

APPM guidelines

Q1. Seizures

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Trusted evidence.
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Summary

This systematic review was performed as part of an APPM guideline on “Symptom management in children and young people receiving palliative care”

Review 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?

Selection criteria

See Methodology report for the full systematic review protocol.

Population

CYP with life limiting conditions and seizures and benefiting from a palliative care approach. This might be defined by complexity, route of drug administration, place of care or phase of illness.

Intervention

- Pharmacological interventions
- Non-pharmacological interventions

Surgical procedures are excluded from this review.

Comparison

- Placebo
- No treatment / usual care
- Cross comparison between any of the above (within group and between group)
- Combinations of the above
- Routes of administration (same drug or same drug class)

Outcomes

Effectiveness, safety, and satisfaction.

Study design

Randomised controlled trials (RCTs) and observational comparative studies were prioritised for inclusion. Evidence from non-comparative studies was recorded; however, the results were not included in the GRADE Summary of Findings tables.

Methods

Search methods

MEDLINE (Ovid) and Embase (Ovid), Cochrane CENTRAL (Wiley) and PsycINFO (OVID) were searched on April 6, 2021. All databases were searched from inception and no language restrictions were used. See Appendix 1 for search strategy details.

Data collection and analysis

Screening, data extraction and risk of bias assessments were performed in duplicate by two independent reviewers.

For the risk of bias assessment, we used the Cochrane 'Risk of Bias' tool for RCTs (Higgins 2011).

Risk ratios (RRs) and their 95% confidence intervals (CI) were calculated for dichotomous outcome data.

Summarising and interpreting results

We used the GRADE approach to interpret findings and create 'Summary of findings' tables following the GRADE handbook (Schünemann 2019).

Search results

We retrieved a total of 2517 records. After deduplication, 2243 unique abstracts were screened. We retrieved the full text of 265 records and after

screening excluded 261 records. We identified one RCT, one case series and two case reports.

See Appendix 2 for PRISMA flowchart of the screening and study selection process, and Appendix 3 for list of excluded studies.

Included studies

One RCT was identified for inclusion. We also identified one cases series and two case reports.

See PRISMA flowchart in Appendix 2 and list of excluded studies with exclusion reason in Appendix 3.

Main results

Pharmacological interventions

1_Hormonal therapy with vigabatrin compared to hormonal therapy alone

We identified one RCT (O'Callaghan 2017) with 377 infants who had a clinical diagnosis of infantile spasms and a hypsarrhythmic (or similar) EEG. The study compared hormonal therapy in combination with vigabatrin (n = 186) versus hormonal therapy alone (n = 191). See Summary of Findings, Characteristics of included studies and Forest plots.

Spams

Combination therapy may increase spasm cessation compared to hormonal therapy alone (RR 1.26; 95% CI 1.08 to 1.47; n = 377; low-certainty evidence). The evidence was downgraded due to indirectness and imprecision.

Time to treatment response

Treatment response may be faster on combination therapy than on hormonal therapy alone (median 2 days vs 4 days; p<0.001; low certainty evidence). The

evidence was downgraded due to indirectness and imprecision.

Adverse events

There may no difference in adverse event reactions (RR 1.08; 95% CI 0.92 to 1.27; n = 377; low certainty evidence) and serious adverse event reactions (RR 1.09; 95% CI 0.57 to 2.09; n = 377; very-low certainty evidence). The evidence was downgraded due to indirectness and imprecision.

2_Phenytoin (no comparison group)

We identified one case series (Miyahara 2009) that reported on the use of Phenytoin in patients with

Progressive myoclonus epilepsy (PME) refractory to Benzodiazepines. See Appendix 4 for a summary of the main results.

Non-pharmacological interventions

1_Ketogenic diet (no comparison group)

One case report (Holler 2021) reported on the use of ketogenic diet delivered via enteral feeding tube in a girl aged 14 with Niemann-Pick type C. See Appendix 4 for a summary of the main results.

2_Monocular eye patching (no comparison group)

Another case report (Choi 2011) reported on the use of alternating monocular eye patching in a 2 year-old boy with Dravet syndrome. See Appendix 4 for a summary of the main results.

Indirect evidence

The Guideline Development Group also identified additional supporting indirect evidence that they considered useful to guide discussion around recommendations. A summary table is presented in Appendix 5.

Characteristics of included studies

Study details	Methods	Participants	Interventions	Outcomes measured in the study	Risk of bias summary														
<p>Ref ID 585</p> <p>O'Callaghan 2017</p> <p>Clinical registration: ISRCTN 54363174; EUDRACT number 2006-000788-27</p> <p>Conflict of interest: not reported</p> <p>Funding: The Castang Foundation, Bath Unit for Research in Paediatrics, National Institute of Health Research, the Royal United Hospitals Bath NHS Foundation Trust, the BRONNER-BENDUNG Stiftung/Gernsbach, and University Children's Hospital Zurich.</p> <p>Contact details: f.o'callaghan@ucl.ac.uk</p>	<p>Study design: multicentre open-label RCT</p> <p>Study dates: March 2007 to May 2014</p> <p>Setting: 102 hospitals (Australia [three], Germany [11], New Zealand [two], Switzerland [three], and the UK [83])</p>	<p>Infants who had a clinical diagnosis of infantile spasms and a hypsarrhythmic (or similar) EEG no more than 7 days before enrolment</p> <p>N = 377</p>	<ul style="list-style-type: none"> • Hormonal therapy with vigabatrin (n = 186) • Hormonal therapy alone (n = 191) 	<ul style="list-style-type: none"> • Spasms • Hospitalisation • Adverse reactions • Mortality 	<p>ROB summary</p> <table border="1"> <thead> <tr> <th>Sequence</th> <th>Allocation</th> <th>Performance</th> <th>Detection</th> <th>Attrition</th> <th>Reporting</th> <th>Other</th> </tr> </thead> <tbody> <tr> <td style="background-color: #90EE90;">+</td> <td style="background-color: #90EE90;">+</td> <td style="background-color: #FF0000;">-</td> <td style="background-color: #90EE90;">+</td> <td style="background-color: #90EE90;">+</td> <td style="background-color: #90EE90;">+</td> <td style="background-color: #90EE90;">+</td> </tr> </tbody> </table>	Sequence	Allocation	Performance	Detection	Attrition	Reporting	Other	+	+	-	+	+	+	+
Sequence	Allocation	Performance	Detection	Attrition	Reporting	Other													
+	+	-	+	+	+	+													

Summary of Findings

SOF 1. Combination therapy versus hormonal therapy alone

Q2. Combination therapy versus hormonal therapy alone for the management of seizures

Patient or population: Infants who had a clinical diagnosis of infantile spasms and a hypsarrhythmic (or similar) EEG no more than 7 days before enrolment

Setting: Australia [three], Germany [11], New Zealand [two], Switzerland [three], and the UK [83])

Intervention: Combination therapy

Comparison: Hormonal therapy

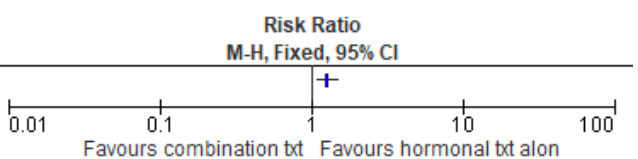
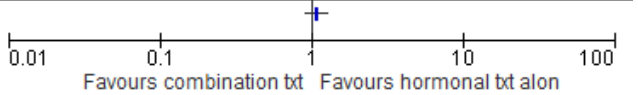
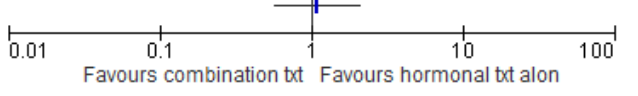
Outcomes	Anticipated absolute effects* (95% CI)		Risk difference with combination therapy	Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with risperidone	Risk with olanzapine					
<p>Cessation of spasms</p> <p>As recorded by parents and carers in a seizure diary</p> <p>Follow-up: 14 to 42 days</p>	-	-	-	RR 1.26 (1.08 to 1.47)	377 (1 RCT) ¹	⊕⊕○○ LOW ^{a, b, c}	<p>Combination therapy may increase spasm cessation compared to hormonal therapy alone.</p> <p>The treatment effect favouring combination therapy in the primary outcome remained significant in a logistic regression analysis that controlled for risk of developmental impairment, type of hormone treatment, and whether or not hormonal treatment was randomised (OR 2.1; 95% CI 1.3 to 3.2); p = 0.001</p>
<p>Time to treatment response</p>	Median 4 days	Median = 2 days		P < 0.001	377 (1 RCT) ¹	⊕⊕○○ LOW ^{a, b, c}	<p>Treatment response may be faster on combination therapy (time 2 days [IQR 2–4 median response]) than hormonal therapy (median response time 4 days [3–6]; z=6.04, p<0.001, Wilcoxon)</p>

Outcomes	Anticipated absolute effects* (95% CI)		Risk difference with combination therapy	Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with risperidone	Risk with olanzapine					
Adverse events				RR 1.08 (0.92 to 1.27)	377 (1 RCT) ¹	⊕⊕○○ LOW ^{a,b,d}	Combination treatment may have little or no impact on adverse event reactions.
Serious adverse events, including deaths				RR 1.09 (0.57 to 2.09)	377 (1 RCT) ¹	⊕○○○ VERY LOW ^{a,b,e}	We do not know about the effect of combination treatment on serious adverse reactions.

1. O'Callaghan 2017

- a. Single study, inconsistency cannot be assessed
- b. Downgraded 1 level due to indirectness (unclear if children are receiving palliative care)
- c. Downgraded 1 level due to imprecision: small sample size
- d. Downgraded 1 level due to imprecision: small sample size and wide confidence interval that incorporates the possibility of harm and no effect
- e. Downgraded 2 levels due to imprecision: small sample size and few events and wide confidence interval that incorporates the possibility of benefit and harm

Forest plots

Outcome	Forest plots						Certainty of the evidence (GRADE)
<p>Cessation of spasms</p> <p>As recorded by parents and carers in a seizure diary</p> <p>Follow-up: 14 to 42 days</p> <p>[RCT]</p>	<p>Study or Subgroup</p> <p>'Callaghan 2017</p>	<p>Combination treatment</p> <p>Events Total</p> <p>133 186</p>	<p>Hormonal txt alone</p> <p>Events Total</p> <p>108 191</p>	<p>Risk Ratio</p> <p>M-H, Fixed, 95% CI</p> <p>1.26 [1.08, 1.47]</p>	 <p>Risk Ratio</p> <p>M-H, Fixed, 95% CI</p> <p>0.01 0.1 1 10 100</p> <p>Favours combination txt Favours hormonal txt alone</p>	<p>⊕⊕○○</p> <p>LOW</p>	
<p>Adverse events</p> <p>[RCT]</p>	<p>Study or Subgroup</p> <p>'Callaghan 2017</p>	<p>Combination treatment</p> <p>Events Total</p> <p>117 186</p>	<p>Hormonal txt alone</p> <p>Events Total</p> <p>111 191</p>	<p>Risk Ratio</p> <p>M-H, Fixed, 95% CI</p> <p>1.08 [0.92, 1.27]</p>	 <p>Risk Ratio</p> <p>M-H, Fixed, 95% CI</p> <p>0.01 0.1 1 10 100</p> <p>Favours combination txt Favours hormonal txt alone</p>	<p>⊕⊕○○</p> <p>LOW</p>	
<p>Serious adverse events</p> <p>[RCT]</p>	<p>Study or Subgroup</p> <p>'Callaghan 2017</p>	<p>Combination treatment</p> <p>Events Total</p> <p>17 186</p>	<p>Hormonal txt alone</p> <p>Events Total</p> <p>16 191</p>	<p>Risk Ratio</p> <p>M-H, Fixed, 95% CI</p> <p>1.09 [0.57, 2.09]</p>	 <p>Risk Ratio</p> <p>M-H, Fixed, 95% CI</p> <p>0.01 0.1 1 10 100</p> <p>Favours combination txt Favours hormonal txt alone</p>	<p>⊕○○○</p> <p>VERY LOW</p>	

References

Included studies

O'Callaghan 2017

O'Callaghan, Finbar J. K., Edwards, Stuart W., Alber, Fabienne Dietrich, Hancock, Eleanor, Johnson, Anthony L., Kennedy, Colin R., Likeman, Marcus, Lux, Andrew L., Mackay, Mark, Mallick, Andrew A., Newton, Richard W., Nolan, Melinda, Pressler, Ronit, Rating, Dietz, Schmitt, Bernhard, Verity, Christopher M., Osborne, John P. 2017. Safety and effectiveness of hormonal treatment versus hormonal treatment with vigabatrin for infantile spasms (ICISS): A randomised, multicentre, open-label trial *The Lancet Neurology*, 16(1): 33-42.

Observational non-comparative studies

Choi 211

Choi C, Khuddus N, Mickler C, Tuli S, Tuli S. Occlusive patch therapy for reduction of seizures in Dravet syndrome. *Clinical pediatrics*. 2011 Sep;50(9):876-8.

Höller 2021

Höller A, Albrecht U, Sigl SB, Zöggeler T, Ramoser G, Bernar B, Karall D, Scholl-Bürgi S. Successful implementation of classical ketogenic dietary therapy in a patient with Niemann-Pick disease type C. *Molecular Genetics and Metabolism Reports*. 2021 Jun 1;27:100723.

Miyahara 2009

Miyahara A, Saito Y, Sugai K, Nakagawa E, Sakuma H, Komaki H, Sasaki M. Reassessment of phenytoin for treatment of late stage progressive myoclonus epilepsy complicated with status epilepticus. *Epilepsy research*. 2009 Apr 1;84(2-3):201-9.

Other references

Sterne 2016

Sterne JAC, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomized studies of interventions. *BMJ* 2016; 355; i4919.

Schünemann 2019

Schünemann HJ, Vist GE, Higgins JPT, Santesso N, Deeks JJ, Glasziou P et al. Interpreting results and drawing conclusions. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editors(s). *Cochrane Handbook for Systematic Reviews of Interventions*. Version 6.0 edition. Available from www.training.cochrane.org/handbook: Cochrane, 2019: Chapter 15.

Declarations of interest

Cochrane Response, which is an evidence consultancy operated by The Cochrane Collaboration, was commissioned to perform this review for the WHO. All Cochrane Response authors declare no conflicts of interest.

All signed declarations of interest can be found on the following link: <https://community.cochrane.org/organizational-info/people/conflict-interest/cet>

Acknowledgments

We thank Elise Cogo (Cochrane Response) for running the search strategy.

Appendix 1. Search strategy

MEDLINE (Ovid) Search Strategy (Revised April 6, 2021)

1. ADOLESCENT/ or MINORS/
2. (adolescen\$ or teen\$ or youth\$ or young or juvenile? or minors or highschool\$).mp,jw,nw.
3. exp CHILD/
4. (child\$ or schoolchild\$ or "school age" or "school aged" or preschool\$ or pre-school* or toddler\$ or kid? or kindergar\$ or boy? or girl?).mp,jw,nw.
5. exp INFANT/
6. (infan\$ or neonat\$ or newborn\$ or baby or babies).mp,jw,nw.
7. exp PEDIATRICS/ or exp PUBERTY/
8. (p?ediatric\$ or pubert\$ or prepubert\$ or pubescen\$ or prepubescen\$).mp,jw,nw.
9. or/1-8
10. limit 9 to ("middle age (45 to 64 years)" or "middle aged (45 plus years)" or "all aged (65 and over)" or "aged (80 and over)")
11. limit 9 to ("all infant (birth to 23 months)" or "all child (0 to 18 years)" or "newborn infant (birth to 1 month)" or "infant (1 to 23 months)" or "preschool child (2 to 5 years)" or "child (6 to 12 years)" or "adolescent (13 to 18 years)")
12. 10 not 11
13. 9 not 12
14. TERMINALLY ILL/
15. ((terminal\$ or final or advance\$ or incurable or life limit\$) adj3 (ill\$ or disease\$ or condition\$)).mp.
16. dying.mp.
17. (end adj3 life).mp.
18. ((approach\$ or close\$ or near\$ or imminent\$ or impending) adj3 death).mp.
19. (Body adj2 (shut? down or shutting down or deteriorat\$)).mp.
20. (deathbed? or death bed? or passing away or passing on or expiring or expiration or syringe driver*).mp.
21. ((last or final) adj1 (hour\$ or days\$ or minute\$)).mp.

22. (last year of life or LYOL or life\$ end).mp.
23. (advance\$ stage? or final stage? or end stage? or last stage? or late stage? or terminal stage?).mp.
24. ((advanced or late or last or end or final or terminal) adj phase\$).mp.
25. RESUSCITATION ORDERS/
26. (resuscitat\$ adj3 (policies or policy or order? or decision? or withhold\$)).mp.
27. ADVANCE DIRECTIVES/
28. advance? directive?.mp.
29. LIVING WILLS/
30. living will?.mp.
31. TERMINAL CARE/
32. (terminal\$ adj3 (care\$ or caring)).mp.
33. PALLIATIVE CARE/
34. palliat\$.mp.
35. HOSPICE CARE/
36. hospice?.mp.
37. or/14-36
38. exp Seizures/
39. (seiz\$ or convuls\$ or epilep* or fits or anticonvulsant*).mp.
40. (midazolam or clobazam or clonazepam or levetiracetam or phenobarbital or diazepam or lorazepam or paraldehyde or phenytoin or cannabinoid* or ketamine or ketogenic diet*).mp.
41. 38 or 39 or 40
42. 9 and 37 and 41
43. 37 and 41
44. limit 43 to ("all infant (birth to 23 months)" or "all child (0 to 18 years)" or "newborn infant (birth to 1 month)" or "infant (1 to 23 months)" or "preschool child (2 to 5 years)" or "child (6 to 12 years)" or "adolescent (13 to 18 years)")

45. 42 or 44

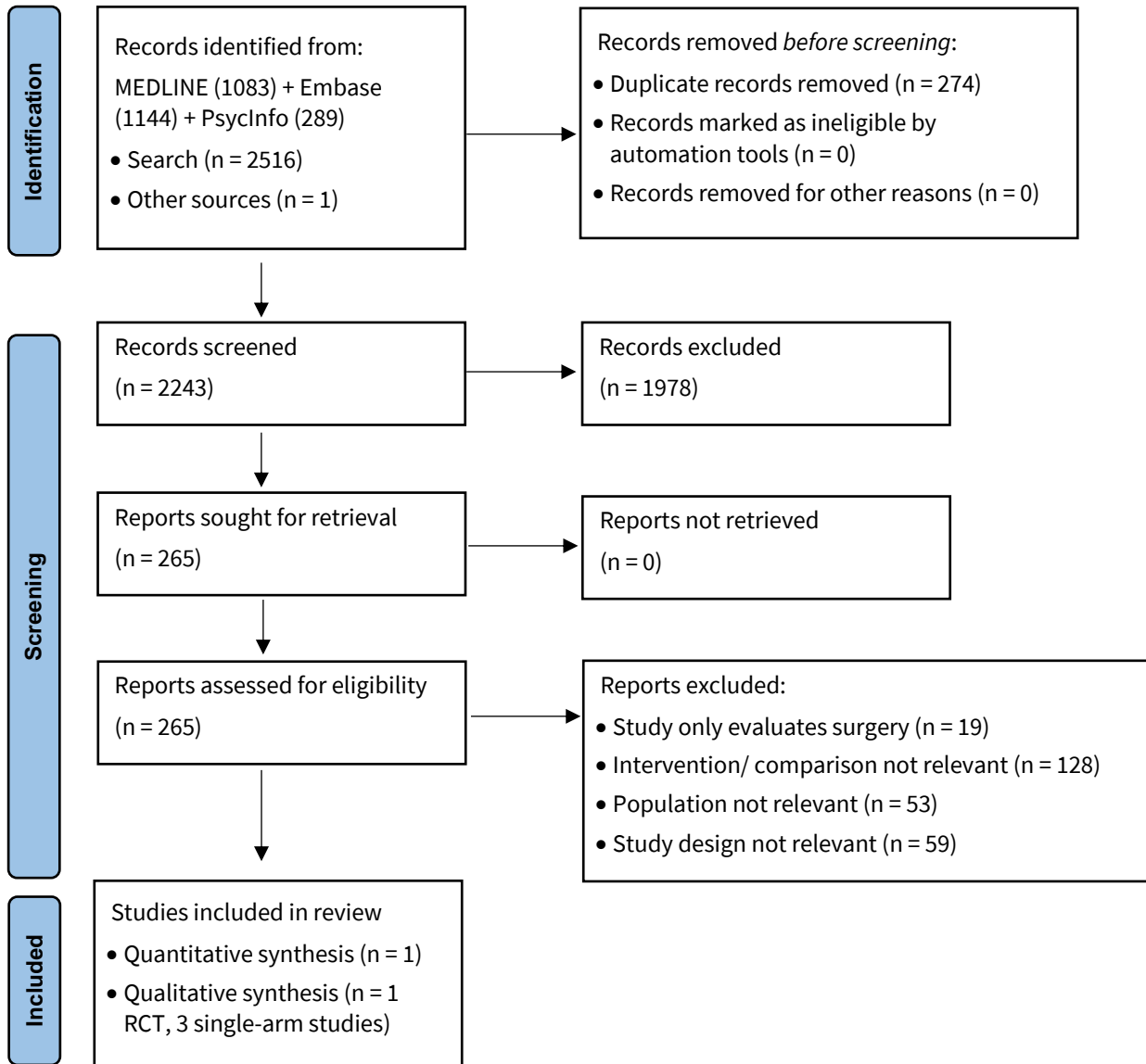
46. exp animals/ not humans/

47. 45 not 46

48. (comment or historical article or news).pt.

49. 47 not 48

Appendix 2. PRISMA flowchart



Appendix 3. Excluded studies

Ref ID	Bibliography	Reason for exclusion
10	Strzelczyk, Adam, Schubert-Bast, Susanne 2021. Expanding the Treatment Landscape for Lennox-Gastaut Syndrome: Current and Future Strategies CNS drugs, 35(1): 61-83.	Study design not relevant
26	Madaan, Priyanka, Gupta, Ajay, Gulati, Sheffali 2021. Pediatric Epilepsy Surgery: Indications and Evaluation Indian journal of pediatrics, #volume#(#issue#): #Pages#.	Study ONLY evaluates surgery
51	Valiakhmetova, Andge, Gorelyshev, Sergey, Konovalov, Alexander, Trunin, Yuri, Savateev, Alexander, Kram, David E., Severson, Eric, Hemmerich, Amanda, Edgerly, Claire, Duncan, Daniel, Britt, Nicholas, Huang, Richard S. P., Elvin, Julia, Miller, Vincent, Ross, Jeffrey S., Gay, Laurie, McCorkle, Joshua, Rankin, Andrew, Erlich, Rachel L., Chudnovsky, Yakov, Ramkissoon, Shakti H. 2020. Treatment of Pediatric Glioblastoma with Combination Olaparib and Temozolomide Demonstrates 2-Year Durable Response The oncologist, 25(2): e198-e202.	Population not relevant
57	Sondhi, Vishal, Sharma, Suvasini 2020. Non-Pharmacological and Non-Surgical Treatment of Refractory Childhood Epilepsy Indian journal of pediatrics, 87(12): 1062-1069.	Study design not relevant
69	Sezer, Taner, Balci Sezer, Oya, Ozcay, Figen, Akdur, Aydinca, Torgay, Adnan, Haberal, Mehmet 2020. Efficacy of Levetiracetam for Epilepsy in Pediatric Liver Transplant Recipients With Posterior Reversible Encephalopathy Syndrome Experimental and clinical transplantation : official journal of the Middle East Society for Organ Transplantation, 18(Suppl 1): 96-98.	Population not relevant
114	Maeda, Sayaka, Kato, Itaru, Umeda, Katsutsugu, Hiramatsu, Hidefumi, Takita, Junko, Adachi, Souichi, Tsuneto, Satoru 2020. Continuous deep sedation at the end of life in children with cancer: experience at a single center in Japan Pediatric hematology and oncology, 37(5): 365-374.	Study design not relevant
121	Lee, Hsiu-Fen, Chi, Ching-Shiang, Tsai, Chi-Ren 2020. Electroclinical variability of pyridoxine-dependent epilepsy caused by ALDH7A1 gene mutations in four Taiwanese children Brain & development, 42(5): 393-401.	Intervention/ comparison not relevant
122	Kwon, Churl-Su, Schupper, Alexander J., Fields, Madeline C., Marcuse, Lara V., La Vega-Talbott, Maite, Panov, Fedor, Ghatan, Saadi 2020. Centromedian thalamic responsive neurostimulation for Lennox-Gastaut epilepsy and autism Annals of clinical and translational neurology, 7(10): 2035-2040.	Intervention/ comparison not relevant
126	Kucerova, I., Krysta, S. 2020. Clinical pharmacy in pediatric palliative care Klinicka Farmakologie a Farmacie, 34(2): 90-92.	Population not relevant
140	Hermann, J., Hermann, T. W. 2020. Bioavailability of drugs from suppositories in clinical practice after 1995 Acta Poloniae Pharmaceutica - Drug Research, 77(3): 417-421.	Study design not relevant
142	Harris, Nicola, Baba, Megumi, Mellor, Charlotte, Rogers, Rebekah, Taylor, Kirsty, Beringer, Antonia, Sharples, Peta 2020. Seizure management in children requiring palliative care: a review of current practice BMJ supportive & palliative care, 10(3): e22.	Intervention/ comparison not relevant
143	Harini, Chellamani, Nagarajan, Elanagan, Bergin, Ann M., Pearl, Phillip, Loddenkemper, Tobias, Takeoka, Masanori, Morrison, Peter F., Coulter, David, Harappanahally, Gita, Marti, Candice, Singh, Kanwaljit, Yuskaitis, Christopher, Poduri, Annapurna, Libenson, Mark H. 2020. Mortality in infantile spasms: A hospital-based study Epilepsia, 61(4): 702-713.	Intervention/ comparison not relevant

153	Garcia-Lopez, Isabel, Cuervas-Mons Vendrell, Margarita, Martin Romero, Irene, de Noriega, Inigo, Benedi Gonzalez, Juana, Martino-Alba, Ricardo 2020. Off-Label and Unlicensed Drugs in Pediatric Palliative Care: A Prospective Observational Study Journal of pain and symptom management, 60(5): 923-932.	Intervention/ comparison not relevant
168	Dangel, Tomasz, Kmiec, Tomasz, Januszaniec, Artur, Wazny, Barbara 2020. Palliative care in 9 children with neurodegeneration with brain iron accumulation Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology, 41(3): 653-660.	Population not relevant
190	A Alomar, Soha, J Saeedi, Rothaina 2020. Different modalities of invasive neurostimulation for epilepsy Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology, 41(12): 3527-3536.	Study design not relevant
204	Weaver, Meaghann S., White, Adam G., Robinson, Jacob 2019. Crossing the Line: Care of a Pediatric Patient with Intractable Seizures and Severe Neuropathic Pain in Absence of Access to Medical Marijuana Journal of palliative medicine, 22(10): 1232-1235.	Study design not relevant
216	Soo, A. K. S. 2019. Improving antiepileptic medication administration time reduces seizure duration and need for intensive care in paediatric status epilepticus Developmental Medicine and Child Neurology, 61(Supplement 1): 55.	Population not relevant
218	Shetty, A. 2019. Neurocutaneous melanosis Journal of the Neurological Sciences, 405(Supplement): 128-129.	Population not relevant
220	Sera, L., Morgan, J., McPherson, M. L. 2019. Are Pediatric Patients Just Short Adults? Most Commonly Prescribed Drugs for Pediatric Hospice Patients (S868) Journal of Pain and Symptom Management, 57(2): 517-518.	Study design not relevant
241	Orsini, Alessandro, Valetto, Angelo, Bertini, Veronica, Esposito, Mariagrazia, Carli, Niccolo, Minassian, Berge A., Bonuccelli, Alice, Peroni, Diego, Michelucci, Roberto, Striano, Pasquale 2019. The best evidence for progressive myoclonic epilepsy: A pathway to precision therapy Seizure, 71(#issue#): 247-257.	Study design not relevant
245	Nct 2019. Outcome Study in Refractory Epilepsy (SOPHIE) https://clinicaltrials.gov/show/NCT03939507 , #volume#(#issue#): #Pages#.	Population not relevant
250	Nct 2019. Decreasing Parental Stress of Caregivers of Infants With Infantile Spasms by Using Telemedicine Technology https://clinicaltrials.gov/show/NCT04086992 , #volume#(#issue#): #Pages#.	Population not relevant
251	Nct 2019. Web-Based Epilepsy Education Program for Adolescents and Parents https://clinicaltrials.gov/show/NCT04144478 , #volume#(#issue#): #Pages#.	Population not relevant
253	Nct 2019. Epilepsy Adherence in Children and Technology (eACT) https://clinicaltrials.gov/show/NCT03817229 , #volume#(#issue#): #Pages#.	Intervention/ comparison not relevant
273	Kuchenbuch, Mathieu, Barcia, Giulia, Chemaly, Nicole, Carme, Emilie, Roubertie, Agathe, Gibaud, Marc, Van Bogaert, Patrick, de Saint Martin, Anne, Hirsch, Edouard, Dubois, Fanny, Sarret, Catherine, Nguyen The Tich, Sylvie, Laroche, Cecile, des Portes, Vincent, Billette de Villemeur, Thierry, Barthez, Marie-Anne, Auvin, Stephane, Bahi-Buisson, Nadia, Desguerre, Isabelle, Kaminska, Anna, Benquet, Pascal, Nabbout, Rima 2019. KCNT1 epilepsy with migrating focal seizures shows a temporal sequence with poor outcome, high mortality and SUDEP Brain: A Journal of Neurology, 142(10): 2996-3008.	Study design not relevant
274	Kokoszka, M., McGoldrick, P., Wolf, S. M., Marcuse, L., Fields, M., Ghatan, S., Panov, F. E. 2019. Abstract #143: Responsive Neurostimulation for Non-Lesional Multifocal Epilepsy in Children Brain Stimulation, 12(2): e49.	Intervention/ comparison not relevant

287	Hqli, F., Santhanam, G. 2019. End of life care in children with neurodisability and concurrent palliative care needs: An audit of local Paediatric palliative services Archives of Disease in Childhood, 104(Supplement 2): A190-A191.	Intervention/ comparison not relevant
293	Gofton, Teneille E., Wong, Nora, Hirsch, Lawrence J., Hocker, Sara E. 2019. Communication Challenges: A Spotlight on New-Onset Refractory Status Epilepticus Mayo Clinic proceedings, 94(5): 857-863.	Study design not relevant
294	Geist, Marcus, Bardenheuer, Hubert, Burhenne, Juergen, Mikus, Gerd 2019. Alteration of drug-metabolizing enzyme activity in palliative care patients: Microdosed assessment of cytochrome P450 3A Palliative medicine, 33(7): 850-855.	Population not relevant
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1708	Wirrell, Elaine, Farrell, Kevin, Whiting, Sharon 2005. The Epileptic Encephalopathies of Infancy and Childhood <i>The Canadian Journal of Neurological Sciences / Le Journal Canadien Des Sciences Neurologiques</i> , 32(4): 409-418.	Study design not relevant
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1789	Jellinger, K. A. 2003. Rett Syndrome -- an update <i>Journal of neural transmission (Vienna, Austria : 1996)</i> , 110(6): 681-701.	Intervention/ comparison not relevant
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1828	Beardsmore, S., Fitzmaurice, N. 2002. Palliative care in paediatric oncology <i>European journal of cancer (Oxford, England : 1990)</i> , 38(14): 1900-10.	Intervention/ comparison not relevant
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1872	Krouwer, H. G., Pallagi, J. L., Graves, N. M. 2000. Management of seizures in brain tumor patients at the end of life <i>Journal of palliative medicine</i> , 3(4): 465-75.	Study design not relevant
1896	Marcdante, Karen Wendelberger 1999. "I Need to See Her Eyes Open" <i>Journal of Palliative Medicine</i> , 2(2): 219-220.	Intervention/ comparison not relevant
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1962	Nebeling, L. C., Lerner, E. 1995. Implementing a ketogenic diet based on medium-chain triglyceride oil in pediatric patients with cancer <i>Journal of the American Dietetic Association</i> , 95(6): 693-7.	Intervention/ comparison not relevant

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1991	Smales, O. R., Smales, E. A., Sanders, H. G. 1993. Flunitrazepam in terminal care <i>Journal of paediatrics and child health</i> , 29(1): 68-9.	Intervention/ comparison not relevant
2003	Matalon, Reuben, Delgado, Lisvania, Michals-Matalon, Kimberlee 1993. Canavan Disease #journal#, #volume#(#issue#): #Pages#.	Intervention/ comparison not relevant
2007	Jansen, Anna C., Andermann, Eva 1993. Progressive Myoclonus Epilepsy, Lafora Type #journal#, #volume#(#issue#): #Pages#.	Population not relevant
2013	Gomez-Ospina, Natalia 1993. Arylsulfatase A Deficiency #journal#, #volume#(#issue#): #Pages#.	Intervention/ comparison not relevant
2023	Carter, Melissa T., Mirzaa, Ghayda, McDonell, Laura M., Boycott, Kym M. 1993. Microcephaly-Capillary Malformation Syndrome #journal#, #volume#(#issue#): #Pages#.	Population not relevant
2054	Stambouly, J. J., Pollack, M. M. 1990. Iatrogenic illness in pediatric critical care <i>Critical care medicine</i> , 18(11): 1248-51.	Intervention/ comparison not relevant
2056	Seigler, R. S. 1990. The administration of rectal diazepam for acute management of seizures <i>Journal of Emergency Medicine</i> , 8(2): 155-159.	Intervention/ comparison not relevant
2064	Froscher, W. 1990. Drug therapy in epilepsy <i>Fortschritte der Medizin</i> , 108(5): 45-55.	Intervention/ comparison not relevant
2073	Shields, W. D. 1989. Status epilepticus <i>Pediatric clinics of North America</i> , 36(2): 383-93.	Population not relevant
2184	Kruse, R., Blankenhorn, V. 1973. Synopsis of experience of the clinical use and the efficacy of clonazepam in various types of epileptic seizures <i>Acta Neurologica Scandinavica</i> , 49(#issue#): 60-71.	Study design not relevant
2186	Leonardis, G., Splendiani, G. 1972. Convulsions in infants. Problems of resuscitation <i>Minerva pediatrica</i> , 24(7): 282-286.	Study design not relevant
2195	Von Studnitz, W. 1969. Secondary cystathionimuria <i>Acta Paediatrica</i> , 58(2): 173-177.	Study design not relevant
2204	Pampiglione, G. 1967. Seizures following resuscitation in children <i>Electroencephalography and clinical neurophysiology</i> , 23(4): 398-399.	Study design not relevant
2209	Kornyey, St 1964. The histopathology of anoxic brain lesions in early childhood <i>Arch. Psychiat.Nervenkr.</i> , 206(2): 237-248.	Study design not relevant
2214	Marie, J., Hennequet, A., Lyon, G., Debris, P., Le Balle, J. C. 1961. Pyridoxine dependency, a metabolic disease manifesting itself by pyridoxine-sensitive convulsive seizures. (First familial cases) <i>Revista de Neurologia</i> , 105(5): 406-419.	Population not relevant
2243	Gupta, R, Appleton, R 2005. Corticosteroids in the management of the paediatric epilepsies #journal#, 90(4): 379.	Study design not relevant

Appendix 4. Summary of results from observational non-comparative studies

Study details	Methods	Participants	Interventions	Outcomes measured in the study	Main conclusions
Ref ID 36 Holler 2021 Austria Clinical trial registration: not reported Funding: not reported Conflict of interest: none Contact details: sabine.scholl-buergi@tirol-kliniken.at	Study design: case report Setting: paediatric hospital Study dates: 2018 - 2021	Female child aged 14 at beginning of the study (17 at time of writing) Diagnosis: Niemann-Pick type C	Ketogenic diet 4:1 ratio type (fat to non-fat) via enteral feeding tube delivered by parents	<ul style="list-style-type: none"> • Seizures • Hospital admissions • Adverse events 	<ul style="list-style-type: none"> • Duration and frequency of seizures fell and alertness increased. • After initiation of KDT no further hospital admissions due to seizure exacerbation were necessary • During the first 3y of KDT, average hospital admissions and inpatient days were fewer within 3y under KDT than during the 3y before (10 vs. 14 and 94 vs. 113 respectively) • The patient received KDT for 3y without any identified KDT-associated side effects.
Ref ID 1414 Choi 2011 USA Clinical trial registration: not reported Funding: Research to Prevent Blindness Conflict of interest: none Contact details: nkhuddus@ufl.edu	Study design: case report Setting: Paediatric Clinic (Epilepsy) Study dates: 2007-2008	2 year-old boy with Dravet syndrome	Alternating monocular eye patching	<ul style="list-style-type: none"> • Seizures 	<ul style="list-style-type: none"> • The number of seizures decreased from 20 seizures in 2007 to 12 seizures in 2008, the year he was being patched.

<p>Ref ID 1528 Miyahara 2009 Japan Clinical trial registration: not reported Funding: not reported Conflict of interest: not reported Contact details: saito@ncnp.go.jp</p>	<p>Study design: case series, retrospective Setting: Paediatric Neurology Hospital Study dates: not reported</p>	<p>Patients with PME refractory to Benzodiazepines, treated with Phenytoin 5 adults & 4 children at the time of the report, but 7 of the patients were children at the beginning of the retrospective analysis (and so are included below) Ages 11–34 years at time of writing report (7 patients <18yrs at beginning of the study) M:F 6:3 Diagnoses: Progressive myoclonus epilepsy (PME) which represents an epilepsy syndrome characterized by myoclonic jerks, generalized seizures, mental retardation, and ataxia. This entity encompasses many hereditary neurodegenerative diseases, including neuronal ceroid lipofuscinosis (NCL), dentatorubral–pallidoluysian atrophy (DRPLA), Gaucher disease, mitochondrial encephalopathy with ragged red fibers (MERRF), Lafora disease, and</p>	<p>In cases of MGSE and GSE as well as prolonged and massive MSE, 10–15 mg/kg PHT was administered to patients as an injection in bolus. In some occasions when the patient was already under treatment with oral PHT, 100–250 mg (as low as 3 mg/kg) PHT was injected.</p>	<ul style="list-style-type: none"> • Treatment response 	<ul style="list-style-type: none"> • 6 out of 7 cases with childhood onset had a 'good' response with respect to cessation of status epilepticus • Prevention of status epilepticus was 'good' in 4 of the paediatric onset patients, 'fair' in 2 and 'poor' in 1 case • Baseline myoclonus was decreased in 4 out of 7 paediatric onset patients, with 2 having 'no change' * patients who were adults at the time that data collection began have been excluded
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disease (ULD).

Appendix 5. Indirect evidence

Study ID	Methods	Population	Intervention(s)	Main conclusions/ recommendations	References	Notes (optional)
Hendrikus GJ et al 2000	Review	Brain tumour patients at the end of life	First aid measures specific to EoLC, rectal medication, infusions	<ul style="list-style-type: none"> • Importance of good nuanced first aid, and advice about when to call an ambulance. 	<ul style="list-style-type: none"> • Stirling LC, Kurowska A, Tookman A. The use of phenobarbitone in the management of agitation and seizures at the end of life. <i>Journal of pain and symptom management</i>. 1999 May 1;17(5):363-8. • Moolenaar F, Jelsma RB, Visser J, Meijer DK. Manipulation of rectal absorption rate of phenytoin in man. <i>Pharmaceutisch weekblad</i>. 1981 Dec 1;3(1):1051-6. • Moolenaar F, Jelsma RB, Visser J, Meijer DK. Manipulation of rectal absorption rate of phenytoin in man. <i>Pharmaceutisch weekblad</i>. 1981 Dec 1;3(1):1051-6. • Arvidsson J, Nilsson HL, Sandstedt P, Steinwall G, Tonnby B, Flesch G. Replacing carbamazepine slow-release tablets with 	Many of the secondary references in the review are very old, but I like the first aid principles, as non-pharm interventions

						carbamazepine suppositories: a pharmacokinetic and clinical study in children with epilepsy. Journal of child neurology. 1995 Mar;10(2):114-7.
Bendle & Laddie 2019	Review	Children with neurodisability	<ul style="list-style-type: none"> • Discussion of joint working between neurology and PPC. Underlying causes to be considered, as well as the LLC. Focus on comfort. Infusions of phenobarbitone and or midazolam closer to EoL. • Conversion from enteral to SC and titrating to effect. 	<ul style="list-style-type: none"> • Recommendation that PPC teams work jointly with neurology on palliative neurodisability patients. • Discussion of the benefits of this. • Differentiation between seizures, and dystonia as a specific issue in this group. 	<ul style="list-style-type: none"> • Association for paediatric palliative medicine master formulary. 3rd ed.. 2015. From, www.appm.org.uk/resources/APPMPMasterFormulary2015protected.pdf • Basic symptom control in paediatric palliative care guidelines. 9th ed., 2013. Available at www.togetherforshorlives.org.uk/professionals/resources. • End of life care for infants, children and young people with life-limiting conditions: planning and management. NICE guidance, 2016. • Goldman A, Hain R, Liben S. Oxford textbook of palliative care for children. 2nd 	Nice to reference the joint working elements and the titration to effect with potential for doctrine of double effect.

					<p>ed. Oxford University Press, 2012.</p> <ul style="list-style-type: none"> • Hain R, Jassal S. Oxford specialist handbook in paediatric palliative medicine. Oxford University Press, 2010. • Larcher Vic, Craig Finella, Bhogal Kiran, Wilkinson Dominic, Brierley Joe. Making decisions to limit treatment in life-limiting and life-threatening conditions in children: a framework for practice. Arch Dis Child 2015; 100: s1e23. https://doi.org/10.1136/archdischild-2014-306666. 2015. 	
Williams et al 2017	Report from a consensus meeting of experts	Batten's disease CLN2	<ul style="list-style-type: none"> • Benzodiazepines (clobazam, clonazepam), ethosuximide, lamotrigine, levetiracetam, phenobarbital, valproic acid, zonisamide; most commonly used is valproate in various add-on combinations • Ketogenic diet 	Mixed approach to seizures with ketogenic diet and combinations of AEDs.	<ul style="list-style-type: none"> • Connolly AM, Beavis E, Mugica-Cox B, Bye AM, Lawson JA. Exploring carer perceptions of training in out-of-hospital use of buccal midazolam for emergency management of seizures (2008e2012). J Paediatr Child Health. 2015;51:704-707. 	Specific advice on Batten's disease only, but focused on palliative approach

					<ul style="list-style-type: none"> • NICE. Epilepsies: Diagnosis and Management (Update); 2016. Available at: https://www.nice.org.uk/guidance/CG137. Accessed December 12, 2016. 	
Gupta & Appleton 2005	Review	Paediatric epilepsy patients	Use of corticosteroids	<p>Although there are some good outcomes in refractory encephalopathic epilepsy, it is recommended that the advice of a paediatric neurologist always be sought for the management of children with the other, more malignant epilepsies including Ohtahara's syndrome, Lennox-Gastaut syndrome, severe myoclonic epilepsy of infancy, episodes of non-convulsive status epilepticus and Rasmussen's encephalitis, when considering the use of corticosteroids in these epilepsy</p>	<ul style="list-style-type: none"> • Snead OC III, Benton JW, Myers GJ. ACTH and prednisone in childhood seizure disorders. <i>Neurology</i> 1983;33:966–70. • Snead OC III, Benton JW Jr, Hosey LC, et al. Treatment of infantile spasms with high-dose ACTH: efficacy and plasma levels of ACTH and cortisol. <i>Neurology</i> 1989;39:1027–31. • Hrachovy RA, Frost JD, Glaze DC. High dose, long duration versus low-dose, short duration corticotropin therapy for infantile spasms. <i>J Pediatr</i> 1994;124:803–6. • Akanuma H, Sekijima Y, Tokuda T, et al. A case of severe status epilepticus of frontal lobe origin 	<p>Useful review of steroids for epileptic encephalopathy. Recommends further research but encourages discussion with neurologists about the role of steroids in treatment resistant encephalopathic epilepsy. Some of the references were very historic (1950s!)</p>

- successfully treated with corticosteroids. Rinsho Shinkeigaku 1998;38:461-4..
- Wiener P. Neuroactive steroids, relaxation and seizure control. Int J Neurosci 2003;113:631-9.
 - Riikonen RS. Steroid or vigabatrin in the treatment of infantile spasms? Pediatr Neurol 2000;23:403-8.
 - Ito M. Extremely low-dose ACTH therapy for West syndrome in Japan. Brain Dev 2001;23:635-41.

Study ID	Methods	Population	Intervention(s)	Main conclusions/ recommendations	Notes (optional)
Harris et al, 2017	Retrospective case note review	19 admissions of children receiving end-of-life care over a 10-year period (2006–2015) in the south-west region of England. 6 had malignancies, 9 had progressive neurological disorders and 3 had static neurological conditions.	Seventeen episodes involved the use of subcutaneous or intravenous midazolam infusion, for a mean of 11 days (range 3–27).	<ul style="list-style-type: none"> • There was a wide range of starting doses of midazolam, and 9/17 (53%) received final doses in excess of current dose recommendations. Six individuals received subcutaneous phenobarbital infusions, with four of these (67%) receiving final doses in excess of current dose recommendations. 	Guidance refers to the APPM formulary, Rainbows manual, BFc. There is an ongoing survey examining prescribing patterns

- Plans for adjustments of infusion rates, maximal doses or alternative approaches should treatment fail were inconsistent or absent
- In 16/18 (88%) cases seizures were successfully controlled prior to the day of the child's death. Staff found the experience of managing seizures at end of life challenging and stressful.
- There were no instances reported where over sedation led to the consideration of flumazenil or physical interventions to support respiration.
- One child on very high concentrations of midazolam suffered skin irritation around the subcutaneous cannula sites, requiring relocation of the infusion on a daily basis.
- There were no reported instances of skin irritation around the phenobarbital infusion sites.