Evidence to Decision (EtD) table: **Seizures**

PICO question

Seizures in the palliative care setting- *prioritising symptom experience over sustaining life at all cost with focus on optimising quality of life from the individual patient and families perspective*

Question

WHAT PHARMACOLOGICAL AND NON-PHARMACOLOGICAL INTERVENTIONS ARE EFFECTIVE FOR THE PRACTICAL MANAGEMENT OF SEIZURES IN INFANTS, CHILDREN AND YOUNG PEOPLE WITH PALLIATIVE CARE NEEDS	
Background	Seizures can be challenging to manage in paediatric palliative care, and little guidance currently exists to support practice. Drugs are often needed by transmucosal and rectal routes, or even by subcutaneous infusion and doses may differ form standard practice. Areas to be addressed: • Seizures benefiting from palliative care intervention or support where they are receiving or have received optimal management from neurology and other specialist services. • Multi-professional approach to seizure management • Management of seizures at end of life when they are expected to be the cause of death (terminal seizures) • Management of seizures as a symptom occurring during the deteriorating and/or end of life phase • Consideration of seizure management at different developmental stages eg neonates, child, adolescent
Objectives	1. Improving Quality of life for patients/carers 2. Seizure reduction and reduction in associated symptoms 3. Support desired place of care 4. Empowering professionals- minimising health carer distress 5. Supporting a good death 6. Standardising paediatric palliative care across UK and across all health care settings 7. Satisfaction experience-families 8. To enable transferability of care between care settings and to optimise choice of care setting 9. Define where seizure management in collaboration with palliative care is recommended 10. To support risk/ benefit discussions with families, including young people when able. 11. To consider liaison with specialist palliative care for complex symptom management when not at end of life. 12. Consideration of transition to adult services

Population	Children with life limiting conditions and complex seizures, benefiting from a palliative care approach. This might be defined by medical complexity, route of drug administration, place of care or phase of illness. This guidance applies to children for whom an active decision has been made to move to a palliative approach to seizuremanagement, prioritising comfort and prefered place of care above escalation to intensive care. Excluding: • CYP best managed by general paediatric or neurology teams for whom a palliative care approach is not (yet) appropriate • CYP who are experiencing seizures who are not life limited • Those aged 19 years and over
Intervention/ comparison	Pharmacological: Midazolam, clobazam, clonazepam, levetiracetam, Phenobarbital, diazepam, lorazepam, paraldehyde, steroids Non-pharmacological - trigger avoidance, music therapy Environmental triggers including sleep / pain/ agitation /constipation Information and support for CYP and Family Ketogenic diet Comparison: Placebo No treatment / usual care Cross comparison between any of the above (within group and between group) Combinations of the above – reducing triggers and pharmacological management. Routes of administration (same drug or same drug class)
Main outcomes	• Reduced frequency or intensity of seizures. • Reduced distress as experienced by child and family. • Care in place of choice. • Improved patient and family experience/ carer satisfaction. • Improved trust in healthcare support/ perceived quality of care / quality of experience. • Reduction in presentation to acute care. • Minimise harm / side effects - e.g. unwanted levels of sedation. • Acceptability to patients / families and professionals. • Achieving a ‘good’ death as determined by patient and family. • Improving confidence and ability to participate in activities of daily living
Setting	UK, Hospital, home, hospice and community settings where skills and resources allow. Supported by Managed clinical network.
Perspective	Professional working with children with life limited conditions, patients and their carers and other health professionals with expertise in seizure management.

Assessment

	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	Is the problem a priority? ☐ No ☐ Probably no ☐ Probably yes ☒ Yes ☐ Varies ☐ Don't know	Seizures were recognised in an APPM survey as 1 of 3 topic priority symptom topics that needed addressing to support clinical practice (APPM member survey 2019).	Seizures are a relatively common event towards the end of life, particularly in the case of progressive neurological disorders and intra-cranial pathology. The distress and burden of seizures close to the end of a child's life also extends to those caring for them. Seizure management strategies used in acute paediatrics, which are predicated on vigorous use of interventions such as intravenous medication, intubation and ventilation, may not be as appropriate for children with a life-limiting illness who require end-of life care, particularly as this may impact their choice of place of care. Specific guidance is therefore needed for the management of seizures at the end of life in children for whom intensive care admission no longer aligns with agreed goals of care. Current practice varies widely, and it is hoped that providing guidance could standardise treatment across the UK. NICE Guidance (NG61) on end-of-life care for infants, children and young people, found a lack of evidence for the pharmacological management of seizures at the end of life and made this a research priority. NICE went on to recommend: • Excluding reversable causes such as fever, electrolyte disturbance, drugs, poor sleep, pain and excessive environmental stimulation • Awareness that other neurological symptoms (such as dystonia) could mimic seizures. • Communicating actively with parents and CYP felt to be at risk of seizures at EoL • Discussing the impact of various treatment choices on preferred place of care • Anticipatory prescribing of first line rescue medication for seizures The APPM guideline development group agreed to adopt these recommendations.
DESIRABLE EFFECTS	How substantial are the desirable anticipated effects? ☐ Trivial ☐ Small ☐ Moderate ☒ Large ☐ Varies ☐ Don't know	*Summary of studies found (Gemma)*	**Non-pharmacological** **<u>Sensory implications in seizures:</u>** Consideration of sensory implications should be given to management of seizures at the end of life. The literature review found a case report of a child with Dravet syndrome who responded to a trial of eye patching resulting in improvement in his seizure activity after a few months of starting the patching (9). The guideline development group also agreed that adapting the patient's environment, for example changing the room lighting, temperature and noise level, at the end of life, may have an impact on reducing seizure activity. **<u>Treatments lying outside the scope of this guideline</u>** The treatments listed below featured in numerous published articles relating to managing seizures in children who have diagnoses requiring palliative care support, however they fall outside of the usual practice of palliative care teams (ie are overseen by other services). They are therefore mentioned below for awareness only.

1.Ketogenic diet

There may be benefits in trialing a ketogenic diet and it is recommended in the NICE guidance for epilepsy which has not responded to standard anti-epileptic drugs (AEDs) (3). The literature review found a case report of a child with Niemann Pick C who responded well to ketogenic diet in combination with levetiracetam and clobazam(4). We recommend liaising with tertiary neurology services to discuss this if deemed appropriate.

2.Epilepsy surgery

Some patients with seizures palliative care needs may benefit from a neurosurgical opinion to consider epilepsy surgery. Referral for this is also via the CESS(5). There are some studies demonstrating improved quality of life following epilepsy surgery for tuberous sclerosis(6, 7). Liaison with neurologists and neurosurgeons is recommended.

3.Neurostimulation

Neurostimulation emerged as a potential treatment for refractory epilepsy within the guideline literature review. Broadly, neurostimulation is divided into invasive and non-invasive procedures (20), with both procedures usually well tolerated. VNS is a type of invasive neurostimulation, which is discussed in further detail below.

Much of the literature from the guideline search used the term 'palliative' although it was often unclear whether the patient was palliative, or whether they had a brain lesion not amenable to traditional neurosurgical intervention. Case reports have suggested an improvement in seizure frequency in paediatric patients following neurostimulation (18).

4.Vagal nerve stimulator (VNS):

VNS works via an implantable device sending regular electrical signals to the left vagus nerve. Although it can take up to 2 years to work, it has been shown to reduce anti-epileptic medication use in patients with complex seizures not amenable to epilepsy surgery(8). In some complex seizure disorders a neurology and/or neurosurgical opinion may be beneficial to consider the role of VNS. Referral is usually via the Children's Epilepsy Surgery Service (CESS)

Pharmacological

Some patients with palliative care needs will have an individualized seizure care plan (3) which should be followed. For clarity, we have considered treatment for status epilepticus separately from other drugs which might be helpful for managing seizures at the end of life.

Status epilepticus treatment:

Step 1: First line management of status epilepticus in both the palliative and non-palliative paediatric setting (8) usually involves benzodiazepines. Buccal midazolam is more commonly used than rectal diazepam as rescue therapy and is twice as potent as rectal diazepam. Intravenous lorazepam is not commonly used in palliative care settings as this administration route is often not available.

Step 2: Repeat benzodiazepine after 10 minutes

Step 3: Rectal paraldehyde (9,10)

Step 4: Phenobarbitone half loading dose 10mg/kg enterally or SC (which can be repeated OR Levetiracetam loading dose added)
Step 5: Continuous infusion of Midazolam OR Levetiracetam OR Phenobarbitone
The proposed steps above are based on the APLS guidance for status epilepticus, but adapted for use in children whose goals of care are not likely to be me by admission to PICU, with intubation & ventialtion. The guideline committee felt that this allowed more fredom of prefered place of care, and reduced the risk of inapproapriate intensification in the context of a dying child with uncrontrolled seizures.

APLS management of seizures suggests two doses of midazolam before moving on to a different medication. In the palliative population the consensus of expert opinion was that people would consider 4 doses of midazolam/24 hours.

If a patient is on a midazolam infusion with increasing frequency of breakthrough seizures or diminished response to successive increases, the consensus of expert opinion was to consider the use of other adjunctive medications.

The guidline group agreed that when caring for patients at the end of life, there is no role for phenobarbitone levels or liver function tests, this was further supported by the results of the Delphi study. Should the patient later stabilise, there may be a role for phenobarbitone levels to inform a review of ongoing anticonvulsant medication.

Other Pharmacological Treatments:

Steroids:
The use of steroids need careful consideration when using in management of seizures at the end of life. Neurology practice can vary across the UK and seeking input from the local team is important.
There was little experience of the use of steroids in seizures in the palliative setting outside of the management of brain tumours, as observed in the Delphi study. However, there is anecdotal evidence of the effective use of steroids in epilepsia continua partialis (epileptic encephalopathy) and infantile spasms in liaison with neurology.

Cannabidiol:
NICE has published specific guidance on cannabidiol with clobazam for treating seizures associated with Lennox-Gastaut syndrome and Dravet syndrome. This is because published randomised controlled trials have focused on the use of pure CBD in people with these conditions only. People with these epilepsy syndromes did however report a very high rate of adverse events. NICE reviewed the limited evidence in other types of epilepsy, and agreed that it did not warrant a practice recommendation. They did not make a recommendation against the use of cannabis-based medicinal products in other situations, as this would restrict further research in this area and would prevent people who are currently apparently benefiting from continuing with their treatment
Specialists, people with epilepsy and their carers should continue to make treatment decisions in the

			best interests of each person with epilepsy. However, people seeking treatment for severe epilepsy should be made aware that currently there is no clear evidence of the safety and effectiveness of cannabis-based medicinal products. NICE has made research recommendations on the use of cannabis-based medicinal products for severe treatment-resistant epilepsy. In practice these are usually prescribed by a specialist neurologist. **Chloral hydrate** A BPNA position statement (15) from 2021, outlines considerations for off-label use of chloral hydrate to manage distressing symptoms in patients with movement and motor disorder when all other therapies have failed. <u>Where use of chloral hydrate is considered appropriate:</u> -informed consent to use chloral hydrate must be obtained and documented -use must be under the supervision of a named consultant with appropriate experience and competency in paediatric neurology, neurodisability, and/or palliative care who must regularly review the patient, being alert to signs of inappropriate use and aiming to de-escalate wherever possible. -A written emergency escalation plan which includes the contact details for the supervising clinical team should be provided to the family and other healthcare professionals. Such plans should specify a maximum number of doses per month or continuous days of treatment above which the patient should be reassessed by the relevant specialist team. The Guideline Group consensus opinion is that chloral hydrate may play a role in reducing triggers for the population group described in this guideline.
UNDESIRABLE EFFECTS	How substantial are the undesirable anticipated effects? ☐ Large ☒ Moderate ☐ Small ☐ Trivial ☐ Varies ☐ Don't know		Treatment aimed at seizure reduction must be weighed against adverse effects such as sedation. In some cases, it may be preferable to tolerate breakthrough seizures, in order to preserve wakefulness, however in the case of refractory status epilepticus, treatment escalation is more clearly appropriate. Along with sedation, the guideline development group also discussed the risk of respiratory depression and felt that both could be ethically tolerated if with the primary intention to relieve distress in refractory seizures at the end of life, and with clear communication with families about anticipated benefits and burdens. Attention also needs to be paid to undesirable effects of particular formulations of certain anti-epileptic medications, such as the high alcohol content of phenobarbitone liquid.

CERTAINTY OF EVIDENCE	What is the overall certainty of the evidence of effects? ☐ Very low ☒ Low ☐ Moderate ☐ High ☐ No included studies	*Gemma can add something from GRADE*	Although there is very limited research evidence available, there is appreciable consensus amongst healthcare professionals in managing seizures in a paediatric palliative care setting. A Delphi study was undertaken to further address areas of uncertainty after the GDG meeting. 31 Healthcare professionals working in PPC replied to this study. Key findings included that few people had had to use phenobarbitone doses larger than those in the APPM formulary, and the group did not advocate monitoring drug levels of phenobarbitone (or liver function tests) when the drug was being used in a palliative context. Around a quarter of respondents had used subcutaneous levetiracetam in a palliative setting. The groups had little experience of using steroids for seizures, outside of their role in brain tumours, but there was some anecdotal use in epileptic encephalopathies (usually in tandem with neurologists). Lastly, we noted a high rate of neutral responses in the Delphi results, potentially confirming lack of confidence among those replying.
VALUES	Is there important uncertainty about or variability in how much people value the main outcomes? ☐ Important uncertainty or variability ☐ Possibly important uncertainty or variability ☐ Probably no important uncertainty or variability ☒ No important uncertainty or variability		Some children, young people or their families may value alertness over complete resolution of seizure clusters, and it is important to establish with them where their priority lies. This balance may also fluctuate over time for the same child or their family. In the case of status epilepticus, the bablance will tilt in favour of treatment. Otherwise, preferemce may depend on the child's age, awareness and perception of their symptoms, and perceived benefits and harms of treatment. Routes of adminsitration are likely to affect the feasability of certain prefered places of care. If parentral therapy is needed, subcutaneous infusions are more likely to make treatment possible in a hospice or at home. Some treatments, such as the use of steroid pulses (other than for treating peri-tumour oedema in CNS cancer) should be undertaken in collaboration with a paediatric neurologist.
BALANCE OF EFFECTS	Does the balance between desirable and undesirable effects favor the intervention or the comparison? ☐ Favors the comparison ☐ Probably favors the comparison ☐ Does not favor either the intervention or the comparison ☐ Probably favors the intervention ☒ Favors the intervention ☐ Varies ☐ Don't know		Most pharmacological intervention for seizures can cause sedating effects and require the use of starting doses with titration to agreed clinical effect or benefit of the individualised CYP. The balance between desirable and undesirable effects of any of the pharmacological interventions may fluctuate over the course of the CYP's illness requiring regular re-evaluation of purpose and benefit of the specific medication and the needs of the CYP. Communication about anticipated benefits and burdens of all treatments with CYP and parents / carers is paramount.

RESOURCES REQUIRED	How large are the resource requirements (costs)? ☐ Large costs ☐ Moderate costs ☒ Negligible costs and savings ☐ Moderate savings ☐ Large savings ☐ Varies ☐ Don't know		The interventions outlined in the guidance are already part of clinical practice, so there should not be significant cost implications in these recommendations. It is important to consider the cost of medications used, as well as any associated cost of human resources (such as community nursing care). Whilst no economic-impact assessment was carried out for this guideline, NICE NG61 considered the cost of community nursing time in delivering subcutaneous infusions to be cost-saving compared to intensive care admission. Most of the pharmacological interventions used to treat seizures are relatively cheap. Buccal preparations of midazolam are more expensive than other preparations of this drug, but their use is important because of their convenience and ease of administration by children, young people and their families and carers. This made it easier to support children and young people in their preferred place of care.
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	What is the certainty of the evidence of resource requirements (costs)? ☐ Very low ☐ Low ☐ Moderate ☐ High ☒ No included studies	*Ref: NICE NG61 health economic impact comparing community nursing care with PICU admission*	
COST EFFECTIVENESS	Does the cost-effectiveness of the intervention favor the intervention or the comparison? ☐ Favors the comparison ☐ Probably favors the comparison ☐ Does not favor either the intervention or the comparison ☒ Probably favors the intervention ☐ Favors the intervention ☐ Varies ☐ No included studies		No formal health economic impact study was conducted (see above)
EQUITY	What would be the impact on health equity? ☐ Reduced ☐ Probably reduced		Children would ideally have equal access to good symptom management regardless of their choice of setting, and wherever they lived within the UK. In reality there may be differences in availability for out of hours support from children's community nurses in different regions (including between rural and urban settings). Availability of 24/7 support (including by phone) from specialist medical professionals

	☐ Probably no impact ☐ Probably increased ☒ Increased ☐ Varies ☐ Don't know		may also not be ubiquitous. Specialist paediatric neurologists may not be involved in the care of all children with seizures who are in receipt of end of life care.
ACCEPTABILITY	Is the intervention acceptable to key stakeholders? ☐ No ☐ Probably no ☐ Probably yes ☐ Yes ☐ Varies ☐ Don't know		It is very important to establish trust with stakeholders: children, young people and their carers. This may be achieved through consistency of message, acknowledging uncertainty, and considering pre-emptive discussions. It is vital to establish the child and family's preferences (eg. routes of administration, preferred place of care) and support these wherever possible. Good timely communication tailored to the family's needs and wishes is key.
FEASIBILITY	Is the intervention feasible to implement? ☐ No ☐ Probably no ☐ Probably yes ☒ Yes ☐ Varies ☐ Don't know		Not a big change in clinical practice. All drugs listed are in APPM formulary The interventions outlined in the guidance are already part of widespread clinical practice, so there should not be significant issues with implementation. There may be the need for some educational support to embed guidance in to clinical practice.

Summary of judgements

	Judgement							Implications
PROBLEM	No ☐	Probably no ☐	Probably yes ☐	Yes ☒		Varies ☐	Don't know ☐	
DESIRABLE EFFECTS	Trivial ☐	Small ☐	Moderate ☐	Large ☒		Varies ☐	Don't know ☐	
UNDESIRABLE EFFECTS	Large ☐	Moderate ☒	Small ☐	Trivial ☐		Varies ☐	Don't know ☐	
CERTAINTY OF EVIDENCE	Very low ☐	Low ☒	Moderate ☐	High ☐			No included studies ☐	
VALUES	Important uncertainty or variability ☐	Possibly important uncertainty or variability ☐	Probably no important uncertainty or variability ☒	No important uncertainty or variability ☐				
BALANCE OF EFFECTS	Favors the comparison ☐	Probably favors the comparison ☐	Does not favor either the intervention or the comparison ☐	Probably favors the intervention ☐	Favors the intervention ☒	Varies ☐	Don't know ☐	
RESOURCES REQUIRED	Large costs ☐	Moderate costs ☐	Negligible costs and savings ☒	Moderate savings ☐	Large savings ☐	Varies ☐	Don't know ☐	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low ☐	Low ☐	Moderate ☐	High ☐			No included studies ☒	
COST EFFECTIVENESS	Favors the comparison ☐	Probably favors the comparison ☐	Does not favor either the intervention or the comparison ☒	Probably favors the intervention ☐	Favors the intervention ☐	Varies ☐	No included studies ☐	
EQUITY	Reduced ☐	Probably reduced ☐	Probably no impact ☐	Probably increased ☐	Increased ☒	Varies ☐	Don't know ☐	
ACCEPTABILITY	No ☐	Probably no ☐	Probably yes ☒	Yes ☐		Varies ☐	Don't know ☐	
FEASIBILITY	No ☐	Probably no ☐	Probably yes ☒	Yes ☐		Varies ☐	Don't know ☐	

Recommendations

TYPE OF RECOMMENDATION	Strong recommendation against the option ☐	Conditional recommendation against the option ☐	Conditional recommendation for either the option or the comparison ☐	Conditional recommendation for the option ☒	Strong recommendation for the option ☐

RECOMMENDATION

General Principles:

- Some CYP will have an individualised seizure plan already in place, which should be followed in the first instance
- Communication with families is a key component of manging seizures at the end of life
- Care should be paid to situations with may lower seizure threshold (intercurrent illness, pain, electrolyte disturbance)

Management Algorithm:

1. Identify those at risk (underlying condition predisposes to seizures or clinical condition compromises seizure control)
2. Be prepared (Discuss treatment options, anticipatory prescribing)
3. Define seizure activity (differentiate from other neurological events, define type / pattern)
4. Pharmacological interventions (stepwise approach as per Harris et al)
5. Supportive Care (maintain calm environment, ensure comfort, align with goals of care)
6. Review and revise

Pharmacological step-wise approach of status epilepticus:

- Initial emergency treatment buccal midazolam / rectal diazepam (or IV lorazepam in a hospital setting)
- Wait 10-15 minutes and repeat
- After a further 10-15 minutes give rectal paraldehyde
- After a further 15 minutes start a subcutaneous infusion of midazolam (unless IV therapy is preferred, in which case follow APLS guidance)
- If this is not adequate to gain acceptable control of seizures, load with phenobarbitone

Other pharmacological options

Steroids: whilst there was little experience outside of the management of raised intracranial pressure, there may be a role in epileptic encephalopathy, when working jointly with paediatric neurology services.

Cannabidiol: evidence is limited to Dravet & Lennox-Gastaut syndromes, and cannabis-based medicinal products should be prescribed by a paediatric neurologist.

Chloral Hydrate: use only in the context of the BPNA statement, and may have a role in reducing seizure triggers in the palliative care population

Non-pharmacological considerations

Consideration of environmental sensory implications should be given to management of seizures at the end of life.

	End of life care In the case of patients felt to be actively approaching end of life, with burdensome continued seizure activity, the doctrine of double effect makes it ethically acceptable to consider the use of higher doses of benzodiazepines and / or phenobarbitone than those in standard formularies, as long as the primary intent is to terminate seizure activity. There is therefor no 'maximum' dose for a subcutaneous infusion of these medications, but such higher doses should usually involve advise from an expert in Paediatric Palliative Care or Paediatric Neurologist.
JUSTIFICATION	In the presence of very limited evidence, recommendations were made based on the opinion of the panel, supported by the Delphi study described above. The panel looked at the NICE recommendations on End-of-Life Care for Infants Children and Young People with Life Limiting Conditions (NG61), as well as other existing guidance on the management of seizures in paediatric palliative populations. Agreed not to provide specific guidance on doses (and refer to BNF and APPM formulary)
SUBGROUP CONSIDERATIONS	Children with inoperable brain tumours (re-use of steroids) Neonates with infantile spasms
IMPLEMENTATION CONSIDERATIONS	• Are there any limitations/ barriers when caring for a child at home / in hospice? • Access to specialist support for complex medications and 24/7 support in the home • Availability of support from Paediatric Neurology where required
MONITORING AND EVALUATION	Clinical audit of guidelines
RESEARCH PRIORITIES	• Prospective data capture on patients treated according to the guidance • Steroid use in epileptic encephalopathy (epilepsia partialis continua) • Phenobarbitone enteral loading (vs other routes) • Midazolam dosing (not ongoing work within the APPM Formulary group)

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