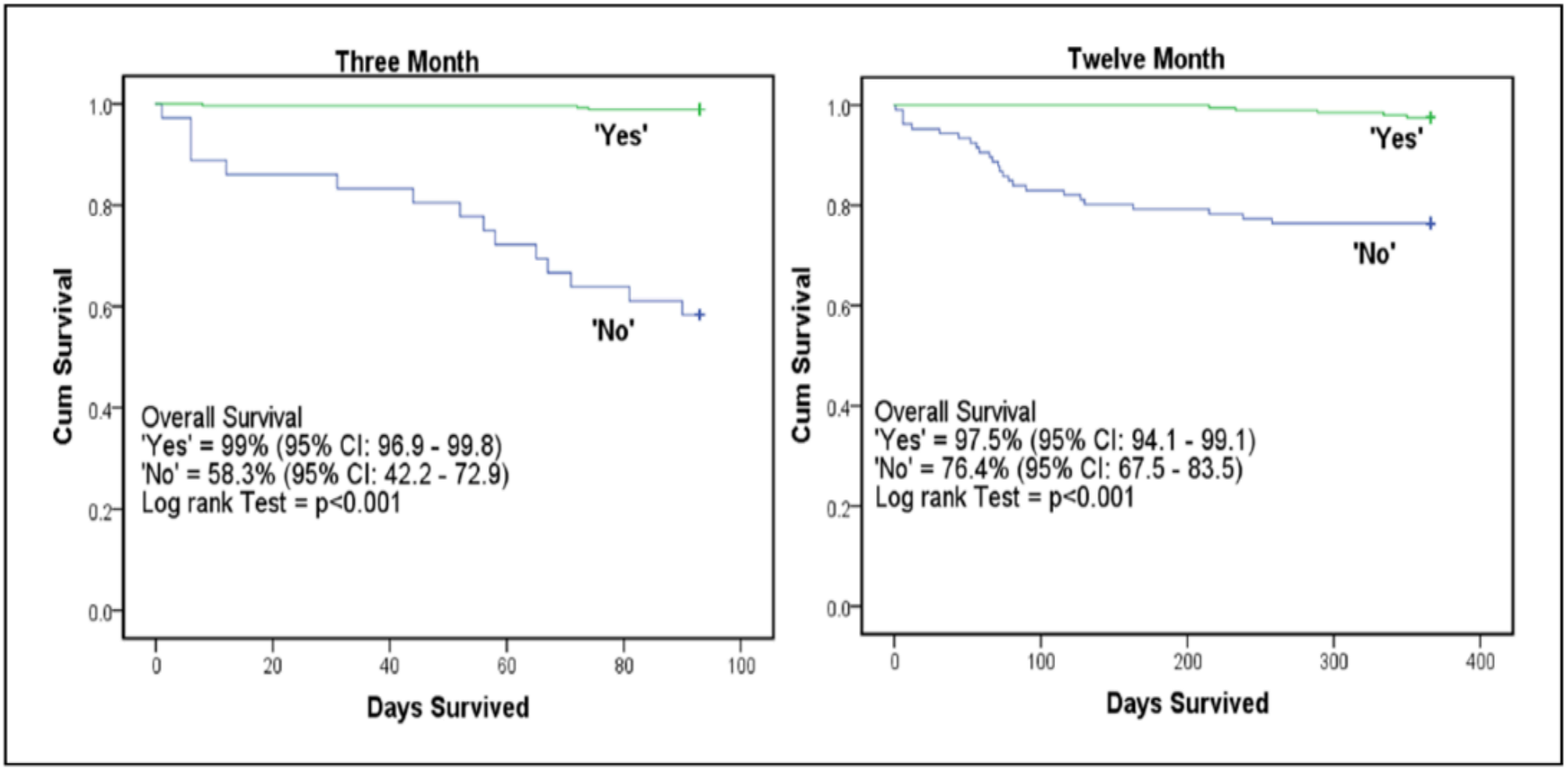
To assess the prognostic accuracy of the surprise question when used by a multidisciplinary team to predict survival outcomes of children with life-limiting conditions over a 3 and 12 month period.

Methods

- Prospective Cohort Study 2011-2013
- 327 children aged 0-20 under hospice care with diagnosis LLC
- Convenience sampling monthly MDT referral and review panel

‘Would you be surprised if this patient died in the next 3 months?’
’Would you be surprised if this patient died in the next 12 months?’

- Majority vote recorded. No consensus - excluded
- Age, Gender, Diagnosis from notes
- Survival outcomes recorded 3m and 12m



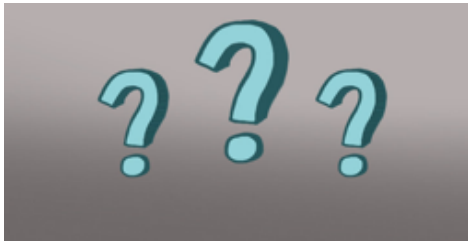
3 Months HR = 22.94 (5.34-98.6) 12 months HR = 6.53 (2.32-18.4) p<0.001

Conclusions & take home messages

- Surprise question - simple, accommodates uncertainty, accurate, valid
- Overpredicts death (PPV)
- Valid contribution to other tools eg SPECTRUM

Appraisal….

- Excellent study….
- Convenience sample but broad representation
- Measurement - variations in MDT
- 23 Exclusions (7% of sample)- a problem for the ‘surprise question’?
- Generalisability - Non hospice, generalist MDT



Subcutaneous levetiracetam for the management of seizures at the end of life

Anna Elizabeth Sutherland,[1] John Curtin,[2] Victoria Bradley,[2] Olivia Bush,[3] Maggie Presswood,[4] Victoria Hedges,[5] Katrien Naessens[6]

BMJ Supportive & Palliative Care

June 2018 Volume 8 Issue 2

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BMJ

Sophie Bertaud

9th APPM Paediatric Palliative Care Study Day

23rd November 2018

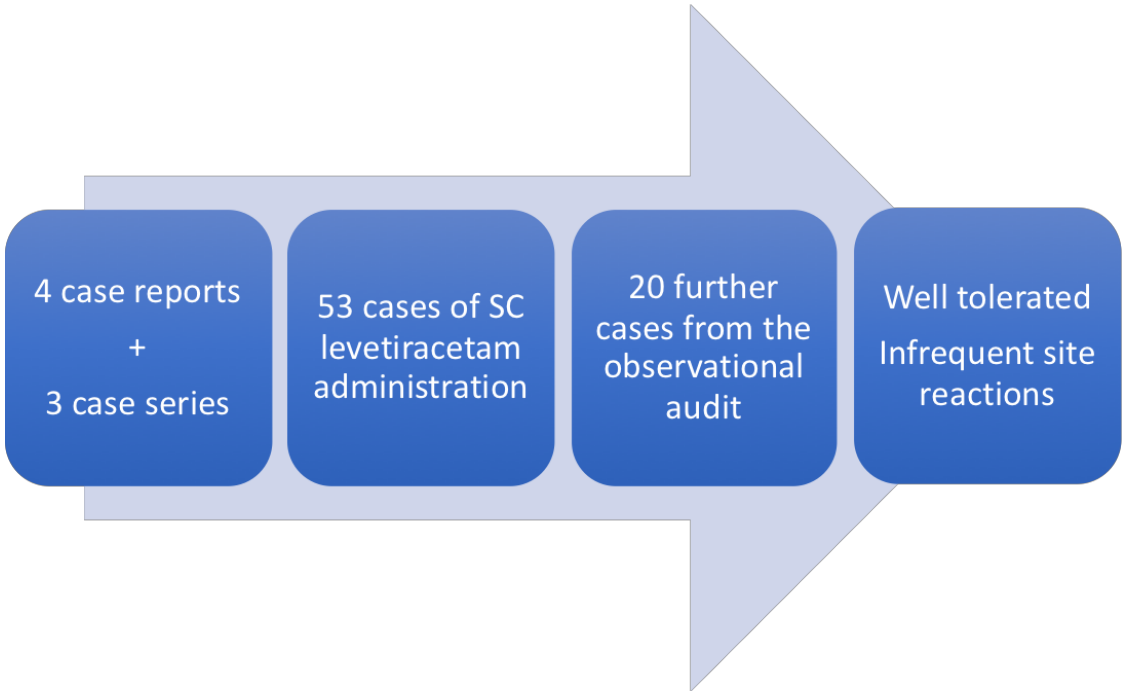
Objectives and Methodology

- Primary outcomes:
- to assess the efficacy of subcutaneous levetiracetam
- to assess the tolerability of subcutaneous levetiracetam

- Combination of a literature review and a prospective observational audit in a regional adult palliative care network

- Why SC levetiracetam?
- non-sedating
- not known to interact with dexamethasone or to induce cytochrome P450
- should not be stopped abruptly

Results



- Doses ranged from 250mg to 4000mg daily
- Oral to SC conversion ratios where stated were 1:1
- 10 patients had seizures, myoclonus or twitching while on SC levetiracetam
- 4 site reactions, 1 sterile abscess
- Drug levels checked in 3 patients and found to be therapeutic

Critical appraisal

- The study asks a relevant question
- Largest number of cases to date and a representative sample, albeit in adults
- Study design unable to answer question of effectiveness
- Insufficient evidence that therapeutic levels are achieved
- Poor quality evidence – case reports and observational data with potential for selection bias and confounding variables
- The authors present honest conclusions

Take home message

- Levetiracetam offers the possibility of non-sedating seizure control at the end of life
- Subcutaneous levetiracetam appears to be well tolerated but evidence for effectiveness is weak
- Advice is to use alone in a syringe driver to avoid site reactions
- Need for further prospective research and studies on the compatibility, stability and bioavailability of SC levetiracetam
- Need for paediatric evidence

ADC Fetal & Neonatal edition

Referrals to a perinatal specialist palliative care consult service in Ireland 2012-2015

McMahan DL et al

Arch Dis Child Fetal Neonatal Ed
2018 **103** F573-6

Objectives and Methodology

- Tertiary children's hospital and university maternity hospital in Ireland
- Referrals and gives advice nationally
- Retrospective review of perinatal referrals over 4 years to end 2015
- Time of referral
- Duration of life
- Place of death
- Medication use

Results: 83 referrals

- 26% antenatal
- 73% postnatal

- 35% chromosomal
- 25% cardiac
- 11% complex neuro
- 4% renal agenesis

- 27 asymptomatic
- 46 need morphine

- 10 IUD
- 36 hours - days
- 22 weeks – few months
- 15 alive

- 24 died in hospital
- 22 at home
- 1 children’s hospice

Critical appraisal / Review

- Unique collaborative service
- Nearly 2000 perinatal deaths in period
- Small proportion referred
- Proportion of deaths outside of hospital?
- Improving referral rate?
- Symptom review
- Service needs

Take home messages

- Importance of growing perinatal palliation
- Reinforces broad specialty and service collaboration
- Ongoing service development needs
- Database of referrals

Intranasal fentanyl for respiratory distress in children and adolescents with life-limiting conditions

Pieper et al. BMC Palliative Care (2018) 17:106

Presented by Ross Smith
Paediatric Palliative Care (GRID) Trainee

Objectives and Methodology

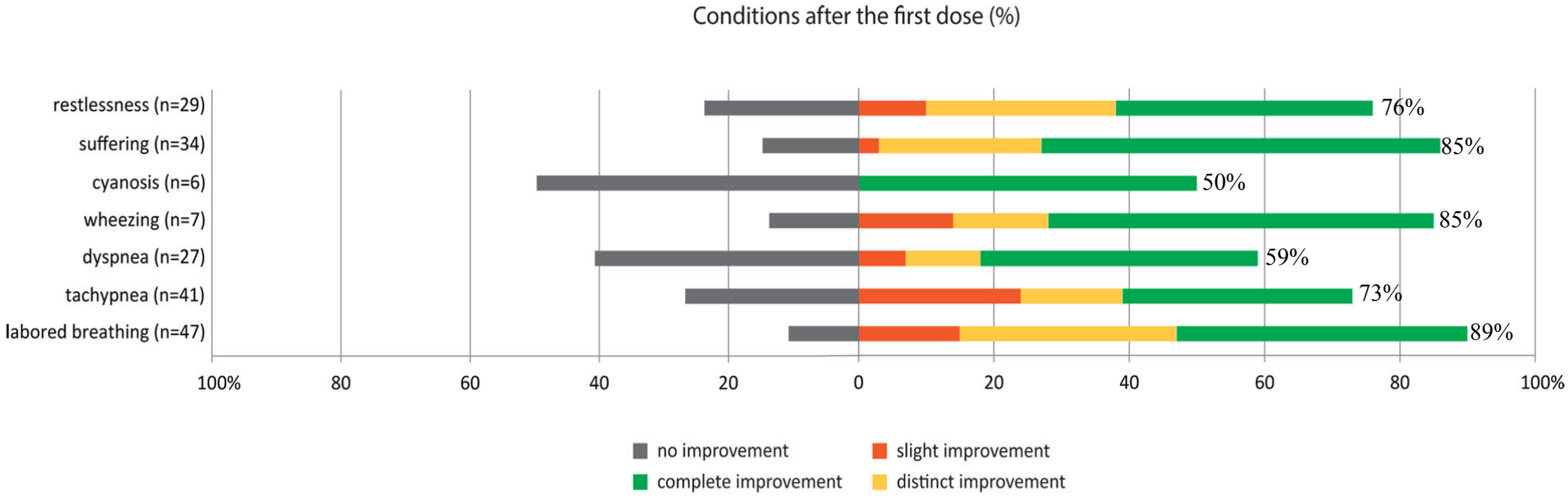
- Intranasal fentanyl (INF) in an acute attack of respiratory distress (AARD)
- circumstances
- outcomes
- adverse events

Methods:

- Retrospective
- Paediatric palliative patients
- Controlled drug register (n= 28)
- Reviewed notes
- AARD using descriptions (**n=16**)
- response
- adverse effects

Results

- 70 Episodes of ARDD (16 children)



- 1 adverse effect

Critical Appraisal/Review

- Relevant
- Paediatric Palliative
- Range of Conditions

- Limitations
- Retrospective
- Small size
- Lack of standardisation
- Confounding medications

Take home message

- On limited evidence, Intranasal fentanyl
- Reduces suffering
- Reduces symptoms and signs of respiratory distress
- Low adverse effects

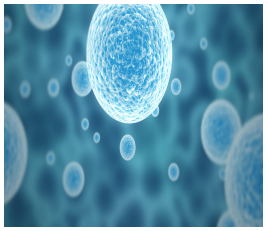
- Further work
- Standardised validated tool
- Prospective studies with control group
- Comparison against other medication
- Appropriate dosage

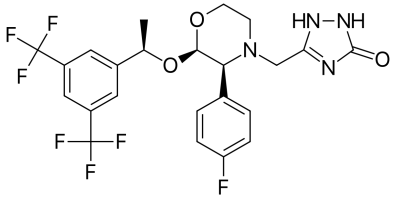
Long-term aprepitant for nausea and vomiting associated with gastroparesis in hematopoietic stem cell transplantation

Justin Jacobse Harmen et al., Journal of Bone Marrow Transplantation April 2018

Presented by: Dr. Emma Al-Khabbaz
International Clinical Fellow Paediatric Palliative Medicine

Introduction





- Nausea & Vomiting (N&V) in the course of allogeneic hematopoietic stem cell transplantation (SCT) is common and sometimes persistent.
- 3 days of antiemetic (fos)aprepitant, a NK1 receptor antagonist is licensed for the tx of CINV. Longer use is unlicensed as sufficient data is lacking
- In the first week of SCT Chx is the most likely cause of N&V symptoms. The DDx of delayed N&V after SCT includes:

GvHD, enteric infections (CMV, herpes viruses etc), **Gastroparesis**, adverse effects of medication, anticipatory vomiting, stress, idiopathic causes

- Gastroparesis seems to be a common cause of N&V and bloating after SCT in the literature.
- This paper shares experience of 3 patients with long-term off-label use of aprepitant to relieve late N&V in the course of SCT.

Patient A: 15 month boy with hemophagocytic lymphohistiocytosis was post BMT from a fully matched unrelated donor.

Conditioning:
treosulfan, fludarabine, alemtuzumab, methotrexate and cyclosporine as graft versus host disease (GvHD) prophylaxis

Multiple antiemetic regimens:
ondansetron, lorazepam, erythromycin, domperidone, alizapride and a PPI

- Upper GI endoscopy and sigmoidoscopy did not show GvHD or infection. Dx with gastroparesis. TPN started no improvement after 3/12
- Aprepitant (1.5 mg/kg once daily, no loading dose) was started. Within 24 h much improved symptoms
- Daily aprepitant for 4 months trial of wean not tolerated. Stopped after 8 months and oral feeds reintroduced. No adverse effects reported.

Patient B: 5-month-old boy was referred for SCT for AML: extramedullary lesions and CNS involvement were present at dx.

Conditioning: anti-thymocyte globulin, thiotepa, treosulfan, and fludarabine, with cyclosporine and prednisone as GvHD prophylaxis. The patient was transplanted with unrelated cord blood

Severe neutropenic enterocolitis so on total TPN, minimal feeds.
Emesis was controlled with granisetron, lorazepam, and fosaprepitant (2 mg/kg once daily, loading dose 3 mg/kg once) in addition to a PPI.

- Elevated LFTs ? TPN? Drugs. Voscoconazole-micafungin, fosaprepitant stopped.
- After 2 wks P.O aprepitant and ondansetron restarted due to N&V. He was eventually discharged with daily aprepitant only, difficult to wean stopped at 3 months (no further rise in LFTs).

Patient C: 19-month-old girl myelodysplastic syndrome with refractory cytopenia post BMT from a fully matched unrelated donor.

Conditioning: anti-thymocyte globulin, treosulfan and fludarabine, with methotrexate and cyclosporine as GvHD prophylaxis. During conditioning- ondansetron given.

Prior to SCT antiemetics: granisetron, chlorpromazine and fosaprepitant (2 mg/kg once daily for 3 wks, loading dose 3mg/kg once). TPN started for 1.5 wks with a PPI for feed intolerance.
D/c in 4th week post SCT on ondansetron

- Due to persistent N&V at 2 wks post d/c (gastroparesis) aprepitant restarted (2mg/kg once daily, loading dose 3 mg/kg once)
- Vomiting ceased shortly after, whereas a mild abdominal pain persisted. Appetite came back and aprepitant was stopped after being used for 3 wks no adverse effects.

Summary and Thoughts

- Gastroparesis is thought to have to have contributed to N&V although detailed information on why this was so not given for all 3 patients.
- 1st report on long term use of aprepitant in children, showed it was effective and safe with no adverse effects reported.
- Interesting case report but needs further study as population is small, a more robust study design needed.

- Translatable information:
- PPC patients also commonly develop gastroparesis/slowing of gut for a number of reasons e.g. medications, and disease progression.
- PPC patients are also having improved survival and consequently a higher symptom burden for longer periods

Long term usage data on symptomatic therapies is therefore important for future practice.

children

MDPI

Link to Publisher's site

Children (Basel). 2018 Jul; 5(7): 86.

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PMCID: PMC6068960

PMID: 29954057

Methadone for Analgesia in Children with Life-Limiting Illness: Experience from a Tertiary Children's Health Service

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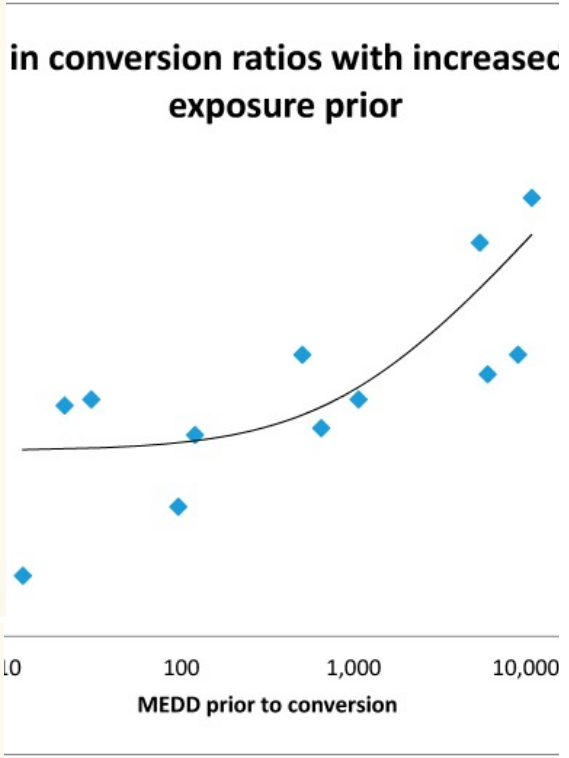
Archana Soman
Consultant in PPM
Sheffield Children's Hospital and Bluebell Wood Children's Hospice
Sheffield

Pt	Approx. MEDD (PO)	Methadone Starting Dose and	Maximal Methadone Dose and	Rapid Conversion or Adjuvant	Reason for Rotation to Methadone	Conversion Ratio (PO Morph:	Breakthrough Analgesia	Side Effects or Issues Noted	Outcome
3	5400 mg	15 mg QID PO	240 mg IV infusion over 24 h	Rapid conversion	Inadequate Analgesia.	90:1	Hydromorph PCA IV.Eventually converted to meth PCA IV	Improved Analgesia.	Died one month after commencing methadone.
4	12 mg	1.5 mg QID PO	3 mg TDS PO. Changed to Fentanyl patch	Rapid conversion	Side effects with morphine—inadequate analgesia and itch. Methadone only alternative slow release opioid that comes as elixir.	2:1	Hydromorph NCA	Unsteadiness attributed to methadone.	Died 3 months after ceasing methadone.
5	6000 mg	150 mg SC infusion over 24 h	150 mg SC infusion over 24 h	Rapid conversion	Inadequate Analgesia.	20:1	Meth SC	Improved analgesia.	Died 7 days after commencing methadone
9	10,800 mg	36 mg IV infusion over 24 h	600 mg IV infusion over 24 h	Rapid conversion	Myoclonus.	150:1	Meth PCA IV	Less mycolonus.	Died 4 days after methadone rotation.
10	288 mg	1 mg IV NOCTE	10 mg QID SL	Adjuvant. Gradual conversion to methadone	Inadequate analgesia.	N/A	NCA fentanyl IV	Improved analgesia.	Weaning Methadone. Alive.



Other findings

- Rapid conversion method is safe
- Half life decreases with use, increases with age
- 7-10 days to reach steady state: caution required
- No clinically significant QTc prolongation

Strengths and limitations

- Observational (mostly retrospective)
- Small numbers- single site
- Cancer and non-cancer LLC
- Although limited numbers, background and response information
- Only children LLC pain (not peri-op or Rx of opiate dependence)
- Significant addition to previously available data

Take home messages

- Efficacious and cost-effective
- Better tolerated/ safer than we think?
- Wide range of doses & conversion ratios: higher mo:me ratios in opioid naïve

- *Should we be using methadone earlier?*
- *APPM/ specialist PPM units in the UK: collect usage data and /or RCT?*

DEVELOPMENTAL MEDICINE & CHILD NEUROLOGY AACPDM CARE PATHWAY

Pharmacological and neurosurgical interventions for managing dystonia in cerebral palsy: a systematic review

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Carolina Perez
Clinical Fellow Paediatric Palliative Care
Evelina London Children´s Hospital
Journal Club APPM Study Day

Objectives and Methodology

- **AIM:** To systematically review evidence for pharmacological and neurosurgical interventions for managing dystonia in individuals with CP to inform a care pathway

- **Method:**
  - Systematic review was carried out according to the American Academy of Neurology guidelines and the PRISMA checklist
  - Search terms: dystonia, cerebral palsy, baclofen, benzodiazepines, clonidine, gabapentin, levodopa, trihexyphenidyl, botulinum toxin, intrathecal baclofen (ITB), or deep brain stimulation (DBS)
  - Inclusion criteria: a minimum of 5 participants; English language studies; a minimum of 50% of the participants with dystonia in CP; articles from 1945 to 2015
  - Outcome measures: dystonia reduction; improved motor function; decreased pain/improved comfort; improved ease caregiving

Results

- 28 articles: 1 levodopa, 5 trihexyphenidyl, 3 botulinum toxin, 6 ITB, and 13 DBS
- No articles for oral baclofen, benzodiazepines, clonidine or gabapentin met the inclusion criteria
- Evidence for reducing dystonia was possibly effective for ITB and DBS; possibly ineffective for trihexyphenidyl; inadequate data for botulinum toxin

Table III: Summary of evidence levels of pharmacological and neurosurgical interventions

	Levodopa	Trihexyphenidyl	Botulinum toxin	ITB	DBS	Summary
↓ dystonia	No evidence	Level C (possibly ineffective)	Level U (inadequate data)	Level C (possibly effective)	Level C (possibly effective)	Support: ITB (level C) and DBS (level C); no support: trihexyphenidyl (level C)
↑ motor function	Level C (possibly ineffective)	Level C (possibly ineffective)	Level U (inadequate data)	Level U (inadequate data)	Level U (inadequate data)	Support: inadequate data; no support: levodopa (level C), trihexyphenidyl (level C)
↓ pain/↑ comfort	No evidence	Level U (inadequate data)	Level U (inadequate data)	No evidence	Level U (inadequate data)	Support: no evidence/inadequate data; no support: no evidence/inadequate data
↑ caregiving	No evidence	Level C (possibly ineffective)	No evidence	No evidence	Level U (inadequate data)	Support: no evidence/inadequate data; no support: trihexyphenidyl (level C)

Critical Appraisal

Relevant article:

- Paediatric Palliative Patients
- Search strategy
- International expert panel review articles
- Level evidence: only class I, class II, and class III studies were included
- Useful discussion around all treatments

Limitations:

- Varied nomenclature of dystonia
- Only English language articles included
- Risk of publication bias
- Only include children with CP

Take home message

- Most studies focus on reducing dystonia, not improving motor function, pain, or ease of caregiving
- ITB and DBS are possibly effective in reducing dystonia. Trihexyphenidyl possibly ineffective
- The majority of pharmacological and neurosurgical management options for dystonia in CP are based on clinical expert opinion
- The development of a care pathway integrating evidence and expert opinion would be useful in the clinical management of dystonia in CP

Cancer

2017 Impact Factor
6.537

Self-Reported Fatigue in Children With Advanced Cancer: Results of the PediQUEST Study

Christina K. Ullrich, Veronica Dussel, Liliana Orellana, Tammy I. Kang, Abby R. Rosenberg, Chris Feudtner and Joanne Wolfe

AIM: To describe **patterns** of both fatigue and **distress associated** with fatigue in **paediatric advanced cancer**.

Methodology

Design and Setting

PediQUEST

DANA-FARBER Boston Children's

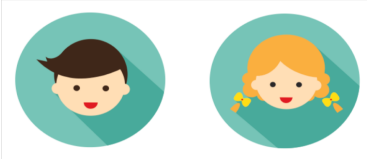
Children's Hospital of Philadelphia℠

Seattle Children's HOSPITAL · RESEARCH · FOUNDATION

Study Instruments

1. PQ Memorial Symptom Assessment Scale (PQ –MSAS)
2. Paediatric Quality of Life Inventory
3. De novo overall sickness question

Participants



> 2 years

2 week history of ***ADVANCED CANCER*** (progressive, recurrent or non-responsive)

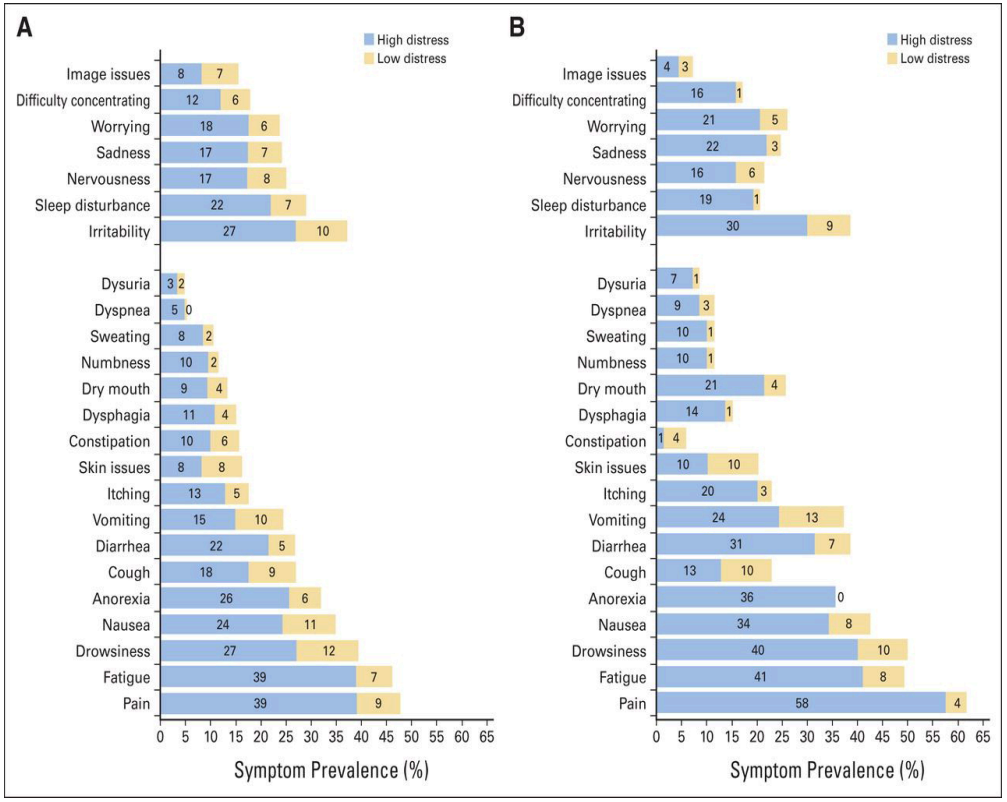
Results

TABLE 3. Factors Associated With Reports of Fatigue and Fatigue Distress: Multivariate Models

Variable	OR	95%CI	*P*[a]
Fatigue			
Age	1.06	1.0-1.13	.04
Hemoglobin	0.79	0.69-0.91	.001
High distress symptoms[b]			
Anorexia	3.37	1.96-5.79	< .001
Nausea	3.29	1.97-5.5	< .001
Difficulty sleeping	2.93	1.70-5.03	< .001
Sadness	1.96	1.06-3.64	.03
Irritability	1.96	1.10-3.50	.02
Fatigue distress[b]			
High distress symptoms[a]			
Nausea	5.01	1.99-12.57	< .001
Cough	4.25	1.41-12.81	.01
Pain	2.3	1.13-4.70	.02
Worry	2.52	0.89-7.11	.08

Critical Appraisal

- Important subject matter
- Appropriate study design
  - Multicenter design
  - Sizeable sample
  - Uni- and multivariate analysis
- Prospective data collection of patient reported outcomes
- **Limitations:**
  - Limited diversity: ethic and racial groups
  - Fatigue assessments not tied to treatment cycles
  - Parental by-proxy reporting



Take home message…

- Fatigue represents a **high degree of burden** for children with advanced cancer.

- Optimal fatigue treatment should be **focused primarily** on **concomitant, uncontrolled symptoms**.

- **Multimodal strategies** are necessary rather than single interventions i.e. Methylphenidate