Seizures in Palliative Care

Focus on levetiracetam

Dr. Fiona Kiely
Masterclass Palliative Care 2019

Aim of talk

- Explore the epidemiology of seizures in palliative care contexts

- Review the evidence for subcutaneous use of newer antiepileptic drug (AED) levetiracetam in palliative care contexts including end of life.

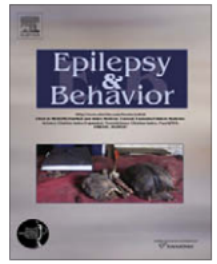
Historical & cultural perspective

Epilepsy & Behavior 17 (2010) 139–146

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh



Review

The epileptic seizure and the mystery of death in Christian painting

Michael W. Mann *

Department of Neurosurgery, Hôpital St. Anne (Pr FX Roux), Paris, France

In many cultures are associated or symbolize death

May be seen as a transient form of death or in some Indo-European cultures perceives death not as the end, but as a step, as a point the life cycle is passing through

Qualitative studies

- Contemporary young student with temporal lobe epilepsy

“The anguish goes through my stomach and comes up to my throat.... I lift my hand to my forehead, lift my eyes: I am behind a glass pane. The landscape has changed, it is mortuary. Deep despair fills me and tells me it is all over. I am going to die.... At that moment there is no time factor. I am there for eternity ... I need to tell someone I am leaving very far away for if there is no one there I will never come back ... I have to scream. I need a human being to pull me up to the surface, to hold me, to give me warmth. For I am going to die. That is a certainty.... I try to make a last movement with my hand or my eye, but I am powerless. I drift into this experience of horror.”

Reflection felt like moving from a physical state

Intellectually knows not going to die, yet everytime it happens is convinced

What is a seizure?

- A seizure is a sudden, uncontrolled electrical disturbance in the brain. It can cause changes in behaviour, movements or feelings, and in levels of consciousness.
- A seizure may be the expression of epilepsy
- Defined as “ the enduring predisposition to generate epileptic seizures and requires the history of at least one seizure”
- Seizures without having epilepsy (eg acute symptomatic provoked seizure)

- Can be challenging symptom control issue
- Distressing and risk brain damage if prolonged
- Palliative care emergency
- Consequences include rehospitalization, ED visits, health economics, QoL, cognitive consequences, carer distress

A Focus on Cerebral Malignancy

Neuro-Oncology Practice

Neuro-Oncology Practice 1(3), 134–140, 2014
doi:10.1093/nop/npu018

Epilepsy in the end of life phase of brain tumor patients: a systematic review

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Seizure 44 (2017) 93–97

Contents lists available at ScienceDirect

Seizure

journal homepage: www.elsevier.com/locate/yseiz

Review

Epilepsy-related brain tumors

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ABSTRACT

Seizures are among the most common presentations of brain tumors. Several tumor types can cause seizures in varying rates; neuroglial tumors and the gliomas are the most common ones. Brain tumors are the second most common cause of focal intractable epilepsy in epilepsy surgery series, with the highest frequency being dysembryoplastic neuroepithelial tumors and gangliogliomas. Seizure management is an important part of the treatment of patients with brain tumors. This review discusses clinical features and management of seizures in patients with brain tumors, including, neuroglial tumors, gliomas, meningioma and metastases; with the help of recent literature data. Tumor-related seizures are focal seizures with or without secondary generalization. Seizures may occur either as initial symptom or during the course of the disease. Brain tumors related epilepsy tends to be resistant to antiepileptic drugs and treatment of tumor is main step also for the seizure treatment. Early surgery and extent of the tumor removal are important factors for achieving seizure freedom particularly in neuroglial tumors and low grade gliomas. During selection of the appropriate antiepileptic drug, the general approach to partial epilepsies can be followed. There are several factors influencing epileptogenesis in brain tumor-related epilepsy which also explains clinical heterogeneity of epilepsy among tumor types. Identification of molecular markers may guide future therapeutic approaches and further studies are needed to prove antitumor effects of different antiepileptic drugs.

- Occur in approx. 13% of palliative care patients

- Most common cancer cause = Brain mets
  - 35% → seizures

- Most common adult 1 brain tumour = Glioma
  - 40 – 60% → seizures (WHO III – IV)

- Systematic review of seizure prevalence in cerebral malignancy, across hospice, home & hospital → 6 – 56%

- Suggestion that prevalence increases towards death

Tradounsky, G. (2013). Seizures in palliative care. Canadian Family Physician Medecin De Famille Canadien, 59(9), 951-5, e401-5.

Koekkoek, J., Dirven, L., Reijneveld, J., Postma, T., Grant, R., Pace, A., . . . Taphoorn, M. (2014). Epilepsy in the end of life phase of brain tumor patients: A systematic review. Neuro-Oncology Practice, 1(3), 134-140.

Seizures – Malignant & Non-Malignant

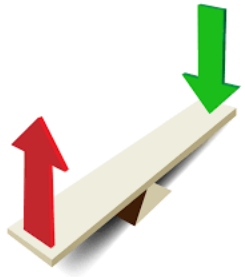
Structural	Systemic
Primary tumours, metastases, abscesses, reversible posterior leukoencephalopathy syndrome, paraneoplastic limbic encephalitis, haemorrhage, or radiation necrosis	Hypoxia, hypoglycemia, hyperglycemia, hyponatremia hypernatremia, low levels of magnesium, hypocalcemia, hypercalcemia, uremia, and hepatic failure, as well as various medications, such as ondansetron, antipsychotics, and chemotherapeutic agents

Most new seizures in adult palliative care are focal onset +- secondary generalization

Cerebral malignancies

- The seizure risk is influenced by a number of factors: type and location of tumour and the number of the lesions, growth rate

Epileptogenesis

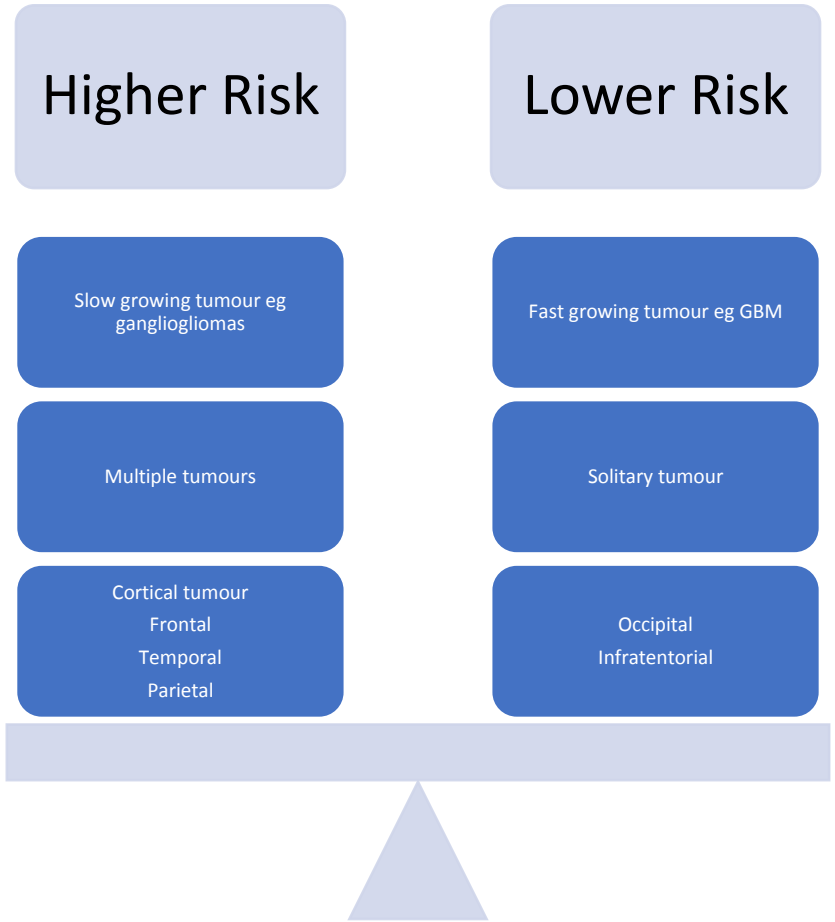


Tumour growth rate

Inversely correlated

Koekkoek, J., Dirven, L., Reijneveld, J., Postma, T., Grant, R., Pace, A., . . . Taphoorn, M. (2014). Epilepsy in the end of life phase of brain tumor patients: A systematic review. *Neuro-Oncology Practice, 1*(3), 134-140.

Epileptogenesis – Risk stratification



Loss of oral route

- Oral route less reliable with PoD and end of life approaches

Dysphagia Prevalence in Brain Tumour	Prognosis
40%	3/12
70%	**1/12**
82%	**Days**

Giuseppe Roberto Giammalva, Domenico Gerardo Iacopino, Giorgio Azzarello, Claudia Gaggiotti, Francesca Graziano, Carlo Gulì, . . . Rosario Maugeri. (2018). End-of-Life Care in High-Grade Glioma Patients. The Palliative and Supportive Perspective. *Brain Sciences, 8*(7), 125.

- Up to 94% of brain tumour patients, progressive confusion or coma are reported in the last days before death.
- Hampers regular oral AED ingestion
- The consequences of discontinuing AEDs in the EOL phase remain largely unknown.
- Sizoo et al (2013) found that seizures took place in 10 of 29 patients (35%) whose AEDs were tapered during the EOL phase.
- Have to assume risk increases

Sizoo, E., Koekkoek, J., Postma, T., Heimans, J., Pasman, H., Deliens, L., . . . Reijneveld, j. (2014). Seizures in patients with high-grade glioma: A serious challenge in the end-of-life phase. BMJ Supportive & Palliative Care, 4(1), 77-80.

Brain tumours

- Clinical trend = newer AEDs
- Lower adverse effect and drug interactions
- Unlike carbamazepine, phenytoin, phenobarbitone, not known to interact with dexamethasone or induce CYP450
- AEDS should not be used prophylactically in absence of history of seizures
  - In RCTs they do not reduce the risk
  - Peri-neurosurgical use possible exception, but results conflicting , most recent Cochrane review (2018) insufficient, low quality evidence
  - If used, prophylactic levetiracetam appears more effective than phenytoin (incidence 0% V 16%)

- *Nasr, Z., Paravattil, B., & Wilby, K. (2016). Levetiracetam for seizure prevention in brain tumor patients: A systematic review. Journal of Neuro-oncology, 129(1), 1-13.*
- van Breemen MSM, Wilms EB, Vecht CJ (2007) Epilepsy in patients with brain tumours: epidemiology, mechanisms, and management. Lancet Neurol 6:421–430.
- *Greenhalgh J, et al (2018). Antiepileptic drugs as prophylaxis for postcraniotomy seizures. Cochrane Database of Systematic Reviews, Issue 5. Art. No.: CD007286. DOI: 10.1002/14651858.CD007286.pub4*
- M.C. Dewan, *et al. (2017).* The influence of perioperative seizure prophylaxis on seizure rate and hospital quality metrics following glioma resection. Neurosurgery, 80, pp. 563-570
- K.L. Fuller, *et al. (2013).* Tolerability, safety, and side effects of levetiracetam versus phenytoin in intravenous and total prophylactic regimen among craniotomy patients: a prospective randomized study Epilepsia, 54, pp. 45-57.

Loss of oral route / impaired consciousness

- IV / PR routes often not possible / desired
- Switch from PO to subcutaneous route = common practice
- SC therapeutic options limited and limited evidence to guide

"Stopping oral levetiracetam and commencing CSCI midazolam.
Starting dose range 10 – 30mg, dose escalated if seizures witnessed.
Addition of phenobarbital if seizures remain uncontrolled"

- Balance effective seizure control against (un)wanted side-effects
- Consider the patient who may regain consciousness following a post-ictal period
- Parenteral levetiracetam offers possibility of seizure control when oral route non-viable with less associated sedation

Levetiracetam

- Levetiracetam (LEV) is one of the newer and most frequently used AEDs
- It has proven effective and safe in treating multiple seizure types, in both adults and children older than one month.
- Can be valuable for acute seizure management

Sourbron, Chan, Wammes-van Der Heijden, Klarenbeek, Wijnen, De Haan, . . . Majoie. (2018). Review on the relevance of therapeutic drug monitoring of levetiracetam. Seizure: European Journal of Epilepsy, 62, 131-135.

S. Ito, I. Yano, S. Hashi, M. Tsuda, M.Sugimoto, A. Yonezawa, et al. (2016) Population pharmacokinetic modeling of levetiracetam in pediatric and adult patients with epilepsy by using routinely monitored data Ther Drug Monit, 38, pp. 371-378

- Class: SV2A Ligand, K, Ca channels
- Pharmacology: Binds to synaptic vesicle protein SV2A in the brain interfering with release of neurotransmitter stored within the vesicle.
- It gains access after neurotransmitter release as vesicles recycled
- It selectively inhibits rapidly firing neurons

- https://vimeo.com/192640952

Levetiracetam - General Population

Neuropsychiatric Disease and Treatment

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ORIGINAL RESEARCH

Levetiracetam for epilepsy: an evidence map of efficacy, safety and economic profiles

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Dovepress
http://dx.doi.org/10.2147/NDT.S181886

Neuropsychiatric Disease and Treatment 2019:15 1–19

Most comprehensive synthesis of up-to-date evidence

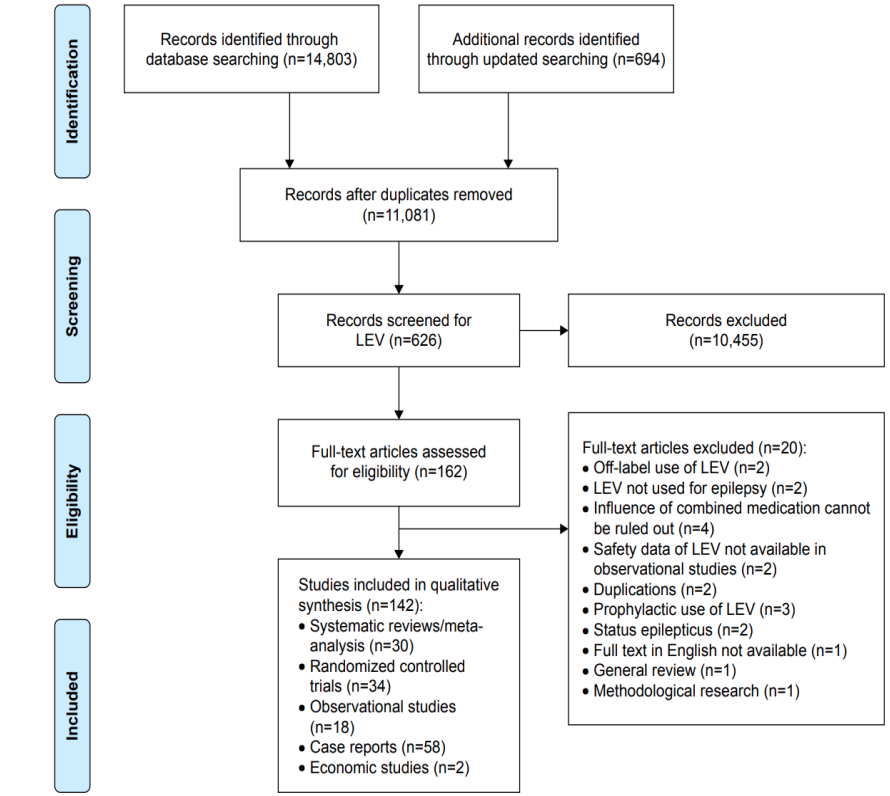

Figure 1 Flow diagram for literature search and study selection.
Abbreviation: LEV, levetiracetam.

"Evaluate the efficacy, safety and economic profiles of LEV compared with all other AEDs for epilepsy, to provide evidence-based information for the rational use of LEV and research agendas"

Efficacy Data – Forest Plot

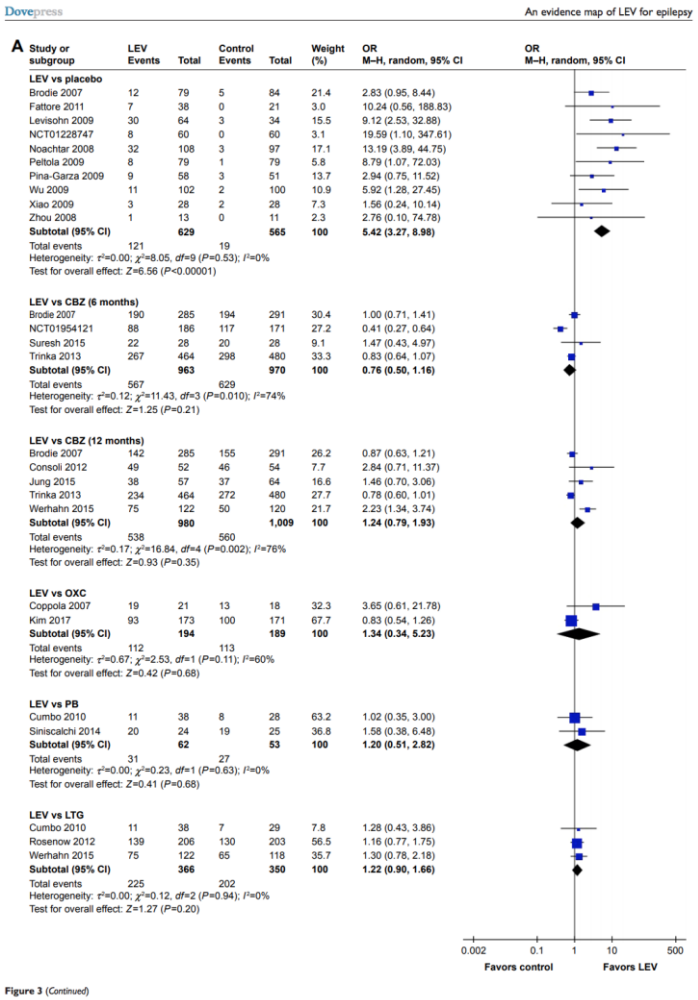

Figure 3 (Continued)

Evidence map indicated that LEV had similar efficacy in seizure freedom compared with conventional AEDs and was superior to placebo in seizure freedom.

Safety

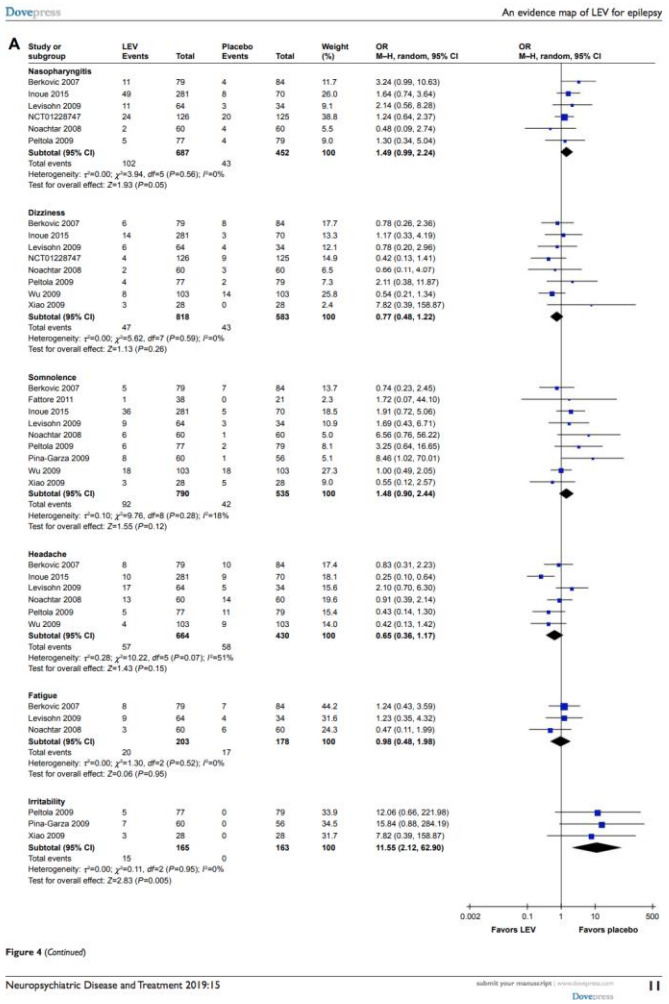

Figure 4 (*Continued*)

LEV lower risk leukopenia, rash, deranged LFTs, nausea than with carbamazepine

Higher risk of irritability with LEV than placebo

It works.
It is non- inferior in efficacy to other AEDs.
Also...lower risk of discontinuation

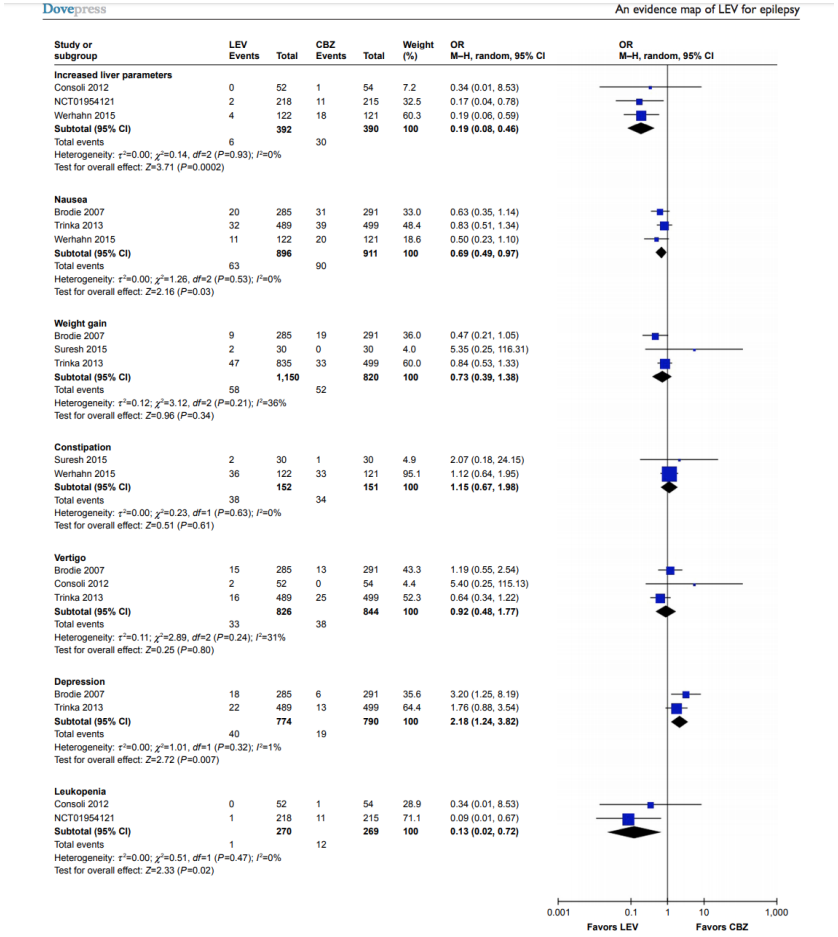

Figure 4 Risk of single adverse events (LEV vs placebo, **A**; LEV vs CBZ, **B**).
Abbreviations: CBZ, carbamazepine; *df*, degrees of freedom; LEV, levetiracetam; M–H, Mantel–Haenszel; random, random-effect model.

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Anticonvulsant therapy for status epilepticus

Cochrane Systematic Review - **Intervention** | Version published: 10 September 2014 **see what's new**

The body of randomised evidence to guide clinical decisions is small. It was uncertain whether any anticonvulsant therapy was better than another in terms of adverse effects, due to few studies and participants identified.

Eighteen studies with 2755 participants were included, heterogenous
Most evidence examines benzodiazepines and they remain first-line treatment (IV lorazepam> diazepam, phenytoin)
Both levetiracetam and lorazepam were equally effective in aborting seizures (RR 0.97, 95% CI 0.44 to 2.13).

Levetiracetam – Oncology Population

J Neurooncol (2016) 129:1–13
DOI 10.1007/s11060-016-2146-5

TOPIC REVIEW

Levetiracetam for seizure prevention in brain tumor patients: a systematic review

Ziad Ghantous Nasr[1] · Bridget Paravattil[1] · Kyle John Wilby[1]

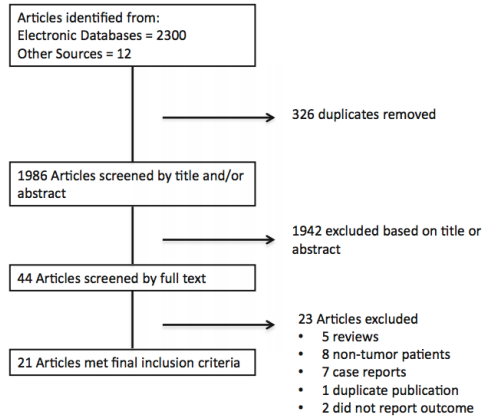

Fig. 1 Flow diagram for study selection and inclusion

3 randomized controlled trials, 7 prospective observational studies, and 11 retrospective observational studies. All studies high risk bias*

Conclusion: Levetiracetam appears effective and safe for reducing seizures in patients with brain tumors and may be considered a first-line agent

Proviso: Urgent need for more high quality prospective data assessing levetiracetam and other antiepileptic drugs in this population

Why attractive?

Safety & tolerance

- NB No interaction with dexamethasone or CYP450

- Less likely to discontinue
- Caution in renal impairment and severe hepatic impairment
- Very common: Fatigue, drowsiness, headache
- Common: Behavioural, depression, diarrhea, ataxia
- Rare: psychosis, AKI, EPSE

Trusted evidence.
Informed decisions.
Better health.

English

Title Abstract

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Cochrane Database of Systematic Reviews

Antiepileptic drugs for treating seizures in adults with brain tumours

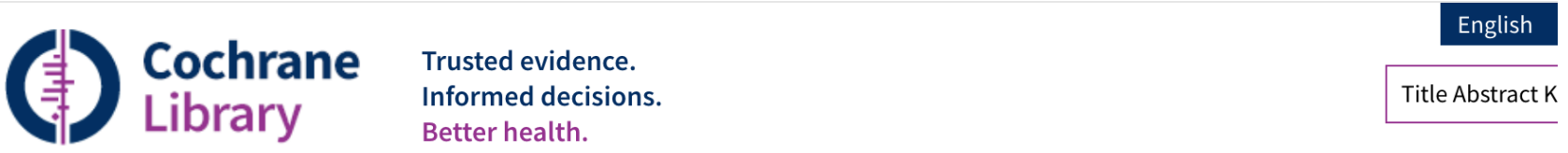
Cochrane Systematic Review - **Intervention** | Version published: 10 August 2011

1 small unblinded randomized trial of switch from phenytoin to levetiracetam for glioma seizure control V phenytoin continuance

Non-inferior and ? Benefit of less drug interactions

10 RCTs (N = 1815)
Limited & low quality evidence

So AED prophylaxis not recommended



Trusted evidence.
Informed decisions.
Better health.

English

Title Abstract K

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Cochrane Database of Systematic Reviews

Antiepileptic drugs as prophylaxis for postcraniotomy seizures

Cochrane Systematic Review - **Intervention** | Version published: 23 May 2018 **see what's new**

A

Levetiracetam – Palliative Care

- Now a commonly used first line choice for seizure management in palliative care
- Focal - secondary
- Efficacy and tolerability compare favorably to other AEDs used in focal seizures
- Few drug interactions, can be used when other AEDs are CI due to hepatic, cardiac issues
- IV / SC / reports compounded suppositories

Methods of administration

- Levetiracetam can be given †SC b.i.d., diluted in 100mL sodium chloride 0.9% and infused over 30min. The dose is the same PO/SC/IV.
- Levetiracetam can also be given by †CSCI diluted with either water for injection or sodium chloride 0.9% when necessary.
- By CSCI, although there are no formal laboratory compatibility data, Generally, sodium chloride 0.9% is used as diluent and local skin reactions occur in about 5% of patients.
- Alternative SC/CSCI anti-epileptics include lacosamide, midazolam, phenobarbital and valproate.
- May be used in status refractory to BDZ, 20 – 30mg/kg single IV bolus. ?equal efficacy to phenytoin, valproate

- *Howard, Paul, Remi, Jan, Remi, Constanze, Charlesworth, Sarah, Whalley, Helen, Bhatia, Rebecca, . . . Wilcock, Andrew. (2018). Levetiracetam. Journal of Pain and Symptom Management, 56(4), 645-649.*

Subcutaneous Levetiracetam

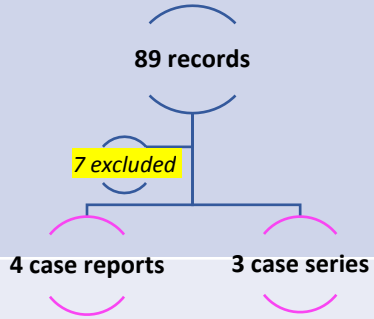
- Small but increasing evidence base to support subcutaneous use
- Case report and small observational studies demonstrate efficacy, tolerability and compatibility
- Sutherland et al (2018)
- *Subcutaneous levetiracetam for the management of seizures at the end of life. BMJ Supportive & Palliative Care, 8(2), 129-135.*

Literature review + Observational study

- Given nature of the available literature, unable to perform meta-analysis

Primary outcomes	Secondary outcomes
Assess efficacy of SC levetiracetam (no. pts with no reported seizure activity over total reported periods) Assess tolerability (no. pts reported to have adverse effects)	Descriptive data on SC administration - Mode - Diluent - Dose - Conversion rate - Breakthrough treatment - Concomitant use of other AEDs - Serum monitoring - Duration of treatment

Literature Review

Database	Search Terms	Results
EMBASE Medline CINAHL Clinical Trials.gov WHO International Trials Registry	“subcutaneous” AND “levetiracetam” OR “subcutaneous” AND “Keppra” OR “levetiracetam SC”	
	Updated search to 2016	

What do the papers say?

- 53 adult patients in 7 papers, with a range of diagnoses

Efficacy	**3/53 reported to have seizures while on LVC** **36/53 concomitantly received other AED (undescribed)**
Safety	**3/53 site reactions (but on other meds)** **1/53 rash**
Mode	**46/53 CSCI (dose range 250 – 4000mg daily) 1:1 conversion** **5/53 intermittent SC bolus (diluted to 2.5mg/ml)** **2/53 intermittent SC (100ml N saline BD over 30 mins)**
Length of treatment	**1 – 47 days** **40/53 continued until death** **3/53 improved and returned to PO** **1/53 stopped due to rash** **5 cases missing**

Prospective observational study

- Data collection sheet informed by the literature review
- 6 centres in Thames Valley region over 1 year
- All patients under care SPC, all inpt (bar 1)
- 20 cases in 18 patients, 19/20 cases had been on oral levetiracetam

Efficacy	**7/18 seizure – 3 resolved with increase Levetiracetam** **13/18 on concomitant AED**
Safety	**1/18 site rxn** **1/18 sterile abscess (after 25/7)**
Mode	**18/18 CSCI (500 – 3000mg daily), X 2 12 hourly SD if >2400mg** **Water for injection**
Duration	**12/18 continued to death** **3/18 recovered oral route**

Impression

- Prospective data compares well with exiting case series
- Appears to be safe and well tolerated and causes site reaction infrequently
- Intermittent SC bolus only reported in 2 cases
- Available data seems to therefore support CSCI over bolus
- ¾ site reactions occurred when levetiracetam was mixed
- Therefore advise keep separate
- Still uncertain re pharmacokinetics, bioavailabilty SC so if breakthrough seizures manage in established way.

- Max 2g CSCI X 24 hours
- Adjust for renal failure
- Off licence use - ?discuss

Antiepileptic Therapy – Guiding Principles

- Respecting patient and family resources and wishes
- QoL
- Consider current & future requirements of therapy
- Ensuring practicality (eg community access and reimbursement)

- Gronheit, W., Popkirov, S., Wehner, T., Schlegel, U., & Wellmer, J. (2018). Practical Management of Epileptic Seizures and Status Epilepticus in Adult Palliative Care Patients. *Frontiers in Neurology, 9*, 595.

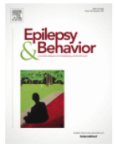
Quirky musings

Survival

Things to consider / Observations

- Definition of “efficacy” to measure success
- - needs to incorporate values, meaning, experience, QoL, not all identifiable quantitatively
- Qualitative research to be incorporated
- Pharmacovigilance studies should be informed by specific side effects eg psychiatric as may not be recognized / volunteered
- Survival data on this population ? Predictor of death

Epilepsy & Behavior
Volume 86, September 2018, Pages 193-199



Review

Incidence rate of sudden death in epilepsy: A systematic review and meta-analysis

Erik Saetre [a], Michael Abdelnoor [b, c]

Show more

https://doi.org/10.1016/j.yebeh.2018.06.037

Epilepsy & Behavior 90 (2019) 99–106

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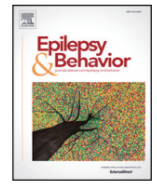

Review

A systematic review of sudden unexpected death in epilepsy (SUDEP) in childhood☆,☆☆,★

Omar Abdel-Mannan [a,*], Henry Taylor [b], Elizabeth J. Donner [c], Alastair G. Sutcliffe [d]

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[c] Department of Neurology, The Hospital for Sick Children, Toronto, Canada
[d] Population, Policy and Practice Unit, UCL Great Ormond Street Institute of Child Health, London, United Kingdom

Non-convulsive status epilepticus (NCSE)

- Continuous or recurrent seizure without convulsive activity
- Diagnostic and therapeutic challenge
- Clinical symptoms may be subtle / masquerade
  - Altered consciousness
  - Automatisms
  - Myoclonus

- Do we consider this in practice? How would people respond to AEDs? Who is at risk

Samala, R., Parala-Metz, A., & Davis, M. (2015). Nonconvulsive Status Epilepticus in a Palliative Care Unit: When Delirium Is a Seizure. *American Journal of Hospice and Palliative Medicine®,32*(2), 243-247.

Lorenzl, Mayer, Feddersen, Jox, Noachtar, & Borasio. (2010). Nonconvulsive Status Epilepticus in Palliative Care Patients. *Journal of Pain and Symptom Management, 40*(3), 460-465.