Seizure Management in End-of-Life Care: Fit for the Future?

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Seizure/Fits/Convulsions

- Common in children with Life-limiting illness
  - Neurological disease (static or progressive)
  - Metabolic disease
  - Malignant disease in CNS
- Not part of the image of a peaceful death

Challenges in Seizure management in End of Life Care

- Seizures may become more frequent, longer, and less responsive to treatment as underlying disease progresses
- Many drugs are not available in a form that is able to be easily administered or absorbed
- How to combine best practice in seizure management, with best practice in palliative care and respect patient choice
  - Acceptable level of medical intervention
  - place of care and place of death

Standard Seizure management

Treatment options

- Wide range of oral medications, used alone or in combination
- Ketogenic diet
- Vagal nerve stimulation
- Surgical approaches

Emergency management

- Buccal midazolam or rectal diazepam
- Rectal paraldehyde
- IV phenytoin or IV lorazepam
- Thiopentone, intubation and ventilation

End of Life Seizure management

Treatment options

- Wide range of oral medications, used alone or in combination
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End-of-Life Seizure management
Emergency management

- Buccal midazolam or rectal diazepam
- Rectal paraldehyde
- Subcutaneous midazolam infusion
- Subcutaneous phenobarbitone infusion

End-of-Life Seizure management
Emergency management

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- Subcutaneous midazolam infusion
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- When to use them? When not to use them?
- Practical issues:
  - Availability
  - Administration
  - Dose
  - Monitoring
- Any alternatives if these are unsuccessful?

Quality Improvement Methodology

Collaboration:
SW CPCN, SWIPE, and SCN

Project Leader: Dr Nicky Harris, Palliative Care Paediatrician and Postgraduate Researcher, UWE.

Team members:

- Dr Megumi Baba, Medical Director, Children's Hospice South West
- Dr Antonia Beringer, Senior Research Associate, UWE
- Dr Charlotte Mellor, Consultant in Paediatric Palliative Care, Bristol
- Rebekah Rogers, Paediatric Pharmacist, Bristol Children's Hospital
- Dr Peta Sharples, Consultant Paediatric Neurologist, Bristol
- Kirsty Taylor, lead nurse, Devon Virgin Care Children's Palliative Care Team

Primary Outcome

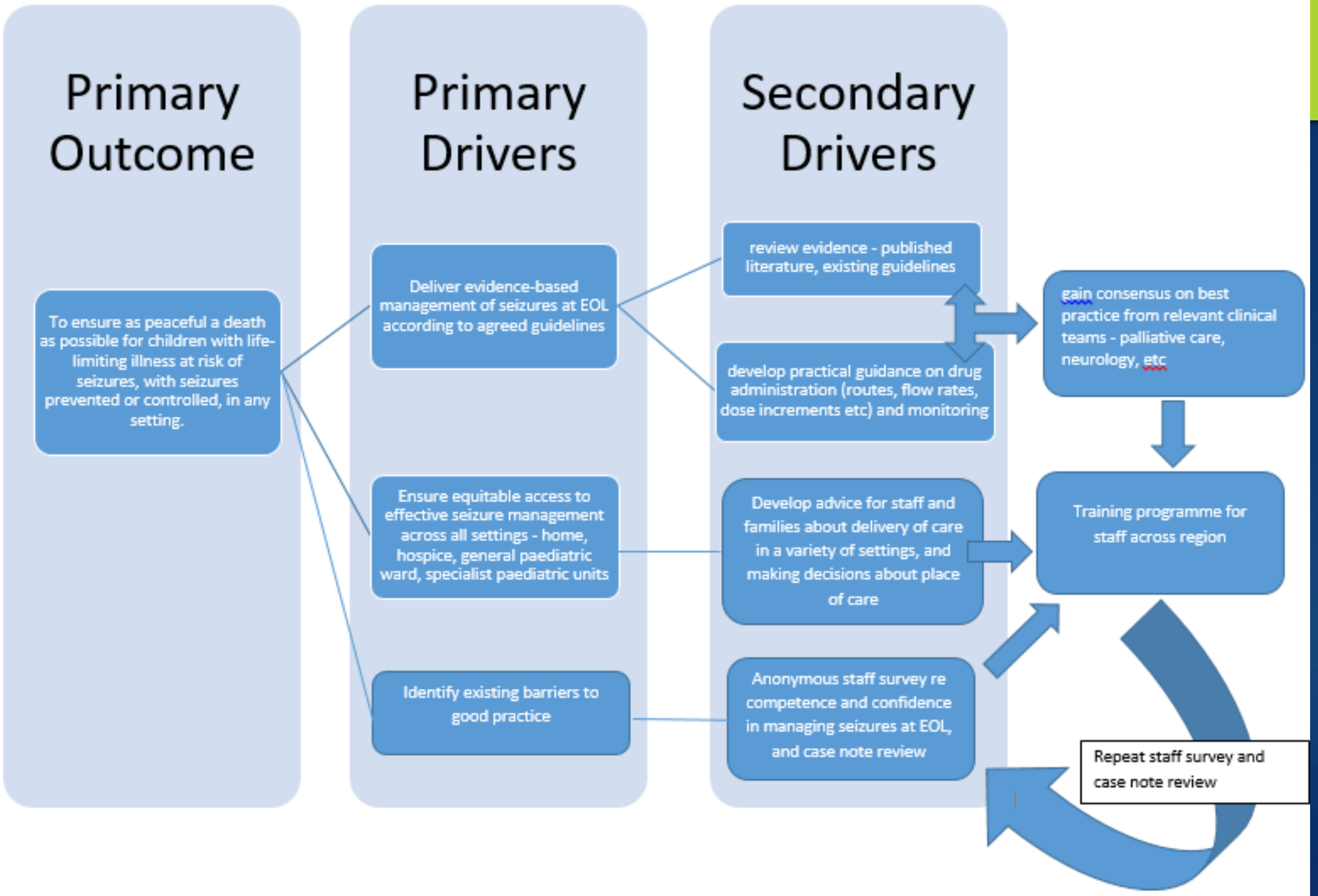
- To ensure as peaceful a death as possible for children with life-limiting illness at risk of seizures, with seizures prevented or controlled, in any setting.

Primary Drivers

- Deliver evidence-based management of seizures at EOL according to agreed guidelines
- Identify and address existing barriers to good practice
- Ensure equitable access to effective seizure management across all settings - home, hospice, general paediatric ward, specialist paediatric units

Secondary Drivers

- Review evidence - published literature, existing guidelines
- Anonymous staff survey re competence and confidence in managing seizures at EOL, and case note review
- Develop practical guidance on drug administration (routes, flow rates, dose increments etc) and monitoring
- Develop advice for staff and families about delivery of care in a variety of settings, and making decisions about place of care
- Gain consensus on best practice from relevant clinical teams - palliative care, neurology, etc
- Training programme for staff across region


Primary Outcome
To ensure as peaceful a death as possible for children with life-limiting illness at risk of seizures, with seizures prevented or controlled, in any setting.
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review evidence - published literature, existing guidelines
develop practical guidance on drug administration (routes, flow rates, dose increments etc) and monitoring
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Anonymous staff survey re competence and confidence in managing seizures at EOL, and case note review
gain consensus on best practice from relevant clinical teams - palliative care, neurology, etc
Training programme for staff across region
Repeat staff survey and case note review

What have we found?

Literature review + available guidance for management of seizures in EOL care

- Remarkably little published in peer-reviewed papers!
  - Case reports and reflections
  - No RCTs
  - No Series reports in children

Literature review + available guidance for management of seizures in EOL care

- Grey literature – guidelines, but limited evidence base

- Midazolam in Children 1 month – 18 years: :
  - Rainbows: start at 50mcg/kg/hr, increase to max 300mcg/kg/hour
    (max 100mg/24 hours, or 150mg/24 hours in specialist units)
  - BNFC: start infusion at 1 mcg/kg/min, increase at 15 -30 min intervals to max 5 mcg/kg/min
  - RCH Melbourne: 0.15mg/kg IV or SC stat, then 2 mcg/kg/min, increasing by 2mcg/kg/min until seizures cease, max 24 mcg/kg/min
    http://www.rch.org.au/rch_palliative/for_health_professionals/Neurological_symptoms/

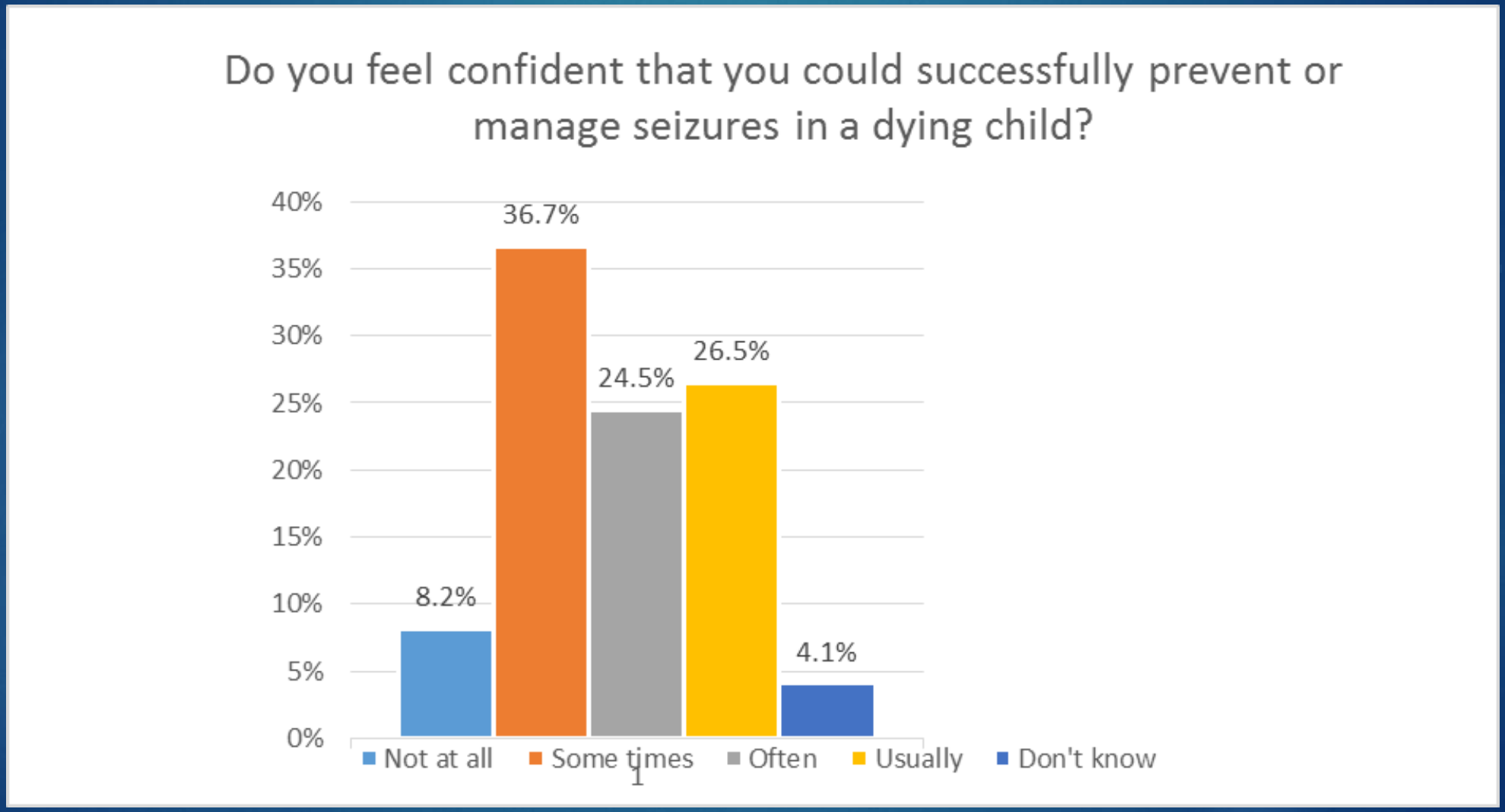
- Adults: If seizures are mentioned (rare):
  - Subcut midazolam 20-30mg/24 hours + prn 5-10mg s/c tds
  - Increase dose as required; max 60mg/24 hours in community

Staff Survey

- 57/261 replies to survey monkey targeted at paediatric teams working in general paeds, epilepsy or neurology, or palliative care

  - 78% had role in seizure management
  - 93% had a role in supporting children who might die

  - 80% had experience of managing seizures in children approaching the end of their lives
  - 92% would anticipate that they would be asked to advise on seizure management in EOL situation


Do you feel confident that you could successfully prevent or manage seizures in a dying child?
40%
35%
30%
25%
20%
15%
10%
5%
0%
8.2%
36.7%
24.5%
26.5%
4.1%
Not at all
Some times
Often
Usually
Don't know

Clinical Vignettes

- 6 clinical scenarios about challenging seizure management in children's palliative care
  - 17 yo CP, chest infection in hospice, not absorbing AEDs, how to control his fits?
  - 9 yo, at home with brain tumour, fear of seizures, ? Best prophylaxis
  - 4 yo, neurodegenerative condition, twitching on ward ? cause
  - 6 yo, battens, high dose midazolam insufficient at home, what next?
  - infant with HIE in A&E, apnoeas on midazolam, what options?
  - 14 yo on PICU, fitting, unable to wean from ventilator, what can you do for him?

feeds poorly, and has abnormal movements almost all of the time. She has an advanced care plan in place, which states that her family would like her to be cared for at home if at all possible. As she has not been absorbing her medications, the community palliative care nursing team started a subcutaneous midazolam syringe driver several days ago at home. This was initially effective in low doses, but over recent days her midazolam dose has escalated to 5 mcg/kg/min (maximum recommended by BNF). You are the on-call doctor, and the community nurse asks you what to do.

Please tell us which of the following actions would you consider to be appropriate (number your top 3):

Action	WHAT actions would be appropriate? (tick if yes)	Comments	How confident are you that this course of action is the most likely to be helpful for this child?			Number your top three actions	Do you know HOW to carry out this activity?
			Very	Somewhat	Not at all		Yes/no
Admit to hospital for further management, as it is not safe to give that much midazolam at home							
Ask GP to review her at home, oversee EOL care, and advise the CCNs re midazolam infusion rates.							
Check U&Es, Ca, LFTs to ensure that treatable causes of seizures are not overlooked	•			•		2	Yes
Add oral phenobarbitone to existing meds							
Refer urgently to hospice for EOL care, even though parents want to be home.							
Advise the palliative care nurse to increase the midazolam further, regardless of BNF limits							
Advise the palliative care nurse to decrease the midazolam, it clearly isn't working							
Add diamorphine to midazolam infusion to keep her comfortable	•		•			1	Yes
Start subcutaneous phenobarbitone infusion	•			•		3	Would look up
Other: Please specify							

medicines, and is vomiting most days, but despite treatment he appears to be in increasing pain and has lost weight.
He is currently in respite care following a recent hospital admission with a chest infection, and this morning had a seizure and vomited. Clinically he has an aspiration pneumonia, with laboured breathing, widespread crackles on the right, and a low-grade temperature. His parents have seen him recover from similar events on many occasions; their biggest concern is that when he is unwell he has more frequent seizures, and they would like to prevent these.
They don't want him to return to an acute ward, but feel that his quality of life was good until a few months ago and hope that this can be restored with appropriate support; there is no written advanced care plan in place.

Action	WHAT actions would be appropriate? (tick if yes)	Comments	How confident are you that this course of action is the most likely to be helpful for this child?			Number your top three actions	Do you know HOW to carry out this activity?
			Very	Somewhat	Not at all		Yes/no
Give his usual oral/gastrostomy antiepileptic medications via the rectal route instead	Yes	If medications are available to use by rectal route and family and young person are happy with this		Yes		1	
Stop all antiepileptic medications, and treat any seizures with buccal midazolam or rectal diazepam	No						
Admit to hospital, cannulate, and change all antiepileptic medications to IV equivalents	No	Aiming to manage at home but if deteriorates may become anecessity					
Start a subcutaneous midazolam infusion	Yes	But…need to try other strategies first		Yes			Specialist nurses do
Start oral phenobarbitone via gastrostomy	No	In discomfort with PEG use….but may become an option		Yes			Specialist nurses do
Start a subcutaneous phenobarbitone infusion	Yes	But…need to ry other strategies first					
Focus on oral antibiotics and oxygen for respiratory support, rather than seizure control	No	Oral antibiotics **and** seizure control					
Focus on analgesia, nursing support, and discussion of future plans for care as he may soon die	Yes	Always good to focus on analgesia and future plans	Yes			2	Yes
Agree and write an Advanced Care Plan with his parents	Yes		Yes			3	Would like more training on advanced care planning
Other: please specify:							

maintain her comfort and maximise quality of life.

n and is currently in hospital for investigation and management of this. She has recently been started on morphine with limited effect, and doses rds. She is drowsy and vomited once today, but has a normal respiratory rate and normal pupil responses. The ward nursing staff report onormal jerky movements and ask for review of seizure management. As the on-call doctor, what would you recommend doing?

	WHAT actions would be appropriate? (tick if yes)	Comments	How confident are you that this course of action is the most likely to be helpful for this child?			Number your top three actions	Do you know HOW to carry out this activity?
			Very	Somewhat	Not at all		Yes/no
movements may increase the	✓ Yes ○ No	Yes could be pain -however need to review this as "morphine with limited effect" ⇒ Maybe dose isn't at the correct level OR other factors causing pain.		✓		#.	Yes
myoclonic jerks uce the morphine.	✓ Yes ○ No	Morphine toxicity does cause myoclonic jerks but (N) pupil reaction and (N) RR : think unlikely but would consider.		✓		#	Yes
a movement ures. Add in henidyl.	✓	if Movement disorders -Yes to trial diazepam and trihexyphenidyl - bigger step already on medication for p		✓		#.	Yes
seizures, so c medications.	✓ Yes ○ No	Yes could be seizure - No seizure so would seek advice from Specialist		I wouldn't independently		P ATD - complex neurology team.	- would seek specialist advice
medications and ort.		Not yet - consider other factors first - constipation what could be corrected.					
increasing due to ntiepileptic ubcut	Need to consider this, but only x1 vomit	- only x1 vomit. - would ensure optimum reflux medication - has the child got a gastrostomy?					
ipated and is now may be n of urine.	✓	May be constipated : ensure BOR - needs bowel with morphine. Yes may have full bladder : check not in retention. - if in retention then catheterise.					
resent end-stage taneous and offer		-correct what can be corrected and see if this improves things. - if not then perhaps maybe moving → EOL care					Yes
		To unpick the cause of the pain needs close observation and monitoring. Also try other comfort measures → stories, music, massage, company, comfort etc.					
y clinical remit: ☐		Why is the child drowsy? Is there another					

Summary of responses

- Wide range of potentially acceptable approaches to most scenarios
- General lack of consensus in therapeutic priorities
- Majority of responses were self-ranked as “somewhat confident” or “not-at-all confident”
- Level of detail in comments confirms complexity of decision-making, and a passion to explore all options to get the best solution.

Case note review:

- **Remit for inclusion**:
  - age 0-25
  - receiving medical care in the south west
  - known life-limiting illness where typical approach to the management of seizures or status epilepticus was limited by previous best-interests decisions
  - time frame = preceding 10 years (2005-2015)
  - experienced difficult epilepsy management at EOL or when receiving palliative care

Identified Cases:

- 22 cases identified via survey monkey and targeted questioning of relevant staff and providers, and interrogation of CD register in hospice.
- 18 patients, (19 episodes of seizure management) met agreed criteria
- 4 patients excluded as although they fit the first 4 criteria, they died from other complications such as chest infections or planned extubation, without exacerbation/complications of epilepsy.

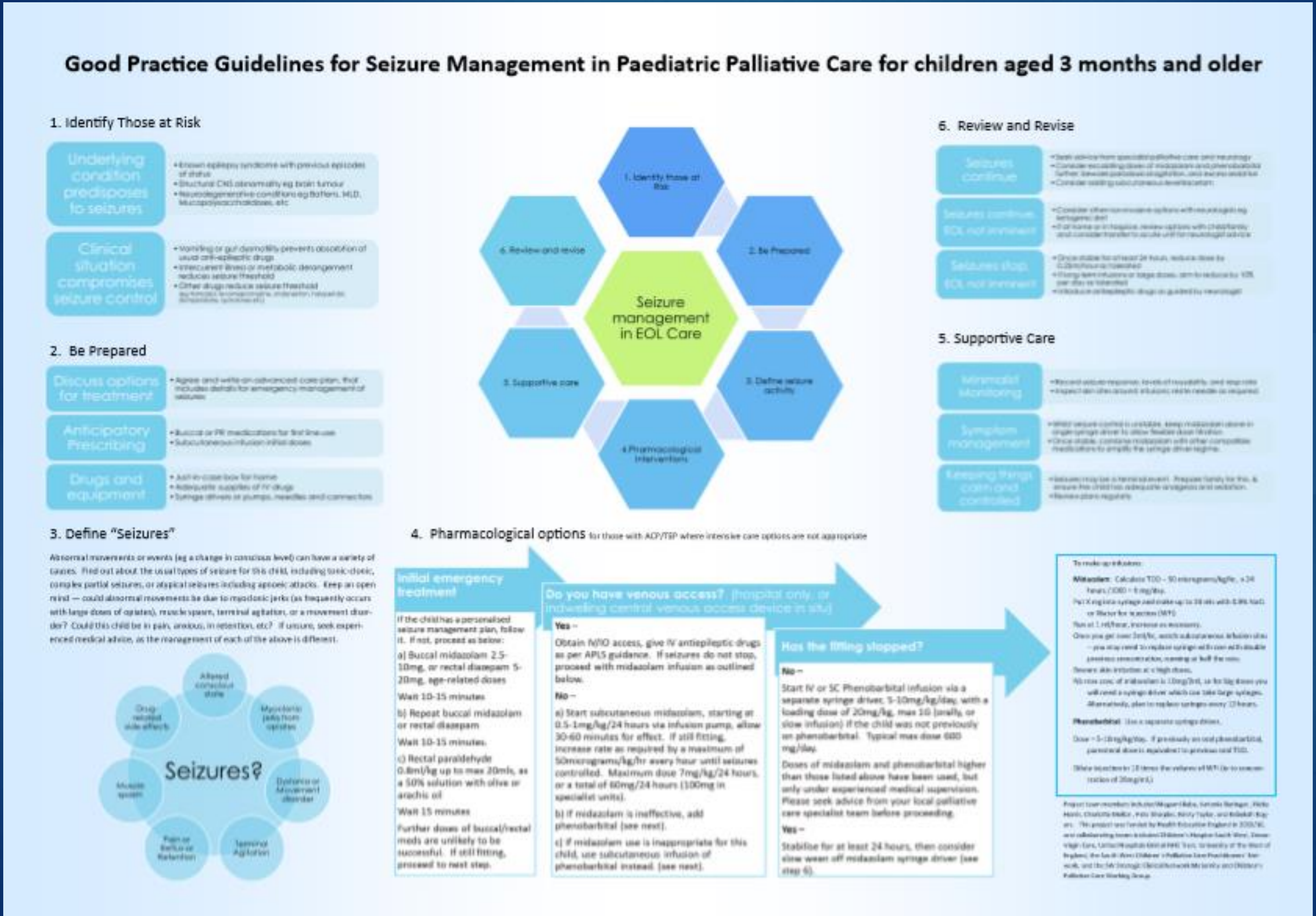
Key findings:

- 17 children received s/c or IV midazolam
  - 9/17 on s/c midaz received doses larger than recommended in APPM guidelines.
- 4/6 children received phenobarbital doses above recommended guidelines
- General reluctance to escalate doses quickly to control symptoms
- Inconsistencies in rates of dose escalation, and identification of maximum doses

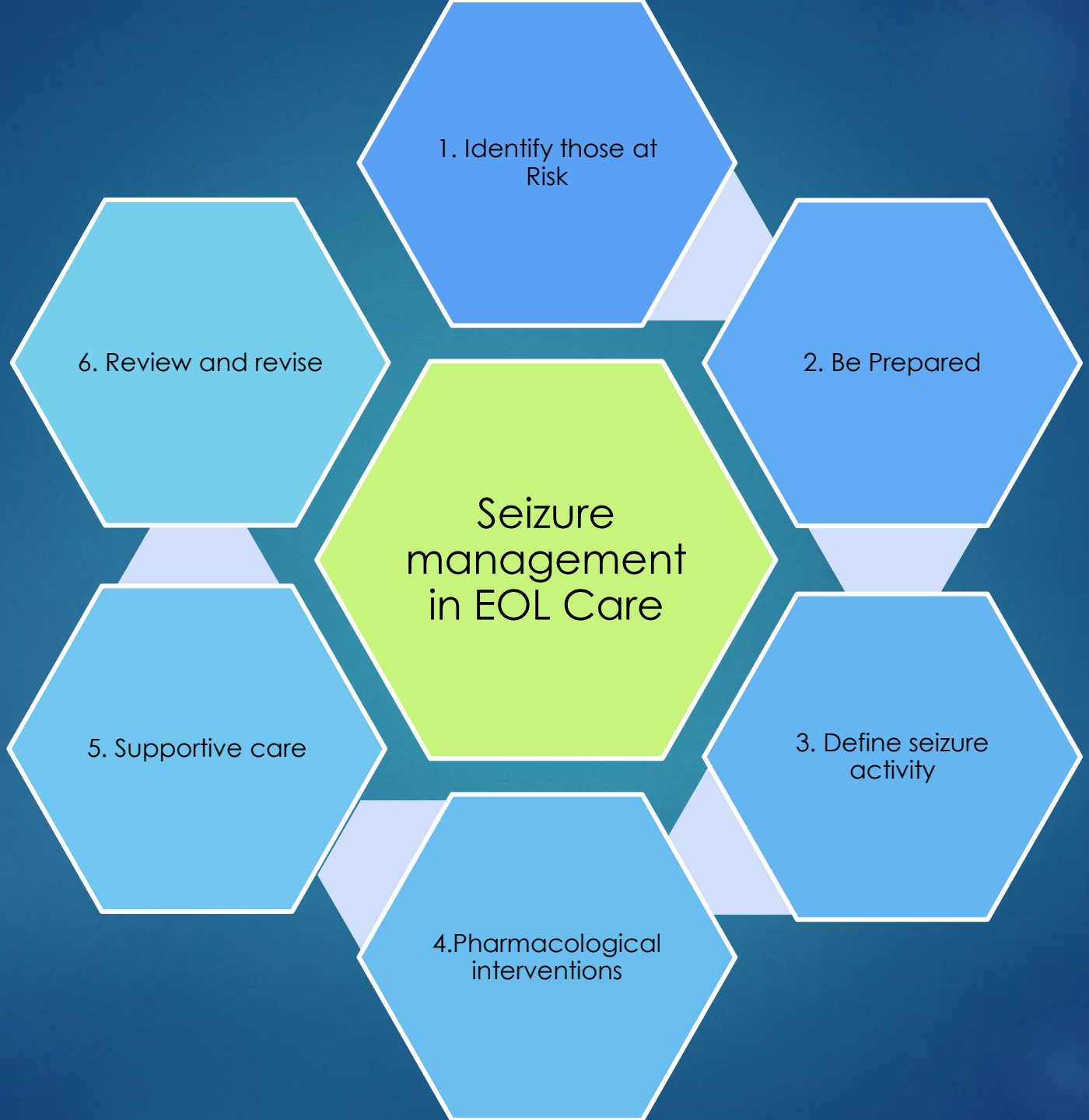
General Comments:

- Difficult area that causes significant clinical concern to staff
  - In context of other simultaneous clinical concerns
  - Impact of Family dynamics/circumstances on decision-making
  - Practical delivery of care
  - Emotional toll of supporting child, family and self

- Managing seizures was “stressful”, or “labour-intensive” or “scary”
- In 50% of cases, staff did not feel fully confident to diagnose or treat seizures



Good Practice Guidelines for Seizure Management in Paediatric Palliative Care for children aged 3 months and older
1. Identify Those at Risk
Underlying condition predisposes to seizures
•Known epilepsy syndrome with previous episodes of status
•Structural CNS abnormality eg brain tumour
•Neurodegenerative conditions eg Battens, MLD, Mucopolysaccharidoses, etc
Clinical situation compromises seizure control
•Vomiting or gut dysmotility prevents absorption of usual anti-epileptic drugs
•Intercurrent illness or metabolic derangement reduces seizure threshold
•Other drugs reduce seizure threshold
2. Be Prepared
Discuss options for treatment
•Agree and write an advanced care plan, that includes details for emergency management of seizures
Anticipatory Prescribing
•Buccal or PR medications for first line use
•Subcutaneous infusion initial doses
Drugs and equipment
•Just-in-case box for home
•Adequate supplies of IV drugs
•Syringe drivers or pumps, needles and connectors
1. Identify those at Risk
2. Be Prepared
3. Define seizure activity
4.Pharmacological Interventions
5. Supportive care
6. Review and revise
Seizure management in EOL Care
6. Review and Revise
Seizures continue
Seizures continue EOL not imminent
Seizures stop EOL not imminent
5. Supportive Care
Minimal Monitoring
Symptom management
Keeping things calm and controlled
3. Define "Seizures"
Abnormal movements or events (eg a change in conscious level) can have a variety of causes. Find out about the usual types of seizure for this child, including tonic-clonic, complex partial seizures, or atypical seizures including apnoeic attacks. Keep an open mind — could abnormal movements be due to myoclonic jerks (as frequently occurs with large doses of opiates), muscle spasm, terminal agitation, or a movement disorder? Could this child be in pain, anxious, in retention, etc? If unsure, seek experienced medical advice, as the management of each of the above is different.
Altered conscious state
Myoclonic jerks from opiates
Dystonia or Movement disorder
Terminal Agitation
Pain or Reflux or Retention
Muscle spasm
Drug related side effects
Seizures?
4. Pharmacological options for those with ACP/TSP where intensive care options are not appropriate
Initial emergency treatment
If the child has a personalised seizure management plan, follow it. If not, proceed as below:
a) Buccal midazolam 2.5-10mg, or rectal diazepam 5-20mg, age-related doses
Wait 10-15 minutes
b) Repeat buccal midazolam or rectal diazepam
Wait 10-15 minutes.
c) Rectal paraldehyde 0.8ml/kg up to max 20mls, as a 50% solution with olive or arachis oil
Wait 15 minutes
Further doses of buccal/rectal meds are unlikely to be successful. If still fitting, proceed to next step.
Do you have venous access? (hospital only, or indwelling central venous access device in situ)
Yes –
Obtain IV/IO access, give IV antiepileptic drugs as per APLS guidance. If seizures do not stop, proceed with midazolam infusion as outlined below.
No –
a) Start subcutaneous midazolam, starting at 0.5-1mg/kg/24 hours via infusion pump, allow 30-60 minutes for effect. If still fitting, increase rate as required by a maximum of 50micrograms/kg/hr every hour until seizures controlled. Maximum dose 7mg/kg/24 hours, or a total of 60mg/24 hours (100mg in specialist units).
b) If midazolam is ineffective, add phenobarbital (see next).
c) If midazolam use is inappropriate for this child, use subcutaneous infusion of phenobarbital instead. (see next).
Has the fitting stopped?
No –
Start IV or SC Phenobarbital infusion via a separate syringe driver, 5-10mg/kg/day, with a loading dose of 20mg/kg, max 1G (orally, or slow infusion) if the child was not previously on phenobarbital. Typical max dose 600 mg/day.
Doses of midazolam and phenobarbital higher than those listed above have been used, but only under experienced medical supervision. Please seek advice from your local palliative care specialist team before proceeding.
Yes –
Stabilise for at least 24 hours, then consider slow wean off midazolam syringe driver (see step 6).


1. Identify those at Risk
2. Be Prepared
3. Define seizure activity
4.Pharmacological interventions
5. Supportive care
6. Review and revise
Seizure management in EOL Care

1. Identify those at risk

Underlying condition predisposes to seizures

- Known epilepsy syndrome with previous episodes of status
- Structural CNS abnormality eg brain tumour
- Neurodegenerative conditions eg Battens, MLD, Mucopolysaccharidoses, etc

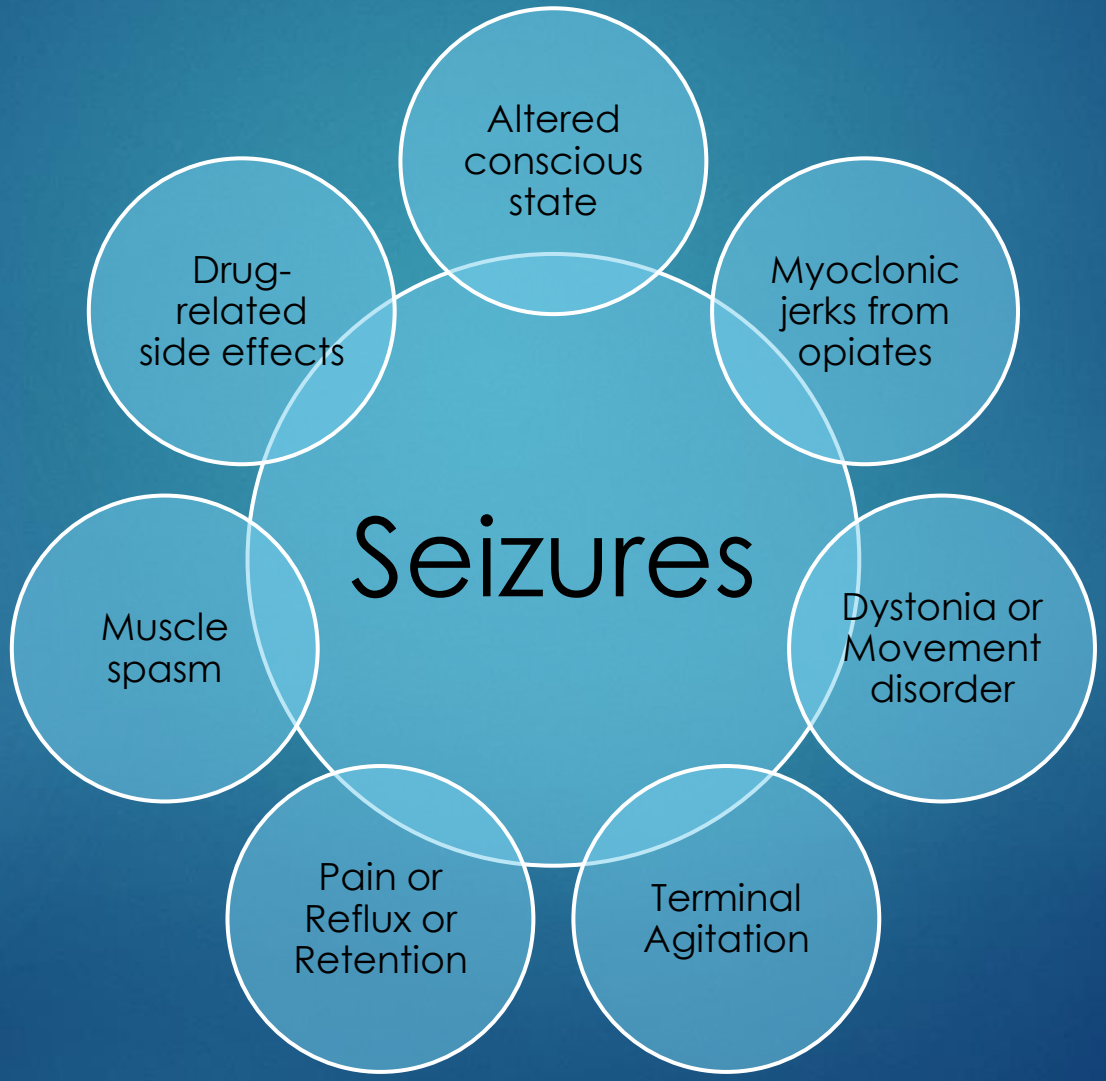
Clinical situation compromises seizure control

- Vomiting or gut dysmotility prevents absorbtion of usual anti-epileptic drugs
- Intercurrent illness or metabolic derangement reduces seizure threshold
- Other drugs reduce seizure threshold
  (eg tramadol, levomepromazine, ondansetron, haloperidol, domperidone, quinolones etc)

2. Be Prepared

Discuss options for treatment	• Agree and write an advanced care plan, that includes details for emergency management of seizures
Anticipatory Prescribing	• Buccal or PR medications for first line use • Subcutaneous infusion initial doses
Drugs and equipment	• Just-in-case box for home • Adequate supplies of IV drugs • Syringe drivers or pumps, needles and connectors

3. Is this Seizure Activity? abnormal movements or events have a variety of possible causes



4. Pharmacological Options for Seizure Management,

for those with ACP/TEP where intensive care options are not appropriate

Initial emergency treatment

If the child has a personalised seizure management plan, follow it. If not, proceed as below:

a) Buccal midazolam 2.5-10mg, or rectal diazepam 5-20mg, age-related doses

Wait 10-15 minutes

b) Repeat buccal midazolam or rectal diazepam

Wait 10-15 minutes.

c) Rectal paraldehyde 0.8ml/kg up to max 20mls, as a 50% solution with olive or arachis oil

Wait 15 minutes

Further doses of buccal/rectal meds are unlikely to be successful. If still fitting, proceed to next step.

Do you have venous access? (hospital only, or indwelling central venous access device in situ)

Yes –

Obtain IV/IO access, give IV phenytoin or IV lorazepam. If seizures do not stop, proceed with midazolam infusion as outlined below.

No –

a) Start subcutaneous midazolam, starting at 50micrograms/kg/hour via infusion pump, allow 30-60 minutes for effect. If still fitting, increase rate as required by 50micrograms/kg/hr every hour until seizures controlled, or you reach 200micrograms/kg/hour or a max 120mg/24 hours.

b) If midazolam is ineffective, add phenobarbital (see next).

c) If midazolam use is inappropriate for this child, use subcutaneous infusion of phenobarbital instead. (see next).

Has the fitting stopped?

No –

Start IV or SC Phenobarbital infusion via a separate syringe driver, 5-10mg/kg/day, with a loading dose of 20mg/kg, max 1G (orally, or slow infusion) if the child was not previously on phenobarbital. Typical max dose 600 mg/day.

Doses of midazolam and phenobarbital higher than those listed above have been used, but only under experienced medical supervision. Please seek advice from your local palliative care specialist team before proceeding.

Yes –

Stabilise for at least 24 hours, then consider slow wean off midazolam syringe driver (see step 6).

5. Supportive care

Minimalist Monitoring

- Record seizure response, levels of rousability, and resp rate
- Inspect skin sites around infusions; resite needle as required

Symptom management

- Whilst seizure control is unstable, keep midazolam alone in single syringe driver to allow flexible dose titration.
- Once stable, combine midazolam with other compatible medications to simplify the syringe driver regime.

Keeping things calm and controlled

- Seizures may be a terminal event. Prepare family for this, & ensure the child has adequate analgesia and sedation.
- Review plans regularly

6. Review and Revise

Seizures continue	• Seek advice from specialist palliative care and/or neurology • Consider escalating doses of midazolam and phenobarbital further; beware paradoxical agitation, and excess sedation • Consider adding subcutaneous levetiracetam
Seizures continue, EOL not imminent	• Consider other non-invasive options with neurologists eg ketogenic diet • If at home or in hospice, review options with child/family and consider transfer to acute unit for neurologist advice
Seizures stop, EOL not imminent	• Once stable for at least 24 hours, reduce midazolam dose by 10-20% per hour as tolerated, and consider switching phenobarbital to enteral administration • Introduce antiepileptic drugs as guided by neurologist

Addressing barriers to good practice

- Myth-busters:
  - Drug administration
  - Drug dosing
  - Supportive Care

- Training programme
  - Pharmacology of management of seizures
  - Advanced care planning
  - Practical guidance about syringe drivers

Gaining Consensus:
Palliative Care Clinicians and Neurologists

Best Practice guidance sent to eminent specialists in the field for comment:

Neurology:

- Chair, British Paediatric Neurology Association
- Lead Clinicians, Paediatric Epilepsy Networks

Paediatric Palliative Medicine:

- Association of Paediatric Palliative Medicine (APPM) Formulary Group
- Authors of Symptom Control Manual for Paediatric Palliative Care
- Regional Children's Palliative Care Clinical Networks

Next Steps

- External Peer Review
  - Publication in BMJ Supportive and Palliative Care
    - Harris N, Baba M, Mellor C et al: *Seizure management in children requiring palliative care: a review of current practice* BMJ Supportive & Palliative Care 2017

      doi:10.1136/ bmjspcare-2017-001366
  - Accepted for presentation at International PPC Conference Rome November 2016 and National RCPCH Scientific Conference May 2017
- Repeat survey, vignettes, case note review in another region
- NICE Guidance for EOL Care for Children and Young Adults 2016 identified seizure management as a research priority area
- Meeting of Expert Panel Group from Paediatric Neurology and PPC in autumn 2018.

Reflections on the process of Quality Improvement for rare EOL challenges:

- Funding opportunity was critical
  - Protected time for staff
  - Timeframe ensured no loss of momentum
- Pick your team to reflect real life challenges
  - Clinical background/Professions
  - Relevant settings
  - Academic partnership
- Rigorous methodology
- Collaboration and Peer Review essential
- Patient and Family Perspective

Seizure Management in End-of-Life Care: Fit for the Future?

- Thank you:
  - Members of SW CPCN, SWIPE, SCN
  - HEE for funding