

FINAL

Epilepsies in children, young people and adults: diagnosis and management

**[15] Evidence review: Prevalence of
psychological disorders in people with
epilepsies**

NICE guideline NG217

*Evidence reviews underpinning recommendations 9.1.1 – 9.1.5
in the NICE guideline*

April 2022

FINAL

Developed by the National Guideline Centre

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ISBN: 978-1-4731-4513-9.

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1 Prevalence of depression, anxiety, learning disability and neurodevelopmental/cognitive difficulties in people with epilepsies

1.1 Review question

What is the prevalence of depression, anxiety, intellectual disability, developmental difficulties and cognitive difficulties in people with epilepsies?

1.1.1 Introduction

Epilepsy is an unusual diagnosis in neurology in that the diagnosis is conferred on the basis of a single symptom, seizures. However, the underlying genetic abnormality or pathology in the brain that results in seizures can also predispose to other disturbances in brain function. Knowledge and awareness of these other disorders are essential for the care of people with epilepsy. Some of the treatments aimed at controlling seizures can have an adverse effect on common co-morbidities.

This chapter examines the prevalence of core mental illnesses (depression, anxiety, psychosis), co-morbid neurodevelopmental disorders (intellectual disability, autistic spectrum disorders, ADHD) and other acquired cognitive difficulties such as dementia in this population.

1.1.2 Summary of the protocol

For full details, see the review protocol in Appendix A

Table 1: PICO characteristics of review question

Population	Inclusion: Children, young people and adults with confirmed epilepsy. Exclusion: New-born babies (under 28 days) with acute symptomatic seizures.
Outcomes/ Comorbidities	In people with Epilepsy, the prevalence of: <ul style="list-style-type: none">• Depression• Anxiety• Learning disabilities• Cognitive difficulties• Dementia• psychosis
Study design	Systematic reviews of all studies reporting period prevalence (limited to period prevalence for all conditions except learning disabilities where point prevalence will also be included).

1.1.3 Methods and process

This evidence review was developed using the methods and process described in [Developing NICE guidelines: the manual](#). Methods specific to this review question are described in the review protocol in appendix A and the methods document

Declarations of interest were recorded according to [NICE's conflicts of interest policy](#).

1.1.4 Prevalence evidence

1.1.4.1 Included studies

A search was conducted for systematic reviews reporting prevalence data of depression, anxiety, learning disabilities, cognitive difficulties, dementia and psychosis in people with epilepsy. Ten studies were included in the review,^{7, 27, 39, 42, 43, 51, 52, 69, 95, 96} these are summarised below. Evidence from these studies is summarised in the clinical evidence summary below (Table 3). See also the study selection flow chart in 39Appendix C, study evidence tables in Appendix D, forest plots in Appendix F.

Most of the included systematic reviews were unable to perform meta-analyses due to insufficient reporting of data, therefore, the data predominantly extracted for this evidence review was the range of prevalence percentages from individual studies. Pooled data for prevalence was only reported in two systematic reviews, Scott 2017⁹⁵ and Scott 2020⁹⁶, where meta-analyses were possible.

The diagnostic method used to measure the comorbidities varied amongst individual studies included in each systematic review; this may explain the wide variation observed in the prevalence statistics.

The risk of bias for the systematic reviews included was assessed using the ROBIS tool, which assesses the risk of bias in systematic reviews by:

1. Assessing the relevance
2. identifying concerns with the review process
3. judging the risk of bias in the review

Please see Appendix E for ROBIS assessment table.

1.1.4.2 Excluded studies

The searches were limited to systematic reviews. Therefore, all individual studies investigating prevalence were excluded.

See the excluded studies list in Appendix G.

1.1.5 Summary of studies included in the prevalence evidence

Table 2: Summary of reviews included in the evidence review

Study	Population	Comorbidity	Comments
Asadi-Pooya 2018 ⁷	26 studies included for people with epilepsy	Depression	High risk of bias Population age not defined
Cobham 2020 ²⁷	8 studies included 784 children and adolescents with epilepsy	Anxiety	High risk of bias
Fiest 2013 ³⁹	14 studies included Adults with epilepsy	Depression	Low risk of bias
Fonseca 2019 ⁴² , Fonseca 2020 ⁴³	33 studies included Children with absence epilepsy	Cognitive difficulties Learning disabilities	Low risk of bias
Jones 2014 ⁵¹	Children and adolescents with epilepsy included	Anxiety	Very high risk of bias Narrative literature review, no methodology

Study	Population	Comorbidity	Comments
			or risk of bias assessment for included studies
Jones 2010 ⁵²	13 studies included	Depression Anxiety Psychosis	High risk of bias Population age not defined
Maryam 2013 ⁶⁹	11 studies included 1095 children (4-19 years) with epilepsy	Depression	High risk of bias
Scott 2017 ⁹⁵	27 studies included 3221 adults with epilepsy	Depression Anxiety	Low risk of bias
Scott 2020 ⁹⁶	23 studies Children with epilepsy	Anxiety Depression	Low risk of bis
Subota 2017 ¹⁰⁵	2 studies included People with epilepsy	Dementia	Low risk of bias population age not defined

See Appendix D for full evidence tables.

1.1.6 Summary of the evidence

Table 3: Clinical evidence summary: Depression

Prevalence in people with Epilepsy	Systematic review	Type of prevalence Time-frame	Population	Risk of bias rating	comments/ Quality rating in review
6.6%-43.4%	Asadi-Pooya 2018 ⁷	Period prevalence, unclear time-frame	Unclear	High	2.9%-12.7% depression in general population
13.2%-36.5%	Fiest 2013 ³⁹	Period prevalence of past 30 days -12 months	Adults with active depression	Low	
4.1%-32.5%	Fiest 2013 ³⁹	Period - Lifetime depression prevalence	Adults with lifetime depression	Low	
18%-39.7%	Jones 2010 ⁵²	Period prevalence, unclear time-frame	Unclear	High	
5.2%-39.6%	Maryam 2013 ⁶⁹	Period prevalence, unclear time-frame	Children	High	Aged 4-19 years old
22.9% pooled prevalence	Subota 2017 ¹⁰⁵	Period prevalence, unclear time-frame	Adults	Low	16 years and older Figure 2 for forest plot
13.5% (95% CI 8.8%–20.2%) pooled prevalence	Scott 2020 ⁹⁶	Period prevalence, unclear time-frame	Children	Low	Up to and including 18 years of age

Table: Clinical evidence summary: Anxiety

Prevalence in people with Epilepsy	Systematic review	Type of prevalence	Population	Risk of bias rating	comments
23.8%-50%	Cobham 2020 ²⁷	Period prevalence, unclear length	Children	High	12.4%-22% anxiety in general population
9%-32%	Jones 2014 ⁵¹	Period: lifetime	Children	Very high	Lifetime anxiety

Prevalence in people with Epilepsy	Systematic review	Type of prevalence	Population	Risk of bias rating	comments
8%-21%	Jones 2014 ⁵¹	Mixed: current and past 12 months	children	Very high	
10%-25%	Jones 2010 ⁵²	Period prevalence, unclear time-frame	Unclear	High	
20.2%	Scott 2017 ⁹⁵	Period prevalence, unclear time-frame	Adults	Low	16 years and older Figure 3 for forest plot
18.9% (95% CI 12.0%–28.5%) pooled prevalence	Scott 2020 ⁹⁶	Period prevalence, unclear time-frame	Children	Low	Up to and including 18 years of age

Table 4: Clinical evidence summary: Learning disabilities

Prevalence in people with Epilepsy	Systematic review	Type of prevalence	Population	Risk of bias rating	comments
Dysgraphia: 26%	Fonseca 2019 ⁴² , Fonseca 2020 ⁴³	Unclear, prevalence determined from school reports	Children	Low	Absence epilepsy
school difficulties/requiring special educational support: 23-70%	Fonseca 2019 ⁴² , Fonseca 2020 ⁴³	Unclear, prevalence determined from school reports	Children	Low	Absence epilepsy

Table 5: Clinical evidence summary: Cognitive difficulties

Prevalence in people with Epilepsy	Systematic review	Type of prevalence	Population	Risk of bias rating	comments
24%	Fonseca 2019 ⁴² , Fonseca 2020 ⁴³	Unclear, prevalence determined from school reports	Children	Low	Absence epilepsy

Table 6: Clinical evidence summary: Dementia

Prevalence in people with epilepsy	Systematic review	Type of prevalence	Population	Risk of bias rating	comments
8.1 to 17.5 per 100 persons	Subota 2017 ¹⁰⁵	Period prevalence	Unclear	Low	No age defined

Table 7: Clinical evidence summary: Psychosis

Prevalence results	Systematic review	Type of prevalence	Population	Risk of bias rating	comments
2-7%	Jones 2010 ⁵²	Period prevalence, unclear time-frame	unclear	High	

1.1.7 Economic evidence

The committee agreed that health economic studies would not be relevant to this review question and so were not sought.

1.1.8 The committee's discussion and interpretation of the evidence

1.1.8.1 The outcomes that matter most

This evidence review sought data for the prevalence of depression, anxiety, learning disabilities, cognitive difficulties, dementia and psychosis in people with epilepsy. The committee considered that recognition of prevalence is important in alerting clinicians to common co-morbidities and to planning and delivering care to people with epilepsy.

1.1.8.2 The quality of the evidence

The systematic reviews included in this review matched the protocol requirement (see Appendix A) for their individual studies inclusion criteria; reviews which deviated from this were excluded. In the absence of a standardised quality assessment tool for epidemiological review questions, the ROBIS tool was applied. The ROBIS tool determines the risk of bias in systematic reviews through a three-phase approach. Firstly, considering the relevance of each included systematic review to the research question, secondly, identifying any concerns with the review process and lastly, judging the risk of bias. The rating from these three phases was used to determine an overall risk of bias rating. The risk of bias across the evidence included for this evidence review ranged from low to very high overall risk of bias. High to very high risk of bias ratings were due to the lack of risk of bias assessment within the review and/or insufficient information available on the review methodology to allow the risk of bias assessments.

1.1.8.3 Benefits and harms

The recognition of the common comorbidities in people with epilepsy will benefit patients individually by ensuring they receive appropriate care and should also help inform the appropriate organisation and delivery of services that are made accessible. This evidence review highlighted the increased psychological difficulties experienced by people with epilepsy, with prevalence rates of

depression and anxiety reported at a range of 4.1-43.4% and 8-50% respectively, compared to the general population, which was reported at 2.9-12.7 and 12.4-22%, respectively. Clinically significant levels of dementia and psychosis were also reported in people with epilepsy at 8.1-17.5% and 7%, respectively. A review looking at data from neuropsychological test results and school prevalence reports found children with epilepsy had high prevalence rates for learning disabilities, 26% for dysgraphia and 23-70% for school difficulties and educational support and cognitive difficulties at 24%. Despite the high to very high risk of bias rating of some of the included reviews, the guideline committee acknowledged the importance of these prevalence statistics and the need for better care-plans for people with epilepsy and comorbidities.

The committee was aware of variation in how services are organised and the patient experience of seeing multiple specialists separately for different aspects of their condition. To ensure appropriate care plans are put in place, the guideline committee considered epilepsy specialists and mental health specialists needed to work better together. The committee acknowledged that often mental health specialists do not have enough information about epilepsy to provide adequate support to people with epilepsy when referred to them. Equally, there is a need for neurologists and paediatricians to recognise the clinical presentation of intellectual difficulties in children with epilepsy. The committee also acknowledged the risk associated between dementia and epilepsy and the need for better collaboration between epilepsy and geriatric services. The results of this review highlighted the close link between epilepsy and depression, anxiety, psychosis and dementia. The committee were also aware of the increased risk of suicide amongst people with epilepsy. Although the prevalence of suicide was not investigated in this review, the committee highlighted the importance of healthcare providers to be aware of this risk. A range of issues including mental health difficulties, social deprivation, and alcohol abuse may be factors that contribute to an increased risk of suicide, and the committee acknowledged the cause is multifactorial and a complex area. However, they agreed early recognition and intervention can mitigate risk. The committee expressed a need for shared working across all specialities involved as a joint multidisciplinary team. The committee noted that this close working relationship should also address the disconnect felt

by people with epilepsy and their families/carers when having care split across separate clinicians. Furthermore, since ASM and anti-psychotic medication have adverse effects when taken together, joint-multidisciplinary working can help manage and review treatment plans.

1.1.9 Cost effectiveness and resource use

Cost effectiveness evidence was not sought as this is a question about prevalence.

The committee discussed the clinical evidence noting the prevalence of mental health co-morbidities, learning disabilities and dementia is increased in people with epilepsy. The committee acknowledged that current best practice for people with epilepsy with mental health co-morbidities is to provide coordinated care using a multidisciplinary team approach and to ensure effective communication and liaison between health care professionals across the relevant services involved in the care of the person with epilepsy. The committee noted that current best practice is observed in around 25% of NHS settings. Therefore, although the recommendations made by the committee reflect current best practice, they do not reflect current practice for the majority of people.

The committee noted that although there will be a change in practice for the majority of health care providers, a multidisciplinary team approach for delivering care will likely be cost-saving in the long run. A multidisciplinary team approach with effective communication and liaison between health care professionals will also allow for better care to be delivered to people with epilepsy who have mental health co-morbidities. The approach enables people to access services simultaneously or consecutively with more effective sharing of information. Sharing of information allows for better-tailored health care plans, and being able to access services simultaneously or consecutively results in cost savings in the form of fewer appointments and less administration time. For example, if a person presenting to a routine epilepsy appointment can then automatically be referred to a mental health service if required, the person in question does not have to access the mental health service through a primary care referral. The mental health service will also be aware of the type of assessment or care required. This will either omit the need for an initial assessment or decrease the face-to-face time required for initial assessment depending on what

is most suitable for the person's health care needs. The committee also noted it may allow for initial appointments to be conducted via telephone, which would also result in cost savings.

The committee also acknowledged that this approach would likely improve the person's quality-of-life as quicker referral times and more coherent health care are likely to make people feel more valued and listened to. The committee noted that an epilepsy diagnosis could be very challenging to live with. Some people receiving care feel as though their voice is not heard and find it demoralising when they have to explain the same problem to different health care professionals a number of times before they receive the appropriate care. This positive impact on patient's quality of life would likely be seen for all epilepsy patients but would be greatest for people who may feel more vulnerable initially (for example, people with anxiety, learning disabilities or dementia).

Although the recommendations made will change practice for a large proportion of people, the costs associated with this change will likely only be short-term whilst healthcare providers adapt to the changes required in communication across services. The additional costs observed will be seen in the form of additional staff time spent liaising with different services, but the committee noted this would be negligible if appropriate systems are put in place. For example, a consultant may have to spend an additional couple of minutes after an appointment with a patient communicating with other teams or organising a referral, but less administration in within the healthcare system will be observed overall compared to if a person had to access a service through a primary care referral.

The committee did note that the recommendations may result in additional appointments within the healthcare service as some people who would not have accessed services on their own may now be referred for an appointment. However, the committee noted this would likely only be a small number of patients. Also, for this group of people their care would have been sub-optimal which would have likely had a negative impact on their quality of life and potentially result in additional costs when accessing services at a later date.

Overall, the recommendations made may result in an initial increase in costs for the NHS but will be cost-saving in the long-run and result in better health outcomes for patients.

1.1.10 Other factors the committee took into account

The committee agreed the comorbidities of learning disabilities and dementia found within the review should be highlighted within the guideline by making a cross referral to existing NICE guidance

Mental health problems in people with learning disabilities: prevention, assessment and management
(<https://www.nice.org.uk/guidance/ng54>)

Learning disabilities and behaviour that challenges: service design and delivery
(<https://www.nice.org.uk/guidance/ng93>)

Dementia: assessment, management and support for people living with dementia and their carers
(<https://www.nice.org.uk/guidance/ng97>)

See also evidence review 16 on Psychological treatments in people with epilepsy for cross-reference to NICE mental health guidance:

Depression in adults with a chronic health problem, Depression in children and young people, Common mental health problems, Generalised anxiety disorder and panic disorder, Psychosis and schizophrenia in adults, and Psychosis and schizophrenia in children and young people.

1.1.11 Recommendations supported by this evidence review

This evidence review supports recommendations 9.1.1 – 9.1.5 in the NICE guideline.

References

1. Abraham N, Buvanawari P, Rathakrishnan R, Tran BX, Thu GV, Nguyen LH et al. A meta-analysis of the rates of suicide ideation, attempts and deaths in people with epilepsy. *International Journal of Environmental Research and Public Health*. 2019; 16(8):1451
2. Allebone J, Kanaan R, Wilson SJ. Systematic review of structural and functional brain alterations in psychosis of epilepsy. *Journal of Neurology, Neurosurgery and Psychiatry*. 2018; 89(6):611-617
3. Amiet C, Gourfinkel-An I, Bouzamondo A, Tordjman S, Baulac M, Lechat P et al. Epilepsy in autism is associated with intellectual disability and gender: evidence from a meta-analysis. *Biological Psychiatry*. 2008; 64(7):577-582
4. Anderson M, Choonara I. A systematic review of safety monitoring and drug toxicity in published randomised controlled trials of antiepileptic drugs in children over a 10-year period. *Archives of Disease in Childhood*. 2010; 95(9):731-738
5. Arana A, Wentworth CE, Ayuso-Mateos JL, Arellano FM. Suicide-related events in patients treated with antiepileptic drugs. *New England Journal of Medicine*. 2010; 363(6):542-551
6. Arico M, Arigliani E, Giannotti F, Romani M. ADHD and ADHD-related neural networks in benign epilepsy with centrotemporal spikes: A systematic review. *Epilepsy & Behavior*. 2020; 112:107448
7. Asadi-Pooya AA, Kanemoto K, Kwon OY, Taniguchi G, Dong Z, Chinvarun Y et al. Depression in people with epilepsy: How much do Asian colleagues acknowledge it? *Seizure*. 2018; 57:45-49
8. Bagary M, Delanty N, McMurray R, Villanueva V. Impact of intellectual disability on the effectiveness, safety and tolerability of eslicarbazepine acetate as a treatment for partial-onset seizures. *Epilepsia*. 2017; 58(Suppl 5):S161
9. Banach R, Boskovic R, Einarson T, Koren G. Long-term developmental outcome of children of women with epilepsy, unexposed or exposed prenatally to antiepileptic drugs: a meta-analysis of cohort studies. *Drug Safety*. 2010; 33(1):73-79
10. Baranowski CJ. The quality of life of older adults with epilepsy: A systematic review. *Seizure*. 2018; 60:190-197

11. Beavis J, Kerr M, Marson AG. Non-pharmacological interventions for epilepsy in people with intellectual disabilities. *Cochrane Database of Systematic Reviews* 2007, Issue 4. Art. No.: CD005502. DOI: 10.1002/14651858.CD005502.pub2.
12. Bell GS, Gaitatzis A, Bell CL, Johnson AL, Sander JW. Drowning in people with epilepsy: how great is the risk? *Neurology*. 2008; 71(8):578-582
13. Bell GS, Gaitatzis A, Bell CL, Johnson AL, Sander JW. Suicide in people with epilepsy: How great is the risk? *Epilepsia*. 2009; 50(8):1933-1942
14. Bell GS, Mula M, Sander JW. Suicidality in people taking antiepileptic drugs: What is the evidence? *CNS Drugs*. 2009; 23(4):281-292
15. Benamer HT, Grosset DG. A systematic review of the epidemiology of epilepsy in Arab countries. *Epilepsia*. 2009; 50(10):2301-2304
16. Besag F, Aldenkamp A, Caplan R, Dunn D, Gobbi G, Sillanpaa M. Psychiatric disturbance in children with epilepsy. *Epilepsy Currents*. 2015; 15(Suppl 1):189-190
17. Beyenburg S, Mitchell AJ, Schmidt D, Elger CE, Reuber M. Anxiety in patients with epilepsy: systematic review and suggestions for clinical management. *Epilepsy & Behavior*. 2005; 7(2):161-171
18. Blickwedel J, Ali A, Hassiotis A. Epilepsy and challenging behaviour in adults with intellectual disability: A systematic review. *Journal of Intellectual and Developmental Disability*. 2019; 44(2):219-231
19. Boot FH, Pel JJM, Evenhuis HM, van der Steen J. Factors related to impaired visual orienting behavior in children with intellectual disabilities. *Research in Developmental Disabilities*. 2012; 33(5):1670-1676
20. Bowley C, Kerr M. Epilepsy and intellectual disability. *Journal of Intellectual Disability Research*. 2000; 44(Pt 5):529-543
21. Brandt C, Mula M. Anxiety disorders in people with epilepsy. *Epilepsy & Behavior*. 2016; 59:87-91
22. Breuer LEM, Boon P, Bergmans JWM, Mess WH, Besseling RMH, de Louw A et al. Cognitive deterioration in adult epilepsy: Does accelerated cognitive ageing exist? *Neuroscience and Biobehavioral Reviews*. 2016; 64:1-11

23. Britton JW, Shih JJ. Antiepileptic drugs and suicidality. *Drug, Healthcare and Patient Safety*. 2010; 2(1):181-189
24. Brodie M, Walker M, Lagae L, Helmstaedter C, Carreno M. Debating the impact of AEDs on behavioural change and cognitive impairment in epilepsy. *Epilepsia*. 2016; 57(Suppl 2):5
25. Butler CR, Zeman AZ. Recent insights into the impairment of memory in epilepsy: Transient epileptic amnesia, accelerated long-term forgetting and remote memory impairment. *Brain: A Journal of Neurology*. 2008; 131(9):2243-2263
26. Cavanna AE, Cavanna S, Bertero L, Robertson MM. Depression in women with epilepsy: Clinical and neurobiological aspects. *Functional Neurology*. 2010; 25(2):83-87
27. Cobham VE, Hickling A, Kimball H, Thomas HJ, Scott JG, Middeldorp CM. Systematic review: Anxiety in children and adolescents with chronic medical conditions. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2020; 59(5):595-618
28. Cubala WJ, Włodarczyk A, Wiglusz MS, Szarmach J. What really is a 'gold standard' in depression recognition among patients with epilepsy? *Epilepsy & Behavior*. 2018; 87:249
29. Cyr S, Guo DX, Marcil MJ, Dupont P, Jobidon L, Benrimoh D et al. Posttraumatic stress disorder prevalence in medical populations: A systematic review and meta-analysis. *General Hospital Psychiatry*. 2021; 69:81-93
30. de Winter CF, Jansen AA, Evenhuis HM. Physical conditions and challenging behaviour in people with intellectual disability: a systematic review. *Journal of Intellectual Disability Research*. 2011; 55(7):675-698
31. Deb S, Akrouf Brizard B, Limbu B. Association between epilepsy and challenging behaviour in adults with intellectual disabilities: systematic review and meta-analysis. *BJPsych Open*. 2020; 6(5):e114
32. Doran Z, Shankar R, Keezer MR, Dale C, McLean B, Kerr MP et al. Managing anti-epileptic drug treatment in adult patients with intellectual disability: A serious conundrum. *European Journal of Neurology*. 2016; 23(7):1152-1157
33. Doran Z, Shankar R, Sander LJ, Lee W, Dale C, Kerr M et al. Prescribing for epilepsy in adult patients with an intellectual disability and/or pervasive developmental disorder: A systematic

- review. *European Journal of Neurology*. 2015; 22(1):389
34. Elliott G, Isaac CL, Muhlert N. Measuring forgetting: A critical review of accelerated long-term forgetting studies. *Cortex*. 2014; 54(1):16-32
35. Ferrer P, Ballarin E, Sabate M, Vidal X, Ibanez L. Antiepileptic drugs and suicide: A systematic review. *Pharmacoepidemiology and Drug Safety*. 2013; 22(S1):52-53
36. Ferrer P, Ballarin E, Sabate M, Vidal X, Rottenkolber M, Amelio J et al. Antiepileptic drugs and suicide: a systematic review of adverse effects. *Neuroepidemiology*. 2014; 42(2):107-120
37. Fiest K, Dykeman J, Patten S, Kaplan G, Wiebe S, Jette N. The relationship between depression & epilepsy: A systematic review and meta-analysis. *Neurology*. 2012; 78(Suppl 1):P01.042
38. Fiest K, Dykeman J, Patten S, Kaplan GG, Wiebe S, Jette N. Measuring depression in epilepsy: A systematic review and meta-analysis. *American Journal of Epidemiology*. 2012; 175(11):S129
39. Fiest KM, Dykeman J, Patten SB, Wiebe S, Kaplan GG, Maxwell CJ et al. Depression in epilepsy: a systematic review and meta-analysis. *Neurology*. 2013; 80(6):590-599
40. Finzel M. Therapy and clinical course of patients with psychosis, epilepsy and intellectual disability. *Epilepsia*. 2009; 50(S6):30
41. Fitzgerald B, Ring H. Epilepsy, mental health, adults with learning disability - reviewing the evidence. *Psychiatry*. 2009; 8(11):422-424
42. Fonseca Wald ELA, Hendriksen JGM, Drenthen GS, Kuijk S, Aldenkamp AP, Vles JSH et al. Towards a better understanding of cognitive deficits in absence epilepsy: A systematic review and meta-analysis. *Neuropsychology Review*. 2019; 29(4):421-449
43. Fonseca Wald ELA, Hendriksen JGM, Drenthen GS, Kuijk S, Aldenkamp AP, Vles JSH et al. Correction to: Towards a better understanding of cognitive deficits in absence epilepsy: A systematic review and meta-analysis. *Neuropsychology Review*. 2020; 30(1):164-165
44. Gandy M, Sharpe L, Perry KN. Cognitive behavior therapy for depression in people with epilepsy: a systematic review. *Epilepsia*. 2013; 54(10):1725-1734

45. Gandy M, Sharpe L, Perry KN. Psychosocial predictors of depression and anxiety in patients with epilepsy: a systematic review. *Journal of Affective Disorders*. 2012; 140(3):222-232
46. GBD 2016 Neurology Collaborators. Global, regional, and national burden of neurological disorders, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurology*. 2019; 18(5):459-480
47. Gill SJ, Lukmanji S, Fiest KM, Patten SB, Wiebe S, Jette N. Depression screening tools in persons with epilepsy: A systematic review of validated tools. *Epilepsia*. 2017; 58(5):695-705
48. Hall KE, Isaac CL, Harris P. Memory complaints in epilepsy: An accurate reflection of memory impairment or an indicator of poor adjustment? A review of the literature. *Clinical Psychology Review*. 2009; 29(4):354-367
49. Johnson AL, McLeish AC, Shear PK, Privitera M. Panic and epilepsy in adults: A systematic review. *Epilepsy & Behavior*. 2018; 85:115-119
50. Johnson KA, Macfarlane MD, Looi JCL. Affective disorders and functional (non-epileptic) seizures in persons with epilepsy. *Australasian Psychiatry*. 2016; 24(6):526-528
51. Jones JE. Treating anxiety disorders in children and adolescents with epilepsy: What do we know? *Epilepsy & Behavior*. 2014; 39:137-142
52. Jones R, Rickards H, Cavanna AE. The prevalence of psychiatric disorders in epilepsy: a critical review of the evidence. *Functional Neurology*. 2010; 25(4):191-194
53. Kanner AM. Depression in epilepsy: prevalence, clinical semiology, pathogenic mechanisms, and treatment. *Biological Psychiatry*. 2003; 54(3):388-398
54. Kanner AM, Balabanov A. Depression and epilepsy: how closely related are they? *Neurology*. 2002; 58(8 Suppl 5):S27-39
55. Kattimani S, Mahadevan S. Treating children with attention-deficit/hyperactivity disorder and comorbid epilepsy. *Annals of Indian Academy of Neurology*. 2011; 14(1):9-11
56. Kavros PM, Clarke T, Strug LJ, Halperin JM, Dorta NJ, Pal DK. Attention impairment in rolandic epilepsy: systematic review. *Epilepsia*. 2008; 49(9):1570-1580
57. Kim M, Kim YS, Kim DH, Yang TW, Kwon OY. Major depressive disorder in epilepsy clinics: A meta-analysis. *Epilepsy & Behavior*. 2018; 84:56-69

58. Kolc KL, Sadleir LG, Scheffer IE, Ivancevic A, Roberts R, Pham DH et al. A systematic review and meta-analysis of 271 PCDH19-variant individuals identifies psychiatric comorbidities, and association of seizure onset and disease severity. *Molecular Psychiatry*. 2019; 24(2):241-251
59. Kolevzon A, Delaby E, Berry-Kravis E, Buxbaum JD, Betancur C. Neuropsychiatric decompensation in adolescents and adults with Phelan-McDermid syndrome: a systematic review of the literature. *Molecular Autism*. 2019; 10:50
60. Kutlubaev MA, Xu Y, Hackett ML, Stone J. Dual diagnosis of epilepsy and psychogenic nonepileptic seizures: Systematic review and meta-analysis of frequency, correlates, and outcomes. *Epilepsy & Behavior*. 2018; 89:70-78
61. Kwok H, Cheung PWH. Co-morbidity of psychiatric disorder and medical illness in people with intellectual disabilities. *Current Opinion in Psychiatry*. 2007; 20(5):443-449
62. Lagogianni C, Gatzonis S, Patrikelis P. Fatigue and cognitive functions in epilepsy: A review of the literature. *Epilepsy & Behavior*. 2020; 114:107541
63. Lai C-W, Trimble MR. Stress and epilepsy. *Journal of Epilepsy*. 1997; 10(4):177-186
64. Lax-Pericall MT, Bird V, Taylor E. Gender and psychiatric disorders in children with epilepsy. A meta-analysis. *Epilepsy & Behavior*. 2019; 94:144-150
65. Loughman A, Bendrups NA, D'Souza WJ. A systematic review of psychiatric and psychosocial comorbidities of genetic generalised epilepsies (GGE). *Neuropsychology Review*. 2016; 26(4):364-375
66. Loughman A, Bowden SC, D'Souza W. Cognitive functioning in idiopathic generalised epilepsies: a systematic review and meta-analysis. *Neuroscience and Biobehavioral Reviews*. 2014; 43:20-34
67. Lukmanji S, Manji SA, Kadhim S, Sauro KM, Wirrell EC, Kwon CS et al. The co-occurrence of epilepsy and autism: A systematic review. *Epilepsy & Behavior*. 2019; 98(Pt A):238-248
68. M HB, Veiby G, B AE, Gilhus NE. Depression and anxiety during pregnancy and the postpartum period in women with epilepsy: A review of frequency, risks and recommendations for treatment. *Seizure*. 2015; 28:39-45

69. Maryam S, Parviz B. Depression in children and adolescents with epilepsy: a 15 year research review of prevalence, and demographic and seizure related correlates. *Iranian Journal of Pediatrics*. 2013; 23(1):1-7
70. Menlove L, Reilly C. Memory in children with epilepsy: a systematic review. *Seizure*. 2015; 25:126-135
71. Michelucci R, Forti A, Rubboli G, Plasmati R, et al. Mental retardation and behavioural disturbances related to epilepsy: A review. *Brain Dysfunction*. 1989; 2(1):3-9
72. Monteagudo-Gimeno E, Sanchez-Gonzalez R, Rodriguez-Urrutia A, Fonseca-Casals F, Perez-Sola V, Bulbena-Vilarrasa A et al. Relationship between cognition and psychopathology in drug-resistant epilepsy: A systematic review. *European Journal of Psychiatry*. 2020; 34(3):109-119
73. Monti G, Meletti S. Emotion recognition in temporal lobe epilepsy: A systematic review. *Neuroscience and Biobehavioral Reviews*. 2015; 55:280-293
74. Muhigwa A, Preux PM, Gerard D, Marin B, Boumediene F, Ntamwira C et al. Comorbidities of epilepsy in low and middle-income countries: systematic review and meta-analysis. *Scientific Reports*. 2020; 10(1):9015
75. Mula M. The clinical spectrum of bipolar symptoms in epilepsy: a critical reappraisal. *Postgraduate Medicine*. 2010; 122(4):17-23
76. Mula M, Hesdorffer DC. Suicidal behavior and antiepileptic drugs in epilepsy: analysis of the emerging evidence. *Drug Healthcare & Patient Safety*. 2011; 3:15-20
77. Mula M, Kaufman KR. Double stigma in mental health: epilepsy and mental illness. *BJPsych Open*. 2020; 6(4):e72
78. Mula M, Marotta AE, Monaco F. Epilepsy and bipolar disorders. *Expert Review of Neurotherapeutics*. 2010; 10(1):13-23
79. National Institute for Health and Care Excellence. Developing NICE guidelines: the manual [updated October 2020]. London. National Institute for Health and Care Excellence, 2014. Available from: <http://www.nice.org.uk/article/PMG20/chapter/1%20Introduction%20and%20overview>
80. Neumann H, Helmke F, Thiels C, Polster T, Selzer LM, Daseking M et al. Cognitive development in children with benign rolandic epilepsy of childhood with centrotemporal spikes - results of a current systematic

- database search. *Fortschritte der Neurologie Psychiatrie*. 2016; 84(10):617-632
81. Otero S. Psychopathology and psychological adjustment in children and adolescents with epilepsy. *World Journal of Pediatrics*. 2009; 5(1):12-17
82. Parnas J, Korsgaard S. Epilepsy and psychosis. *Acta Psychiatrica Scandinavica*. 1982; 66(2):89-99
83. Patten SB, Williams JVA, Lavorato DH, Wang JL, Jette N, Sajobi TT et al. Patterns of association of chronic medical conditions and major depression. *Epidemiology & Psychiatric Science*. 2018; 27(1):42-50
84. Pinquart M, Shen Y. Anxiety in children and adolescents with chronic physical illnesses: a meta-analysis. *Acta Paediatrica*. 2011; 100(8):1069-1076
85. Pinquart M, Shen Y. Behavior problems in children and adolescents with chronic physical illness: a meta-analysis. *Journal of Pediatric Psychology*. 2011; 36(9):1003-1016
86. Quintas R, Raggi A, Giovannetti AM, Pagani M, Sabariego C, Cieza A et al. Psychosocial difficulties in people with epilepsy: a systematic review of literature from 2005 until 2010. *Epilepsy & Behavior*. 2012; 25(1):60-67
87. Ramanujam B, Bajaj BK, Kaur K, Anand KS, Buxi G. Is depression related to low folate levels in people with epilepsy? An observational study and meta-analysis. *Journal of Neurosciences in Rural Practice*. 2017; 8(3):381-388
88. Reilly C, Kent E, Neville BGR. Review: Psychopathology in childhood epilepsy. *Child & Adolescent Mental Health*. 2013; 18(2):65-75
89. Reilly C, Neville BGR. Academic achievement in children with epilepsy: A review. *Epilepsy Research*. 2011; 97(1-2):112-123
90. Ricciardi L, Demartini B, Fotopoulou A, Edwards MJ. Alexithymia in neurological disease: A review. *Journal of Neuropsychiatry and Clinical Neurosciences*. 2015; 27(3):179-187
91. Richard AE, Scheffer IE, Wilson SJ. Features of the broader autism phenotype in people with epilepsy support shared mechanisms between epilepsy and autism spectrum disorder. *Neuroscience and Biobehavioral Reviews*. 2017; 75:203-233
92. Rodenburg R, Stams GJ, Meijer AM, Aldenkamp AP, Dekovic M. Psychopathology in

- children with epilepsy: a meta-analysis. *Journal of Pediatric Psychology*. 2005; 30(6):453-468
93. Sajatovic M. Self-management for adults with epilepsy: aggregate Managing Epilepsy Well Network findings on depressive symptoms. *Epilepsia*. 2019; 60(9):1921-1931
94. Sanya EO. Peculiarity of epilepsy in elderly people: A review. *West African Journal of Medicine*. 2010; 29(6):365-372
95. Scott AJ, Sharpe L, Hunt C, Gandy M. Anxiety and depressive disorders in people with epilepsy: A meta-analysis. *Epilepsia*. 2017; 58(6):973-982
96. Scott AJ, Sharpe L, Loomes M, Gandy M. Systematic review and meta-analysis of anxiety and depression in youth with epilepsy. *Journal of Pediatric Psychology*. 2020; 45(2):133-144
97. Secinti E, Thompson EJ, Richards M, Gaysina D. Research Review: Childhood chronic physical illness and adult emotional health - a systematic review and meta-analysis. *Journal of Child Psychology and Psychiatry and Allied Disciplines*. 2017; 58(7):753-769
98. Seethalakshmi R, Krishnamoorthy ES. Depression in epilepsy: Phenomenology, diagnosis and management. *Epileptic Disorders*. 2007; 9(1):1-10
99. Sen A, Capelli V, Husain M. Cognition and dementia in older patients with epilepsy. *Brain: A Journal of Neurology*. 2018; 141(6):1592-1608
100. Srinivas HV, Shah U. Comorbidities of epilepsy. *Neurology India*. 2017; 65(Supplement):S18-S24
101. Stevelink R, Koeleman BPC, Sander JW, Jansen FE, Braun KPJ. Refractory juvenile myoclonic epilepsy: a meta-analysis of prevalence and risk factors. *European Journal of Neurology*. 2019; 26(6):856-864
102. Stewart E, Catroppa C, Lah S. Theory of mind in patients with epilepsy: A systematic review and meta-analysis. *Neuropsychology Review*. 2016; 26(1):3-24
103. Stewart E, Lah S, Smith ML. Patterns of impaired social cognition in children and adolescents with epilepsy: The borders between different epilepsy phenotypes. *Epilepsy & Behavior*. 2019; 100(Part B):9
104. Strasser L, Downes M, Kung J, Cross JH, De Haan M. Prevalence and risk factors for autism spectrum disorder in epilepsy: a systematic review and meta-analysis. *Developmental*

- Medicine and Child Neurology. 2018; 60(1):19-29
105. Subota A, Pham T, Jette N, Sauro K, Lorenzetti D, Holroyd-Leduc J. The association between dementia and epilepsy: a systematic review and meta-analysis. *Epilepsia*. 2017; 58(6):962-972
106. Tao K, Wang X. The comorbidity of epilepsy and depression: diagnosis and treatment. *Expert Review of Neurotherapeutics*. 2016; 16(11):1321-1333
107. Taylor RS, Sander JW, Taylor RJ, Baker GA. Predictors of health-related quality of life and costs in adults with epilepsy: a systematic review. *Epilepsia*. 2011; 52(12):2168-2180
108. Theodore WH, Spencer SS, Wiebe S, Langfitt JT, Ali A, Shafer PO et al. Epilepsy in North America: A report prepared under the auspices of the Global Campaign against Epilepsy, the International Bureau for Epilepsy, the International League Against Epilepsy, and the World Health Organization. *Epilepsia*. 2006; 47(10):1700-1722
109. Thomson L, Fayed N, Sedarous F, Ronen GM. Life quality and health in adolescents and emerging adults with epilepsy during the years of transition: a scoping review. *Developmental Medicine and Child Neurology*. 2014; 56(5):421-433
110. Tramoni-Negre E, Lambert I, Bartolomei F, Felician O. Long-term memory deficits in temporal lobe epilepsy. *Revue Neurologique*. 2017; 173(7-8):490-497
111. Trimble MR, Krishnamoorthy ES. Neuropsychiatric disorders in epilepsy: some transcultural issues. *Epilepsia*. 2003; 44(Suppl 1):21-24
112. Trinkka E, Kwan P, Lee B, Dash A. Epilepsy in Asia: Disease burden, management barriers, and challenges. *Epilepsia*. 2019; 60(Suppl 1):7-21
113. Tuchman R, Cuccaro M. Epilepsy and autism: neurodevelopmental perspective. *Current Neurology and Neuroscience Reports*. 2011; 11(4):428-434
114. van Ool JS, Snoeijen-Schouwenaars FM, Schelhaas HJ, Tan IY, Aldenkamp AP, Hendriksen JGM. A systematic review of neuropsychiatric comorbidities in patients with both epilepsy and intellectual disability. *Epilepsy & Behavior*. 2016; 60:130-137
115. Vannest J, Tenney JR, Gelineau-Morel R, Maloney T, Glauser TA. Cognitive and behavioral outcomes in benign childhood

- epilepsy with centrotemporal spikes. *Epilepsy & Behavior*. 2015; 45:85-91
116. Vazquez B, Devinsky O. Epilepsy and anxiety. *Epilepsy & Behavior*. 2003; 4(Suppl 4):S20-S25
117. Verche E, San Luis C, Hernandez S. Neuropsychology of frontal lobe epilepsy in children and adults: Systematic review and meta-analysis. *Epilepsy & Behavior*. 2018; 88:15-20
118. Verrotti A, Matricardi S, Rinaldi VE, Prezioso G, Coppola G. Neuropsychological impairment in childhood absence epilepsy: Review of the literature. *Journal of the Neurological Sciences*. 2015; 359(1-2):59-66
119. Vonberg FW, Bigdeli TB. Genetic correlation between schizophrenia and epilepsy. *JAMA Neurology*. 2016; 73(1):125-126
120. Wade DT, Hewer RL. Epidemiology of some neurological diseases. With special reference to work load on the NHS. *International Rehabilitation Medicine*. 1986; 8(3):129-137
121. Walsh S, Donnan J, Fortin Y, Sikora L, Morrissey A, Collins K et al. A systematic review of the risks factors associated with the onset and natural progression of epilepsy. *Neurotoxicology*. 2017; 61:64-77
122. Walsh S, Levita L, Reuber M. Comorbid depression and associated factors in PNES versus epilepsy: Systematic review and meta-analysis. *Seizure*. 2018; 60:44-56
123. Werhahn KJ. Epilepsy in the elderly. *Deutsches Arzteblatt*. 2009; 106(9):135-142
124. Wickens S, Bowden SC, D'Souza W. Cognitive functioning in children with self-limited epilepsy with centrotemporal spikes: A systematic review and meta-analysis. *Epilepsia*. 2017; 58(10):1673-1685
125. Wiglusz MS, Cubala WJ, Galuszko-Wegielnik M, Jakuszkowiak-Wojten K, Landowski J. Mood disorders in epilepsy - diagnostic and methodological considerations. *Psychiatria Danubina*. 2012; 24(Suppl 1):S44-50
126. Williams AE, Giust JM, Kronenberger WG, Dunn DW. Epilepsy and attention-deficit hyperactivity disorder: links, risks, and challenges. *Neuropsychiatric Disease and Treatment*. 2016; 12:287-296
127. Yang Y, Yang M, Shi Q, Wang T, Jiang M. Risk factors for depression in patients with epilepsy: A meta-analysis. *Epilepsy & Behavior*. 2020; 106:107030

128. Yoong M. Quantifying the deficit-imaging neurobehavioural impairment in childhood epilepsy. *Quantitative Imaging in Medicine & Surgery*. 2015; 5(2):225-237
129. Yroni A, Arbus C, Valton L, Schmitt L. Mood disorders and epilepsy surgery: A review. *Encephale*. 2017; 43(2):154-159
130. Zapata Barco AM, Restrepo-Martinez M, Restrepo D. Depression in people with epilepsy. What is the connection? *Revista Colombiana de Psiquiatria*. 2020; 49(1):53-61

Appendices

Appendix A Review protocols

A.1 Review protocol for prevalence of depression, anxiety, learning disability and behavioural/cognitive difficulties in people with epilepsies

ID	Field	Content
1.	Review title	Prevalence of depression, anxiety, learning disability and behavioural/cognitive difficulties in people with epilepsies.
2.	Review question	What is the prevalence of depression, anxiety, intellectual disability, developmental difficulties and cognitive difficulties in people with epilepsies?
3.	Objective	To determine the prevalence of depression, anxiety, intellectual disability, developmental difficulties, and cognitive difficulties in people with epilepsies
4.	Searches	<p>The following databases (from inception) will be searched:</p> <ul style="list-style-type: none"> • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE • PsycInfo <p>Searches will be restricted by:</p> <ul style="list-style-type: none"> • English language studies • Human studies <p>Other searches:</p>

		<ul style="list-style-type: none"> • Inclusion lists of systematic reviews <p>The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant.</p> <p>The full search strategies will be published in the final review.</p>
5.	Condition or domain being studied	
6.	Population	<p>Inclusion: Children, young people and adults with confirmed epilepsy</p> <p>Exclusion: New-born babies (under 28 days) with acute symptomatic seizures.</p>
7.	Types of study to be included	Systematic reviews of all studies reporting period prevalence (limited to period prevalence for all conditions except learning disabilities where point prevalence will also be included)
8.	Other exclusion criteria	<p>Point prevalence reviews will be excluded as they risk an underestimation of the true prevalence (except for lifetime conditions i.e., learning disabilities)</p> <p>Non-English language studies.</p> <p>Conference abstracts will be excluded as it is expected there will be sufficient full text published studies available.</p>
9.	Context	Psychological difficulties are common comorbidities in patients with epilepsy, with a significant negative impact on quality of life. Many children and young people with epilepsy between the ages of 4 and 15 have one or more additional neurological disorders. Learning disabilities, for example, are more prevalent in individuals with epilepsy than in the general population. Cognitive impairment, including, but not limited to, memory difficulties, are observed in people with epilepsy. Such impairments can range from poor concentration and minor forgetfulness to those that have a significant impact on a person's ability to function independently. There are also emerging data relating to bidirectional links between epilepsy and dementia. All of these potential comorbidities are often under-recognised and may be improperly managed in people with epilepsies.
10.	Primary outcomes (critical outcomes)/ comorbidities	<p>In people with Epilepsy, the prevalence of:</p> <ul style="list-style-type: none"> • Depression • Anxiety • Learning disabilities • Cognitive difficulties

		<ul style="list-style-type: none"> • Dementia • Psychosis
11.	Data extraction (selection and coding)	<p>EndNote will be used for reference management, sifting, citations and bibliographies. All references identified by the searches and from other sources will be screened for inclusion. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above.</p> <p>A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4).</p> <p>10% of all evidence reviews are quality assured by a senior research fellow. This includes checking:</p> <ul style="list-style-type: none"> • papers were included /excluded appropriately • a sample of the data extractions • correct methods are used to synthesise data • a sample of the risk of bias assessments <p>Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary.</p>
12.	Risk of bias (quality) assessment	<p>ROBIS tool for assessing risk in systematic reviews.</p> <p>10% of all evidence reviews are quality assured by a senior research fellow. This includes checking:</p> <ul style="list-style-type: none"> • papers were included /excluded appropriately • a sample of the data extractions • correct methods are used to synthesise data • a sample of the risk of bias assessments <p>Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary.</p>
13.	Strategy for data synthesis	Extracting prevalence as reported by systematic reviews.
14.	Analysis of sub-groups	<p>Stratification:</p> <ul style="list-style-type: none"> • Adults (>16 years) and children (≤16 years)

		Subgroup: none		
15.	Type and method of review	<input type="checkbox"/>	Intervention	
		<input type="checkbox"/>	Diagnostic	
		<input type="checkbox"/>	Prognostic	
		<input type="checkbox"/>	Qualitative	
		<input checked="" type="checkbox"/>	Epidemiologic (Prevalence)	
		<input type="checkbox"/>	Service Delivery	
		<input type="checkbox"/>	Other (please specify)	
16.	Language	English		
17.	Country	England		
18.	Anticipated or actual start date			
22.	Anticipated completion date			
19.	Stage of review at time of this submission	Review stage	Started	Completed
		Preliminary searches	<input type="checkbox"/>	<input type="checkbox"/>
		Piloting of the study selection process	<input type="checkbox"/>	<input type="checkbox"/>
		Formal screening of search results against eligibility criteria	<input type="checkbox"/>	<input type="checkbox"/>
		Data extraction	<input type="checkbox"/>	<input type="checkbox"/>
		Risk of bias (quality) assessment	<input type="checkbox"/>	<input type="checkbox"/>

		Data analysis	<input type="checkbox"/>	<input type="checkbox"/>
20.	Named contact	5a. Named contact National Guideline Centre 5b Named contact e-mail NGCEpilepsies@nice.org.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and the National Guideline Centre		
21.	Review team members	National Guideline Centre:		
2.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.		
23.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.		
24.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual . Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10112/documents		
25.	Other registration details			
26.	Reference/URL for published protocol			
27.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as:		

		<ul style="list-style-type: none"> • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE. 	
28.	Keywords		
29.	Details of existing review of same topic by same authors		
30.	Current review status	<input type="checkbox"/>	Ongoing
		<input type="checkbox"/>	Completed but not published
		<input type="checkbox"/>	Completed and published
		<input type="checkbox"/>	Completed, published and being updated
		<input type="checkbox"/>	Discontinued
31.	Additional information		
32.	Details of final publication	www.nice.org.uk	

Appendix B Literature search strategies

This literature search strategy was used for the following review:

- What is the prevalence of depression, anxiety, intellectual disability, developmental difficulties and cognitive difficulties in people with epilepsies?

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.⁷⁹

For more information, please see the Methodology review published as part of the accompanying documents for this guideline.

B.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies for interventions as these concepts may not be well described in title, abstract or indexes and therefore difficult to retrieve. Search filters were applied to the search where appropriate.

Table 8: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 18 February 2021	Systematic review studies Exclusions
Embase (OVID)	1974 – 18 February 2021	Systematic review studies Exclusions
The Cochrane Library (Wiley)	Cochrane Reviews to 2021 Issue 2 of 12 CENTRAL to 2021 Issue 2 of 12	None
PsycINFO (ProQuest)	Inception – 18 February 2021	Systematic review studies

Medline (Ovid) search terms

1.	exp epilepsy/
2.	seizures/
3.	exp status epilepticus/
4.	seizures, febrile/
5.	(dravet syndrome or epilep* or convuls* or continuous spike wave or slow sleep or landau kleffner syndrome or lennox gastaut syndrome or infant* spasm* or seizure* or west syndrome).ti,ab.
6.	or/1-5
7.	letter/
8.	editorial/
9.	news/
10.	exp historical article/
11.	Anecdotes as Topic/
12.	comment/
13.	case report/

14.	(letter or comment*).ti.
15.	or/7-14
16.	randomized controlled trial/ or random*.ti,ab.
17.	15 not 16
18.	animals/ not humans/
19.	exp Animals, Laboratory/
20.	exp Animal Experimentation/
21.	exp Models, Animal/
22.	exp Rodentia/
23.	(rat or rats or mouse or mice).ti.
24.	or/17-23
25.	6 not 24
26.	limit 25 to English language
27.	Meta-Analysis/
28.	exp Meta-Analysis as Topic/
29.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
30.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
31.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
32.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
33.	(search* adj4 literature).ab.
34.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
35.	cochrane.jw.
36.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
37.	or/27-36
38.	cognitive dysfunction/
39.	((cognit* or neurocognit*) adj (dysfunction* or impair* or defec* or declin* or disorder* or deteriorat* or deficit* or difficult* or disabilit* or disabl*)).ti,ab.
40.	depression/ or depressive disorder/
41.	anxiety/
42.	(anxiet* or anxious or depression or low mood or tearfulness or nervousness or sadness or depress* or melanchol*).ti,ab.
43.	exp Mental Disorders/
44.	((concentrat* or memory) adj2 (disorder* or difficult* or poor or lack* or impair* or disabilit* or disable*)).ti,ab.
45.	((attention or behavior* or behaviour* or intellectual* or language or neurodevelopment* or neurological* or perception or psych* or learning) adj3 (deficit* or difficult* or disabilit* or disabl* or disorder* or impair* or declin* or deteriorat*)).ti,ab.
46.	(mental* adj3 (illness or ill or disorder* or factor* or impairment*)).ti,ab.
47.	((psychiatric or psychological*) adj3 (illness or ill or factor*)).ti,ab.
48.	Learning Disabilities/
49.	dementia/ or alzheimer disease/
50.	(alzheimer* or dement*).ti,ab.
51.	Psychotic Disorders/
52.	(psychotic* or psychoses or psychosis).ti,ab.
53.	or/38-52
54.	26 and 37 and 53

Embase (Ovid) search terms

1.	exp *epilepsy/
2.	*landau kleffner syndrome/
3.	exp *seizure/
4.	"seizure, epilepsy and convulsion"/
5.	(dravet syndrome or epilep* or continuous spike wave or slow sleep or landau kleffner syndrome or lennox gastaut syndrome or infant* spasm* or seizure* or west syndrome).ti,ab.
6.	or/1-5
7.	letter.pt. or letter/
8.	note.pt.
9.	editorial.pt.
10.	case report/ or case study/
11.	(letter or comment*).ti.
12.	or/7-11
13.	randomized controlled trial/ or random*.ti,ab.
14.	12 not 13
15.	animal/ not human/
16.	nonhuman/
17.	exp Animal Experiment/
18.	exp Experimental Animal/
19.	animal model/
20.	exp Rodent/
21.	(rat or rats or mouse or mice).ti.
22.	or/15-21
23.	6 not 22
24.	limit 23 to English language
25.	systematic review/
26.	meta-analysis/
27.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
28.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
29.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
30.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
31.	(search* adj4 literature).ab.
32.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
33.	cochrane.jw.
34.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
35.	or/25-34
36.	*cognitive defect/
37.	((cognit* or neurocognit*) adj (dysfunction* or impair* or defec* or declin* or disorder* or deteriorat* or deficit* or difficult* or disabilit* or disabl*)).ti,ab.
38.	depression/
39.	*anxiety/
40.	(anxiet* or anxious or depression or low mood or tearfulness or nervousness or sadness or depress* or melanchol*).ti,ab.
41.	exp mental disease/

42.	((concentrat* or memory) adj2 (disorder* or difficult* or poor or lack* or impair* or disabilit* or disable*)):ti,ab.
43.	((attention or behavior* or behaviour* or intellectual* or language or neurodevelopment* or neurological* or perception or psych* or learning) adj3 (deficit* or difficult* or disabilit* or disabl* or disorder* or impair* or declin* or deteriorat*)):ti,ab.
44.	(mental* adj3 (illness or ill or disorder* or factor* or impairment*)):ti,ab.
45.	((psychiatric or psychological*) adj3 (illness or ill or factor*)):ti,ab.
46.	learning disorder/
47.	dementia/
48.	(alzheimer* or dement*):ti,ab.
49.	psychosis/
50.	(psychotic* or psychoses or psychosis):ti,ab.
51.	or/36-50
52.	24 and 35 and 51

Cochrane Library (Wiley) search terms

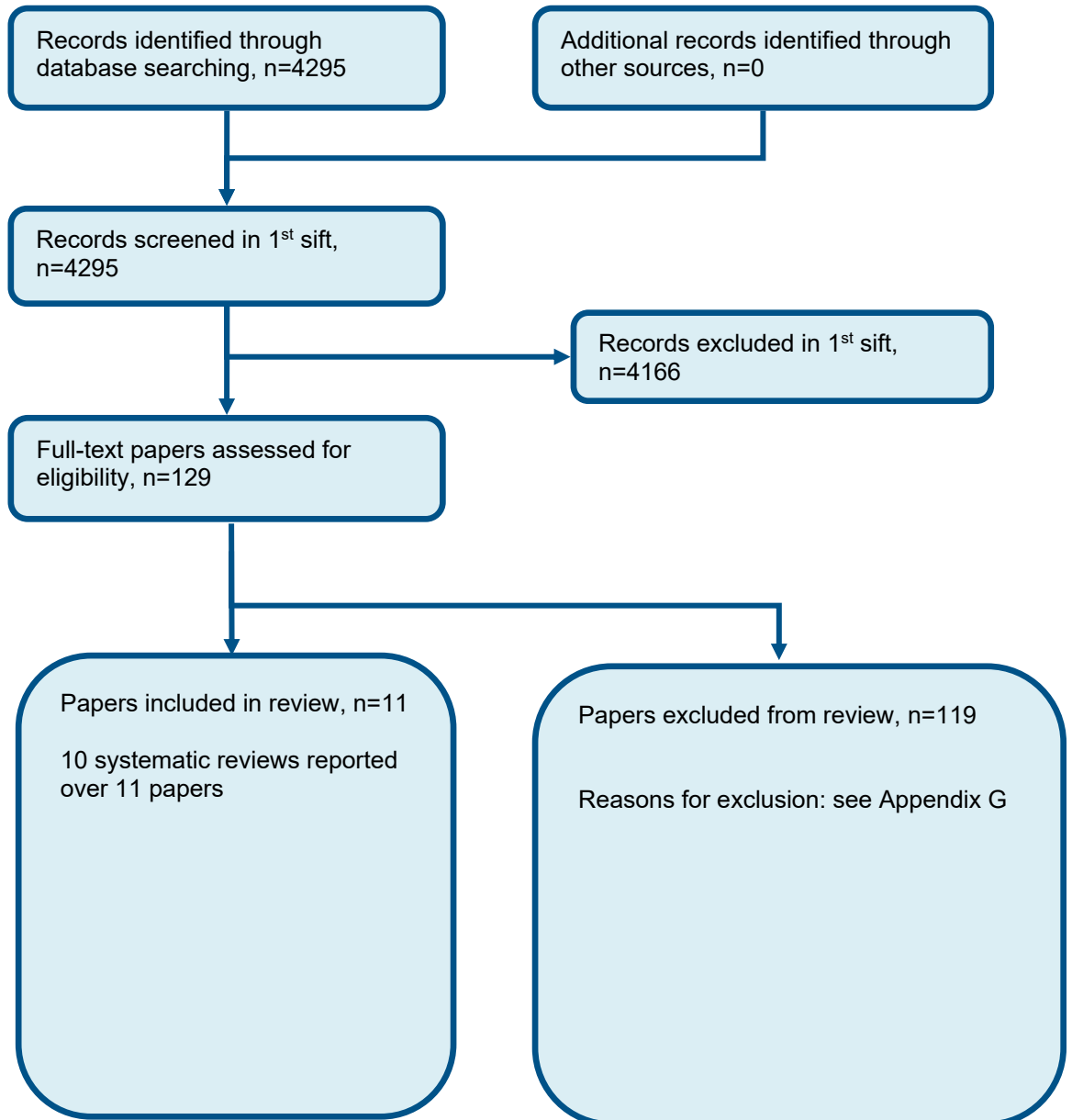
#1.	MeSH descriptor: [Epilepsy] explode all trees
#2.	MeSH descriptor: [Seizures] this term only
#3.	MeSH descriptor: [Status Epilepticus] explode all trees
#4.	MeSH descriptor: [Seizures, Febrile] this term only
#5.	(dravet syndrome or epilep* or convuls* or continuous spike wave or slow sleep or landau kleffner syndrome or lennox gastaut syndrome or infant* spasm* or seizure* or west syndrome):ti,ab
#6.	(or #1-#5)
#7.	MeSH descriptor: [Cognitive Dysfunction] explode all trees
#8.	((cognit* or neurocognit*) near/1 (dysfunction* or impair* or defec* or declin* or disorder* or deteriorat* or deficit* or difficult* or disabilit* or disabl*)):ti,ab
#9.	MeSH descriptor: [Depression] explode all trees
#10.	MeSH descriptor: [Anxiety] explode all trees
#11.	(anxiet* or anxious or depression or low mood or tearfulness or nervousness or sadness or depress* or melanchol*):ti,ab
#12.	MeSH descriptor: [Mental Disorders] explode all trees
#13.	((concentrat* or memory) near/2 (disorder* or difficult* or poor or lack* or impair* or disabilit* or disable*)):ti,ab
#14.	((attention or behavior* or behaviour* or intellectual* or language or neurodevelopment* or neurological* or perception or psych* or learning) near/3 (deficit* or difficult* or disabilit* or disabl* or disorder* or impair* or declin* or deteriorat*)):ti,ab
#15.	(mental* near/3 (illness or ill or disorder* or factor* or impairment*)):ti,ab
#16.	((psychiatric or psychological*) near/3 (illness or ill or factor*)):ti,ab
#17.	MeSH descriptor: [Learning Disabilities] explode all trees
#18.	MeSH descriptor: [Dementia] explode all trees
#19.	MeSH descriptor: [Alzheimer Disease] explode all trees
#20.	(alzheimer* or dement*):ti,ab
#21.	MeSH descriptor: [Psychotic Disorders] explode all trees
#22.	(psychotic* or psychoses or psychosis):ti,ab
#23.	(or #7-#22)
#24.	#6 and #23

PsycINFO (ProQuest) search terms

1.	<p>((MJMAINSUBJECT.EXACT.EXPLODE("Epilepsy") OR MAINSUBJECT.EXACT("Seizures") OR MAINSUBJECT.EXACT("Status Epilepticus") OR TI,AB(dravet syndrome OR epilep* OR continuous spike wave OR slow sleep OR landau kleffner syndrome OR lennox gastaut syndrome OR infant* spasm* OR seizure* OR west syndrome)) AND ((MAINSUBJECT.EXACT("Cognitive Impairment") OR MAINSUBJECT.EXACT("Major Depression") OR MAINSUBJECT.EXACT("Anxiety") OR MAINSUBJECT.EXACT("Mental Disorders") OR MAINSUBJECT.EXACT("Dementia") OR MAINSUBJECT.EXACT("Alzheimer's Disease") AND MAINSUBJECT.EXACT("Psychosis"))) OR TI,AB((cognit* OR neurocognit*) adj (dysfunction* OR impair* OR defec* OR declin* OR disorder* OR deteriorat* OR deficit* OR difficult* OR disabilit* OR disabl*)) OR TI,AB(anxiet* OR anxious OR depression OR low mood OR tearfulness OR nervousness OR sadness OR depress* OR melanchol*) OR TI,AB((concentrat* OR memory) NEAR/2 (disorder* OR difficult* OR poor OR lack* OR impair* OR disabilit* OR disable*)) OR TI,AB((concentrat* OR memory) NEAR/2 (disorder* OR difficult* OR poor OR lack* OR impair* OR disabilit* OR disable*)) OR TI,AB((attention OR behavior* OR behaviour* OR intellectual* OR language OR neurodevelopment* OR neurological* OR perception OR psych* OR learning) NEAR/3 (deficit* OR difficult* OR disabilit* OR disabl* OR disorder* OR impair* OR declin* OR deteriorat*)) OR TI,AB(mental* NEAR/3 (illness OR ill OR disorder* OR factor* OR impairment*)) OR TI,AB((psychiatric OR psychological*) NEAR/3 (illness OR ill OR factor*)) OR TI,AB(alzheimer* OR dement*) OR TI,AB(psychotic* OR psychoses OR psychosis))) AND (((SU.EXACT("Literature Review") OR RTYPE(review) OR ti(review) OR me(literature review)) AND (ti,ab(systematic OR evidence OR methodol* OR quantitative*))) OR (SU.EXACT("Meta Analysis") OR ti,ab(meta-analys* OR metanalys* OR metaanalys* OR meta analys*) OR ti,ab((systematic OR evidence* OR methodol* OR quantitative*) NEAR/3 (review* OR overview*)) OR ti,ab((pool* OR combined OR combining) NEAR/2 (data OR trials OR studies OR results)) OR RTYPE(systematic OR meta*) OR ME(meta analysis OR systematic review)))</p>
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Appendix C Evidence study selection

Figure 1: Flow chart of clinical study selection for the review of prevalence of psychological disorders



Appendix D Clinical evidence

Reference	Asadi-Pooya 2018 ⁷
Study type and analysis	Systematic review of studies looking at depression prevalence in people with epilepsy.
Number of participants and characteristics	26 studies were included in the review. Studies included were published between 1947 and 2017. Studies which focussed on special groups e.g., elderly and veterans were excluded. Specialists were invited from several countries to give prevalence data of depression for their respective countries.
Country	Counties across Asia
Outcomes/ Comorbidities	Prevalence of depression in people with Epilepsy
Results	<ul style="list-style-type: none"> • Japan: 18.6% of people with epilepsy had depression, measured using the Japanese version of the Neurological Disorders Depression Inventory for Epilepsy (NDDI-E) was used to diagnose depression. The prevalence of major depression in the general population was reported at 2.9%, diagnostic information for this statistic was not given. • South Korea: 21.5-27.8% of people with epilepsy had major depressive disorder compared to 3.3-5.6% life-time prevalence of major depressive disorder in the general population. The Korean version of the Neurological Disorders Depression Inventory for Epilepsy (K-NDDI-E) was used to diagnose depression, with a cut-off score of 11 suggesting major depressive disorder. • China: 16.5-43.4% of people with epilepsy had depression compared to 3.6% life-time prevalence of major depressive disorder in the general population. The Chinese version of the Neurological Disorders Depression Inventory for Epilepsy (C-NDDI-E) was used to diagnose depression, cut-off score of 12 suggesting major depressive disorder. • Taiwan: national health insurance research database showed people newly diagnosed with Epilepsy had higher occurrence of depression that people without epilepsy, HR 7.16 (95% CO 4.87-10.5), diagnostic information for this statistic was not given. Using the hospital anxiety and depression scale (HADS) in one clinic-based study of 260 PWE, 8.5% had scores suggestive of moderate to severe depression and 14.2% of mild depression. Psychiatric comorbidities were present in 24.6% of children with epilepsy, diagnostic information for this statistic was not given.

Reference	Asadi-Pooya 2018 ⁷
	<ul style="list-style-type: none"> Iran: In one cross-sectional hospital-based study of 74 adult PWE 26 (35%) patients had symptoms of depression identified with the Beck Depression Inventory (BDI). 12.7% period prevalence of major depressive-disorder in the general population over 12 months was measured using the validated Persian translation of the Composite International Diagnostic Interview (CIDI; version 2.1). <p>Overall range for depression in people with Epilepsy from the 26 studies included was 6.6-43.4%</p>
Comments	No age group specified when searching papers, all data mixed for children and adults.
ROBIS rating	Overall rating: High risk of bias, this was due to the lack of risk of bias assessments carried out in the review for included studies.

Reference	Cobham 2020 ²⁷
Study type and analysis	Systematic review of studies looking at anxiety prevalence in children with chronic medical conditions, i.e., epilepsy.
Number of participants and characteristics	8 studies included, 784 participants, focussing on anxiety in children and adolescents with Epilepsy. Studies included were published between 1990 and 2018.
Country	Studies included were carried out in Nigeria, USA, Norway, Italy.
Outcomes/ Comorbidities	Anxiety
Results	The prevalence rates for any anxiety disorder in children with epilepsy was 23.8 to 50%, compared to 12.4 to 22% in healthy controls. The scales used to diagnose anxiety were Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) combining parent and child interviews, Diagnostic Interview Schedule for Children (DISC-IV), Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS).
Comments	Study reported prevalence of other chronic conditions, only epilepsy data extracted.

Reference	Cobham 2020 ²⁷
ROBIS rating	Overall rating: High risk of bias, this was due to the lack of risk of bias assessments carried out in the review for included studies.

Reference	Fiest 2013 ³⁹
Study type and analysis	Systematic review of studies looking at depression prevalence in people with epilepsy.
Number of participants and characteristics	14 studies were included, 4 reported lifetime depression, 6 reported depression over the past 12 months and 4 reported depression over the past 30 days. The age of people included ranged from 37.2 to 52.4 years. Studies included were published between 1996 and 2011 and limited to cohort and cross-sectional design.
Country	Canada, USA, Europe, Asia, UK, Brazil
Outcomes/ Comorbidities	Depression
Results	<p>Prevalence of active depression in adults with Epilepsy was taken from 9 studies (studies looking at past 30 days and 12 months) ranging from 13.2 to 36.5%.</p> <p>Lifetime depression in adults with Epilepsy was reported by 4 studies with a prevalence of 4.1 to 32.5%.</p> <p>Diagnosis of anxiety: World Mental Health Composite International Diagnostic Interview (WMH CIDI), outpatient visits, GP diagnosis, Schedule for Affective Disorders and Schizophrenia (SADS), Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), self-reported of diagnosis by health professional, Composite International Diagnostic Interview - Short Form (CIDI-SF), Kessler 6 mental health scale, Centre for Epidemiology Studies–Depression Scale (CES-D) score of 15 or above, Hospital Anxiety and Depression Scale (HADS) 7 or above, HADS 8 or above.</p>
Comments	Adults included in the review, but the search was not restricted to adults. Odds ratios were reported however this evidence review is focussing on prevalence and not association, therefore odds ratio data were not extracted.
ROBIS rating	Low risk of bias.

Reference	Fonseca 2019 ⁴² , Fonseca 2020 ⁴³
Study type and analysis	Systematic review looking at prevalence of cognitive deficits in children with absence epilepsy.
Number of participants and characteristics	33 studies were included Absence epilepsy: defined as 3–4Hz spike-wave complexes or a syndromic classification of childhood absence epilepsy and juvenile absence epilepsy
Country	Not stated
Outcomes/ Comorbidities	Cognitive difficulties, learning disabilities
Results	Results from single studies found the following cognitive deficits in children with absence epilepsy; 24% cognitive difficulties and 26% dysgraphia. Data taken from school reports. Four studies looking investigating either school difficulties/requiring special educational support found a prevalence of 23-70% in children with absence epilepsy. Diagnosis: neuropsychological test results.
Comments	No pooled data was provided in this review.
ROBIS rating	Low risk of bias

Reference	Jones 2014 ⁵¹
Study type and analysis	Narrative review of studies looking at anxiety prevalence in children and adolescents with epilepsy.
Number of participants and characteristics	No information given regarding studies included, characteristics of populations reviewed.
Country	Not stated

Reference	Jones 2014 ⁵¹
Outcomes/ Comorbidities	Anxiety
Results	<p>The prevalence of lifetime anxiety ranged from 9-32% in children and adolescents with epilepsy compared to current/past 12-month prevalence of rates of 8-21%.</p> <p>Diagnostic scales: Anxiety and Depression in Adolescents; A Self-Test, Anxiety and Depression in Children; A Test for Parents, Beck Anxiety Inventory for Youth (BYI_II), Multidimensional Anxiety Scale for Children (MASC 2). Revised Children's Manifest Anxiety Scale-Second Edition (RCMAS-2), Self-Report for Childhood Anxiety Related Emotional Disorders (SCARED), Spence Children's Anxiety Scale (SCAS), Self-Trait Anxiety Inventory for Children (STAIC).</p>
Comments	This was a narrative summary of studies reporting anxiety prevalence's in children and adolescence. There were no details on methodology given in the review. In the absence of this information, this review will be downgraded in the ROBIS assessment.
ROBIS rating	Very high risk of bias due to the lack of methodology data and no risk of bias assessment.

Reference	Jones 2010 ⁵²
Study type and analysis	Systematic review of select studies to investigate prevalence of psychiatric disorders in epilepsy
Number of participants and characteristics	13 studies included in this review looking at prevalence of psychiatric disorders in people with epilepsy.
Country	Not stated
Outcomes/ Comorbidities	<p>Depression</p> <p>Anxiety</p> <p>psychosis</p>

Reference	Jones 2010 ⁵²
Results	<p>Depression prevalence: 18-39.7%, diagnosis: community-based self-report mail survey, Diagnostic and Statistical Manual of Mental Disorders (DSM) defined</p> <p>Anxiety disorders prevalence: 10-25%, diagnosis: DSM defined.</p> <p>Psychosis prevalence: 2-7%, diagnosis: DSM defined.</p>
Comments	<p>This review also reported the prevalence of mood disorders at 24-75% and personality disorders at 1-2% in people with epilepsy.</p> <p>Populations were not defined based on adults or children.</p>
ROBIS rating	High risk of bias due to lack of information on protocol details and study selection.

Reference	Maryam 2013 ⁶⁹
Study type and analysis	Systematic review focussing on depression in children and adolescents with epilepsy.
Number of participants and characteristics	11 cross-sectional studies included total of 1095 children and adolescents ages 4-19 years old. Searches carried out for studies published in the past 15 years.
Country	USA, UK, Nigeria, Turkey, Brazil
Outcomes/ Comorbidities	Depression
Results	<p>Prevalence of depression in children and adolescents with epilepsy ranged from 5.2-39.6%.</p> <p>Diagnosis: Diagnostic and Statistical Manual of Mental Disorders (DSM) or International Classification of Diseases (ICD) criteria.</p>
Comments	One study found higher depression scores from parents (39.5%) compared to self-assessment from the children (23.1%). No risk of bias assessment reported.
ROBIS rating	High risk of bias due to the lack of risk of bias assessments.

Reference	Scott 2017 ⁹⁵
Study type and analysis	Systematic review of studies looking at the prevalence of anxiety and depression in people with Epilepsy. Meta-analysis of the prevalence data was carried out to deduce pooled prevalence values.
Number of participants and characteristics	27 studies and total of 3221 adults, aged 16 years and older, with epilepsy were included. Databases were searched for relevant studies up until July 2016.
Country	Not stated
Outcomes/ Comorbidities	Depression anxiety
Results	Overall pooled prevalence of depression disorders in people with epilepsy was 22.9%. (Figure 2) Overall pooled prevalence of anxiety disorders in people with epilepsy was 20.2%. (Figure 3) Diagnosis: Diagnostic and Statistical Manual of Mental Disorders (DSM IV), International Classification of Diseases Tenth Revision (ICS 10),
Comments	
ROBIS rating	Low risk of bias

Reference	Scott 2020 ⁹⁶
Study type and analysis	Systematic review of studies looking at the prevalence of anxiety and depression in youths with Epilepsy. Meta-analysis of the prevalence data was carried out to deduce pooled prevalence values.
Number of participants and characteristics	Databases were searched for relevant studies up until October 2018. 23 studies were included with children aged up to and including 18 years with a confirmed diagnosis of epilepsy.

Reference	Scott 2020 ⁹⁶
Country	USA, Africa, Europe
Outcomes/ Comorbidities	Anxiety Depression
Results	The overall pooled prevalence of anxiety disorders in children with epilepsy was 18.9% (95% CI 12.0%–28.5%), and for depression the pooled prevalence was 13.5% (95% CI 8.8%–20.2%). Diagnosis: Diagnostic and Statistical Manual of Mental Disorders (DSM III), Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS), Diagnostic Interview Schedule for Children (DISC-IV)
Comments	
ROBIS rating	Low risk of bias

Reference	Subota 2017 ¹⁰⁵
Study type and analysis	Systematic review of studies looking at the prevalence of dementia in people with epilepsy.
Number of participants and characteristics	Of the 8 studies included in this review, only 2 studies were in people with epilepsy who later developed dementia that prevalence data for dementia
Country	Sweden, USA
Outcomes/ Comorbidities	Dementia
Results	The period prevalence of dementia ranged from 8.1 to 17.5 per 100 persons among persons with epilepsy. Diagnosis: National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA), International Classification of Diseases Ninth Revision (ICD-9)

Reference	Subota 2017¹⁰⁵
Comments	Populations were not defined based on adults or children. Meta-analysis could not be carried out due to insufficient data.
ROBIS rating	Low risk of bias

Appendix E ROBIS assessment

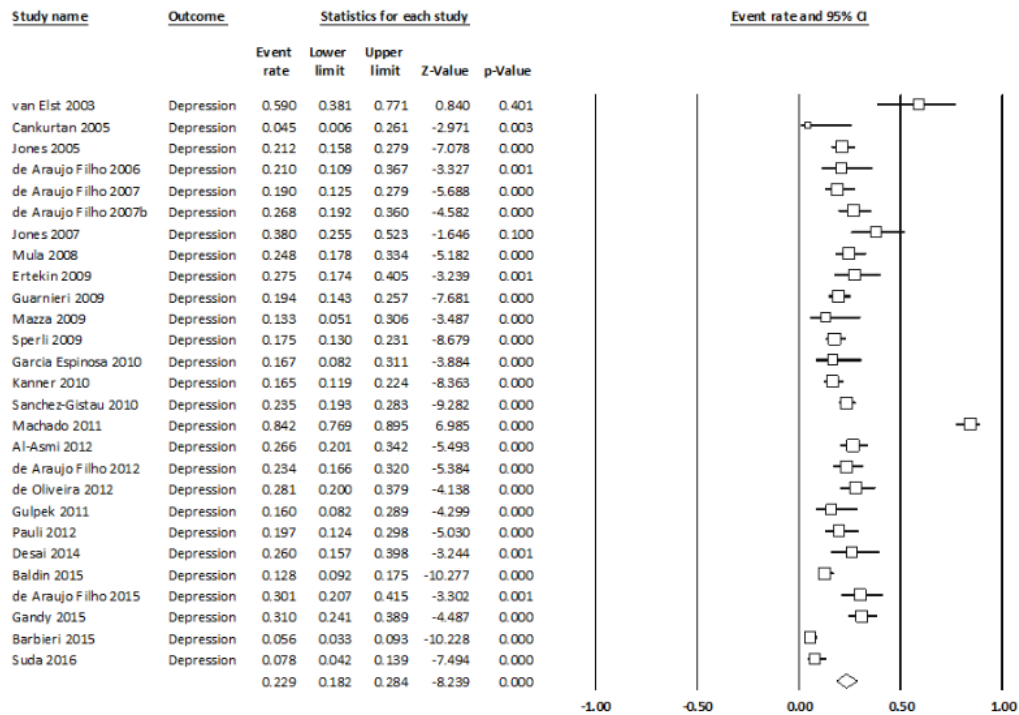
Study	Phase 2			Phase 3	
	1. STUDY ELIGIBILITY CRITERIA	2. IDENTIFICATION AND SELECTION OF STUDIES	3. DATA COLLECTION AND STUDY APPRAISAL	4. SYNTHESIS AND FINDINGS	RISK OF BIAS IN THE REVIEW
Asadi-Pooya 2018	Low	Low	High	Low	High ¹
Cobham 2020	Low	Low	High	Low	High ¹
Fiest 2013	Low	Low	Low	Low	Low
Fonseca 2019, 2020	Low	Low	Low	Low	Low
Jones 2014	High	High	High	Low	Very high ^{1,2}
Jones 2010	High	High	Low	low	High ²
Maryam 2012	Low	Low	High	Low	High ¹
Scott 2017	Low	Low	Low	Low	Low
Scott 2019	Low	Low	Low	Low	Low
Subota 2017	Low	Low	Low	Low	Low

¹There was no details on risk of bias assessment in this review.

²There was insufficient information on the review methodology

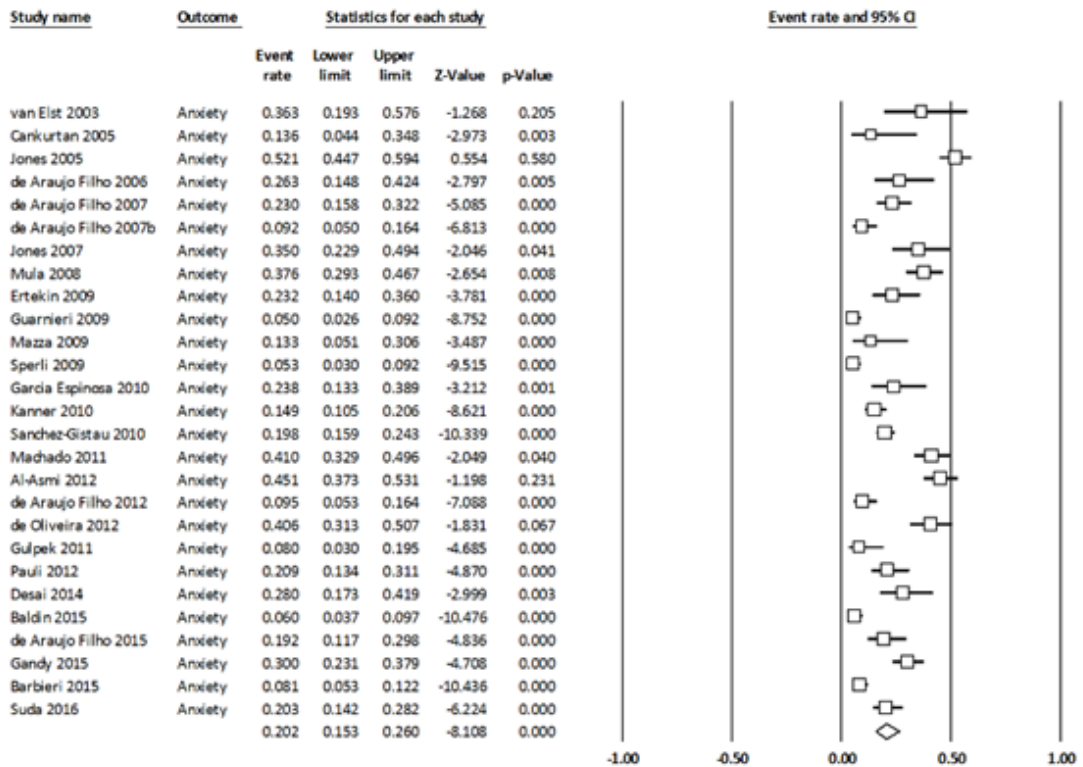
Appendix F Forest plots

Figure 2: Prevalence of depression in adults with Epilepsy



Scott 2017⁹⁵

Figure 3: Prevalence of anxiety in adults with Epilepsy



Scott 2017⁹⁵

Appendix G Excluded studies

G.1 Clinical studies

Table 9: Studies excluded from the clinical review

Reference	Exclusion reason
Sajatovi, 2019 ⁹³	Systematic review investigating Self-management strategies of epilepsy
Abraham, 2019 ¹	Systematic review investigating suicide rates
Allebone, 2018 ²	Systematic review did not investigate prevalence of psychosis
Amiet, 2008 ³	association study for autism, learning disability and epilepsy focussing on an autistic population
Anderson, 2010 ⁴	Systematic review focussed on drug monitoring and safety
Arana, 2010 ⁵	Systematic review investigating suicide rates
Arico, 2020 ⁶	Systematic review did not investigate prevalence
Bagary, 2017 ⁸	Conference abstract
Banach, 2010 ⁹	looking at effects of prenatal AEDs on children's intellectual development
Baranowski, 2018 ¹⁰	Systematic review investigating quality of life in epilepsy
Beavis, 2007 ¹¹	Systematic review did not investigate prevalence
Bell, 2008 ¹²	Systematic review investigating drowning
Bell, 2009 ¹³	Systematic review investigating suicide rates
Bell, 2009 ¹⁴	Systematic review investigating suicide rates
Benamer, 2009 ¹⁵	systematic review focussed on the prevalence of epilepsy
Besag, 2015 ¹⁶	Systematic review on epileptic surgery
Beyenburg, 2005 ¹⁷	Systematic review did not investigate prevalence
Blickwedel, 2019 ¹⁸	Systematic review did not investigate prevalence
Boot, 2012 ¹⁹	Systematic review did not investigate prevalence
Bowley, 2000 ²⁰	Incorrect population
Brandt, 2016 ²¹	Systematic review did not investigate prevalence
Breuer, 2016 ²²	Systematic review did not investigate prevalence
Britton, 2010 ²³	Systematic review did not investigate prevalence
Brodie, 2016 ²⁴	Conference abstract
Butler, 2008 ²⁵	Systematic review did not investigate prevalence
Cavanna, 2010 ²⁶	Systematic review did not investigate prevalence
Cobham, 2020 ²⁷	
Collaborators, 2019 ⁴⁶	systematic review looking at the prevalence of epilepsy
Cubała, 2018 ²⁸	Conference abstract
Cyr, 2021 ²⁹	Systematic review did not investigate prevalence
de Winter, 2011 ³⁰	Systematic review did not investigate prevalence
Deb, 2020 ³¹	Systematic review did not investigate prevalence
Doran, 2016 ³²	Systematic review did not investigate prevalence
Doran, 2015 ³³	Conference abstract

Reference	Exclusion reason
Elliott, 2014 ³⁴	Systematic review with incorrect population
Ferrer, 2013 ³⁵	Conference abstract
Ferrer, 2014 ³⁶	Systematic review did not investigate prevalence
Fiest, 2012 ³⁷	Conference abstract
Fiest, 2012 ³⁸	Conference abstract
Fiest, 2013 ³⁹	
Finzel, 2009 ⁴⁰	conference abstract
Fitzgerald, 2009 ⁴¹	Incorrect population
Fonseca Wald, 2019 ⁴²	
Gandy, 2012 ⁴⁵	risk prediction review
Gandy, 2013 ⁴⁴	Systematic review did not investigate prevalence
Gill, 2017 ⁴⁷	Systematic review did not investigate prevalence
Hall, 2009 ⁴⁸	No prevalence data
Johnson, 2018 ⁴⁹	review on panic attacks
Johnson, 2016 ⁵⁰	No prevalence data
Kanner, 2003 ⁵³	No prevalence data
Kanner, 2002 ⁵⁴	No prevalence data
Kattimani, 2011 ⁵⁵	No relevant data
Kavros, 2008 ⁵⁶	No prevalence data
Kim, 2018 ⁵⁷	point prevalence data only
Kolc, 2019 ⁵⁸	Systematic review did not investigate prevalence
Kolevzon, 2019 ⁵⁹	Incorrect population
Kutlubae, 2018 ⁶⁰	Systematic review did not investigate prevalence
Kwok, 2007 ⁶¹	Incorrect population
Lagogianni, 2020 ⁶²	review focussing on fatigue
Lai, 1997 ⁶³	Not focussing on prevalence
Lax-Pericall, 2019 ⁶⁴	Looking at gender as a risk factor for psychiatric disorders in epilepsy
Loughman, 2016 ⁶⁵	Not focussing on prevalence
Loughman, 2014 ⁶⁶	Not focussing on prevalence
Lukmanji, 2019 ⁶⁷	Not relevant information, review focussing on autism
M, 2015 ⁶⁸	point prevalence data only
Maryam, 2013 ⁶⁹	
Menlove, 2015 ⁷⁰	No prevalence data
Michelucci, 1989 ⁷¹	Incorrect population
Monteagudo-Gimeno, 2020 ⁷²	Not focussing on prevalence
Monti, 2015 ⁷³	Not focussing on prevalence
Muhigwa, 2020 ⁷⁴	Not focussing on prevalence of psychological disorders
Mula, 2010 ⁷⁵	Not focussing on prevalence

Reference	Exclusion reason
Mula, 2011 ⁷⁶	Reviewing suicide rates
Mula, 2020 ⁷⁷	The only relevant data is a summary of Fiest 2013 which is already included
Mula, 2010 ⁷⁸	Not focussing on prevalence
Neumann, 2016 ⁸⁰	Not in English
Otero, 2009 ⁸¹	Not focussed on prevalence
Parnas, 1982 ⁸²	Not focussed on prevalence
Patten, 2018 ⁸³	Not focussed on prevalence
Pinquart, 2011 ⁸⁵	Review not focussing on prevalence
Pinquart, 2011 ⁸⁴	Not focussed on Epilepsy and prevalence
Quintas, 2012 ⁸⁶	Not focussed on prevalence
Ramanujam, 2017 ⁸⁷	Systematic review aspect of study was not focussed on prevalence
Reilly, 2013 ⁸⁸	No relevant data
Reilly, 2011 ⁸⁹	Looking at academic performance in children with and without learning difficulties in an epilepsy population
Ricciardi, 2015 ⁹⁰	Not focussed on prevalence
Richard, 2017 ⁹¹	Not focussed on prevalence
Rodenburg, 2005 ⁹²	Not focussed on prevalence
Sanya, 2010 ⁹⁴	Not focussed on prevalence
Secinti, 2017 ⁹⁷	Not focussed on prevalence
Seethalakshmi, 2007 ⁹⁸	Not focussed on prevalence
Sen, 2018 ⁹⁹	Not focussed on prevalence
Srinivas, 2017 ¹⁰⁰	Not focussed on prevalence of conditions in protocol
Stevellink, 2019 ¹⁰¹	Not focussed on prevalence of conditions in protocol
Stewart, 2016 ¹⁰²	Not focussed on prevalence
Stewart, 2019 ¹⁰³	Not focussed on prevalence
Strasser, 2018 ¹⁰⁴	No relevant data
Tao, 2016 ¹⁰⁶	Not focussed on prevalence
Taylor, 2011 ¹⁰⁷	Not focussed on prevalence, HRQoL and costing
Theodore, 2006 ¹⁰⁸	Not focussed on prevalence of conditions in protocol
Thomson, 2014 ¹⁰⁹	Not focussed on prevalence, HRQoL
Tramoni-Negre, 2017 ¹¹⁰	Not focussed on prevalence
Trimble, 2003 ¹¹¹	Not focussed on prevalence
Trinka, 2019 ¹¹²	Looking at prevalence of epilepsy
Tuchman, 2011 ¹¹³	Not focussed on prevalence
van Ool, 2016 ¹¹⁴	Not focussed on prevalence
Vannest, 2015 ¹¹⁵	Not focussed on prevalence
Vazquez, 2003 ¹¹⁶	Not focussed on prevalence
Verche, 2018 ¹¹⁷	Not focussed on prevalence

Reference	Exclusion reason
Verrotti, 2015 ¹¹⁸	Not focussed on prevalence
Vonberg, 2016 ¹¹⁹	Conference abstract
Wade, 1986 ¹²⁰	looking at the prevalence of long-term diseases
Walsh, 2017 ¹²¹	Not focussed on prevalence
Walsh, 2018 ¹²²	Not focussed on prevalence
Werhahn, 2009 ¹²³	Not focussed on prevalence
Wickens, 2017 ¹²⁴	Not focussed on prevalence
Wiglusz, 2012 ¹²⁵	Not focussed on prevalence
Williams, 2016 ¹²⁶	No relevant data
Yang, 2020 ¹²⁷	Not focussed on prevalence
Yoong, 2015 ¹²⁸	Not focussed on prevalence
Yronji, 2017 ¹²⁹	Not in English
Zapata Barco, 2020 ¹³⁰	Not in English