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
- Ketogenic diet
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- Buccal midazolam or rectal diazepam
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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

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

- 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
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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

- 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
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?

- 36.7% Some times
- 24.5% Often
- 26.5% Usually
- 8.2% Not at all
- 4.1% 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):

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

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<tr>
<td>Give his usual oral/gastrostomy antiepileptic medications via the rectal route instead</td>
<td>Yes</td>
<td>If medications are available to use by rectal route and family and young person are happy with this</td>
<td>Yes</td>
<td>1</td>
<td>Yes/no</td>
</tr>
<tr>
<td>Stop all antiepileptic medications, and treat any seizures with buccal midazolam or rectal diazepam</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Admit to hospital, cannulate, and change all antiepileptic medications to IV equivalents</td>
<td>No</td>
<td>Aiming to manage at home but if deteriorates may become an necessity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Start a subcutaneous midazolam infusion</td>
<td>Yes</td>
<td>But...need to try other strategies first</td>
<td>Yes</td>
<td></td>
<td>Specialist nurses do</td>
</tr>
<tr>
<td>Start oral phenobarbitone via gastrostomy</td>
<td>No</td>
<td>In discomfort with PEG use...but may become an option</td>
<td>Yes</td>
<td></td>
<td>Specialist nurses do</td>
</tr>
<tr>
<td>Start a subcutaneous phenobarbitone infusion</td>
<td>Yes</td>
<td>But...need to try other strategies first</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Focus on oral antibiotics and oxygen for respiratory support, rather than seizure control</td>
<td>No</td>
<td>Oral antibiotics and seizure control</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Focus on analgesia, nursing support, and discussion of future plans for care as he may soon die</td>
<td>Yes</td>
<td>Always good to focus on analgesia and future plans</td>
<td>Yes</td>
<td>2</td>
<td>Yes</td>
</tr>
<tr>
<td>Agree and write an Advanced Care Plan with his parents</td>
<td>Yes</td>
<td></td>
<td>Yes</td>
<td>3</td>
<td>Would like more training on advanced care planning</td>
</tr>
<tr>
<td>Other: please specify:</td>
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</table>
A patient is currently in hospital for investigation and management of a condition. She has recently been started on morphine with limited effect, and doses are increased. She is drowsy and vomited once today, but has a normal respiratory rate and normal pupil responses. The ward nursing staff report normal jerky movements and ask for review of seizure management. As the on-call doctor, what would you recommend doing?

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<tr>
<td>movements may increase the</td>
<td></td>
<td>Very</td>
<td>Somewhat</td>
<td>Not at all</td>
</tr>
<tr>
<td>myoclonic jerks increase the morphine.</td>
<td></td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>a movement increase. Add in phenytoin.</td>
<td></td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>seizures, so a treatment. Add in antiepileptic medication.</td>
<td></td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>increasing due to antiepileptic medication.</td>
<td></td>
<td>Consider this treatment with only one dose.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>spasticity and increased tone of urine.</td>
<td></td>
<td>May be considered: ensure BDR - needs reassessment with morphine.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>present end-stage care: continue and offer</td>
<td></td>
<td>Music, massage, company, comfort, etc.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Clinical remit: ☑️
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
   - Clinical situation compromises seizure control

2. Be Prepared
   - Discuss options for treatment
   - Anticipatory Prescribing
   - Drugs and equipment

3. Define “Seizure”
   - Abnormal movements or events (e.g. change in conscious level) from a variety of causes
   - Find out about the usual types of seizure for this child (e.g. tonic-clonic, complex partial seizures, or status epilepticus including options attacks)

4. Pharmacological options
   - For those with AED/TSEP where intensive care options are not appropriate

5. Supportive Care

6. Review and Revise
   - Seizure management in EOL Care
   - Seizures continue
   - Seizures stop

Seizure management in EOL Care

1. Identify those at risk
2. Be Prepared
3. Define seizure activity
4. Pharmacological interventions
5. Supportive care
6. Review and revise

Initial emergency treatment

- If the child has a personalized seizure management plan, follow it. If not, proceed as below:
  - Buccal midazolam 1.5-10mg, or rectal diazepam 5-70mg, age-related doses
  - Wait 10-15 minutes
  - Repeat bucical midazolam or rectal diazepam
  - Focal onset seizures, i.e. facial, arm, or abdominal
  - Wait 15 minutes
  - Further doses of buccal/rectal midazolam are unlikely to be successful. If still fitting, proceed to next step

Has the fitting stopped?

- No
  - Initiate IV or SC Phenobarbital via a separate syringe: 5-10mg/kg/hour, with a starting dose of 20mg/kg, max 100mg (oral or slow infusion) if the child was not previously exposed to phenobarbital
  - If no warning signs or no large changes in conscious state, proceed to next step

- Yes
  - Discontinue IV or SC Phenobarbital
  - Administer antiepileptic drugs as per AED/TSEP
  - Stabilize for at least 24 hours, then consider wean off antiepileptic drug (see step 4)

To make an estimate:

- Midazolam: Calculation 700 - 1500mg/m²/day (34-69 mg/kg/day)
- Phenobarbital: Calculation 600 - 900mg/m²/day (33-47 mg/kg/day)

Note: If the child is not known to have epilepsy, nor antiepileptic drugs or seizures, then consider other causes for the fit (e.g. hypoglycemia, hypovolemia, drug withdrawal, etc.).
Seizure management in EOL Care

1. Identify those at Risk
2. Be Prepared
3. Define seizure activity
4. Pharmacological interventions
5. Supportive care
6. Review and revise
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 (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
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

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