Appendix F

Evidence tables

Evidence tables were prepared for each key clinical question where a full evidence review was undertaken.

Evidence summaries are presented for only those studies where recognised quality criteria are available, that is systematic reviews, randomised controlled trials, cohort studies, diagnostic studies, and health economic evaluations.

1.1 Systematic reviews

First Author	Year	Title	Description	Search Strategy	N	Included studies	Excluded studies	Results and Conclusions	Quality
AHCPR	2001	Management of newly diagnosed patients with epilepsy: a systematic review of the literature	Two phases - stakeholder meeting to develop matrix framework, followed by full systematic review	MEDLINE, EMBASE and Cochrane Library searched. Study bibliographies perused. Relevant web sites checked.	120 studies meeting eligibility criteria - 70 interventional, 50 observational	Studies reporting results of any diagnostic, treatment, or monitoring intervention pertinent to newly diagnose epilepsy in adults or children. Total sample size of at least 10 patients. English language.		(Refer to text in chapters)	Comprehensive literature search. No quantitative syntheses possible - due to insufficient / inconsistent reporting of results. Included other studies than RCTs.
Anon	1996	Practice Parameter: a guideline for discontinuing antiepileptic drugs in seizure-free patients - Summary Statement	Guideline statement to help physicians in their decisions to withdraw AEDs	MEDLINE searched.	53 studies identified, of which 17 discussed all factors of interest (namely: sex, age of onset, seizure type, aetiology, neurologic examination/IQ, duration of seizure, freedom on AEDs, treatment regimen, age at relapse, normalization of the EEG)	Studies of both children and adults were included and considered separately. Retrospective, prospective, and non-RCTs included.	Patients on reduced dose of medication not included	Clinical characteristics emerged that may predict successful remission. The longer the duration of seizure control with AEDs, the better the prognosis.	Limited literature search.
Appleton	CR	Drug management for acute tonic-clonic convulsions including convulsive status epilepticus in children	Review of the evidence comparing diazepam, lorazepam, phenobarbitone, phenytoin and paraldehyde in treating acute tonic-clonic convulsions and convulsive status epileptics in children	(See Cochrane Epilepsy Group Search Strategy.) Searched: Cochrane Epilepsy Group Trials Register, Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE.	One study identified meeting main inclusion criteria	RCTs, quasi-RCTs. Non-randomised controlled studies. Children aged between 1 month and 16 years presenting to an Accident and Emergency department or to a hospital ward in an acute tonic-clonic convulsion and who received treatment with an anticonvulsant drug, irrespective of the duration of the presenting convulsion. Children presenting de novo with a first convulsion and those with an established diagnosis of epilepsy. Trials were included if they compared one treatment (or protocol) with another or with placebo. Drugs included the benzodiazepines, phenytoin, phenobarbitone and paraldehyde.		Only one paediatric study was identified, a quasi-randomised study with inherent methodological problems. No clear evidence to support the use of intraevenous lorazepam as being either more effective or safer than diazepam in treating an acute tonic-clonic convulsion and convulsive status epilepticus in children.	Comprehensive literature search. Limited data available.
Berg	1991	The risk of seizure recurrence following a first unprovoked seizure: a quantitative review	Quantitative review to determine which factors identify individuals at higher and lower risk of experiencing a recurrent seizure and quantifying those risks	Cumulated Index Medicus searched. Bibliographies of studies scanned.	16 studies	Studies addressing risk recurrence following a first unprovoked seizure	Studies considering patients with previously recognized seizures, or previous nonconvulsive seizures that presented at the time of first convulsion, or typical absence or myoclonic seizures which virtually never come to medical attention at the time of the first seizure would all be excluded.	Overall risk of recurrent seizure at or near 2 years following the initial seizure was 42%. Patients with idiopathic seizures and normal EEGs have a low risk of recurrence of about 24% at 2 years.	Mainly cohort studies. Findings must be interpreted with caution.

First Author	Year	Title	Description	Search Strategy	N	Included studies	Excluded studies	Results and Conclusions	Quality
Berg	1994	Relapse following discontinuation of antiepileptic drugs: a meta-analysis	Meta-analysis 1) to derive a typical estimate of the risk of relapse at 1 year and 2 years after discontinuation of medication, and 2) to determine relative risk of relapse associated with three commonly assessed clinical factors: age of onset of epilepsy,, the presence of an underlying brain abnormality, and the EEG.	Computerized literature searches of Index Medicus. Review of reference lists of identified articles and of several systematic reviews.	42 studies	Published articles in which methods and results of the study were adequately described. Addressing question of relapse following discontinuation of AEDs. Articles in English, French, Spanish. Italian, German included.	Studies excluded if patients were a "haphazardly assembled" group, rather than a series of patients partaking in a study on discontinuation of AEDs.	Risk of relapse overall was 25% at 1 year, 29% at 2 years. Relative to child onset, epilepsy of adolescent onset was associated with a relative risk of relapse of 1.79 (95% C.I., 1.46 to 2.19).	Limited detail of search given (however this meta-analysis was published in 1994). Well cited
Bradley	CR	Epilepsy clinics versus general neurology or medical clinics	Review to compare the effectiveness of 1) special epilepsy clinics and general neurology clinics, 2) special epilepsy clinics and general medical paediatric or psychiatric clinics	Cochrane Library, MEDLINE, EMBASE, PsycINFO, CINAHL.	0 RCTs	RCTs using adequate or quasi-randomised methods. Participants: any age/sex. Referred with a suspected new diagnosis of epilepsy or established diagnosis of epilepsy. Terms "specialist epilepsy nurse" and "specialist epilepsy clinics" were defined.		not applicable	
Bradley	CR	Specialist epilepsy nurses for treating epilepsy	Overview of the evidence from RCTs investigating the effectiveness of specialist epilepsy nurses compared to routine care.	Cochrane Library, MEDLINE, EMBASE, PsycINFO, CINAHL, GEARS, ECRI, Effectiveness Healthcare Bulletin, Effectiveness Matters.	3 trials	RCTs using adequate or quasi-randomised methods. Participants: any age/sex. Referred with a suspected new diagnosis of epilepsy or established diagnosis of epilepsy.		Heterogeneity of studies rendered pooling inappropriate.	
Brown	1998	Role of propofol in refractory status epilepticus (RSE)	Review proposed mechanism of action, clinical efficacy, adverse effects and then consider association with use of propofol in the management of RSE.	MEDLINE. Bibliographies of selected articles. English Language.	16 case reports	Unclear - studies addressing efficacy of propofol in RSE?		Propofol promising in management of RSE. However, controlled trials are needed.	No RCTs - based on case reports. Limited detail provided.
Carter	2003	Propofol for resistant status epilepticus: A question of choice - compliance in medicine taking: a preliminary review.	Rapid review of literature on compliance with medication. Narrative, qualitative, review.		12?			Non-compliance with specific aspects of epilepsy medication is relatively common. Communication and support programs to promote empowerment are necessary. Adolescents, people with learning disabilities, minority groups have special needs.	
Chilcott	1999	Working group on acute purchasing: the effectiveness of surgery in the management of epilepsy.	Guidance note for purchasers	MEDLINE, EMBASE, HealthSTAR, DARE, NHS EED, HTA resources	3. One RCT comparing 2 treatments, two case series. No RCTs of surgery identified.	Not specified - Reports of trials on surgery in epilepsy?		RCT evidence lacking, as unethical and impractical to conduct. Unlikely to become available in future. Agreement in conclusions of the consensus panels.	Also included health economic information (relatively old)
Claassen	2002	Treatment for refractory status epilepticus with Pentobarbital , profolol, or midazolam: A systematic review	Systematic review of the treatment for refractory status epilepticus	MEDLINE, and bibliographies of retrieved articles	28. Only two comparisons of treatment	Reports of treatment for refractory status epilepticus in adults	Partial or absence status. Intermittent iv drugs.	Treatment with pentobarbital or any continuous iv AED infusion may be more effective than other strategies.	Detailed inclusion/exclusion, but although summary statistics were given, there was no details of the technique used to calculate this.

First Author	Year	Title	Description	Search Strategy	N	Included studies	Excluded studies	Results and Conclusions	Quality
Corabian	2001	Vagus nerve stimulation for refractory epilepsy	Report to inform policymakers, practitioners and the public on the current use of vagus nerve stimulation (VNS) for RSE in children and adults.	MEDLINE, EMBASE and Cochrane Library, Health STAR, ECRI, Best Evidence, database, NHS CRD databases. Websites. Study bibliographies examined.	?	Articles examining safety and effectiveness of VNS in people with refractory epilepsy, reporting quality of life in people with a VNS device implanted.	Animal studies, case reports, abstracts, letters, technical reports.	VNS safe and effective when added to existing treatment regimen for some patients age (>12 years) in terms of reduction in frequency of partial onset seizures.	Details of search strategy given. Technology assessment.
Couldridge	2001	A systematic overview - a decade of research'. The information and counselling needs of people with epilepsy.	Aims to locate, appraise and synthesise evidence from key primary research published between 1990 and 2000 in order to answer the stated research questions (a lack of understanding and knowledge seems to exist despite information being freely available; patients do not receive adequate information because they do not ask questions or do not know how to ask; personal and social barriers to receiving and utilizing information may exist, knowledge may be inaccurate or outdated, or there may be underlying prejudice, negative attitudes, perceived or actual stigma) and to highlight areas where little research evidence exists.	MEDLINE, CINAHL, PsycLit, Sociofile, BIDS, NHS CRD database (DARE), Cochrane Library, RCN Nurse ROM searched with filter for identification of RCTs and systematic reviews, plus specific subject terms. Specialist journals handsearched. Some grey literature also considered but not included.	15	Studies in English language and carried out in developed countries were included.		Results suggest patients require information on: epilepsy in general, diagnosis and treatment options, medication and side effects, seizures and seizure control, injury prevention, psychological issues, social security, driving and insurance, employment, prognosis, lifestyle and social issues. Counselling issues identified were anxiety, depression, emotional support and information. patients who had seen an epilepsy specialist nurse more likely to have discussed a wide range of epilepsy-related issues with their GP.	Scientific design used, although meta-analysis not considered appropriate, due to qualitative nature of methods to investigate the patient's perspective. Literature search seems thorough.
Deckers	1997	Adverse effects in epilepsy therapy. Wait and see or go for it?	To identify the effects of different approaches (wait and see vs go for it)	MEDLINE only	7	Only papers discussing either carbamazepine or valproate monotherapy		Different approaches in detection strategies for AEs result in differences in the numbers found of certain AEs. Recommend baseline measurements and active checking for sedation, cognitive impairments, sexual dysfunction, hair changes, nystagmus, tremor and gait. Routine laboratory monitoring is of doubtful value in patients who are not known to be at risk of idiosyncratic reactions.	Only searched MEDLINE.
Engelberts	2002	The effectiveness of psychological interventions for patients with relatively well-controlled epilepsy.	Investigated what the contribution of the psychologist can be for the large group of patients with relatively well-controlled epilepsy (in terms of psychological outcome measurement and, where data available, in terms of seizure outcome).	MEDLINE and PsycINFO	7	Studies in English language, including: studies of relatively well-controlled epilepsy patients only, and studies in which some patients had relatively well-controlled epilepsy were included. Studies classified according to type of intervention used.		Although results of two studies are encouraging (in terms of improvement in psychological outcome and seizure reduction), a very limited number of studies found and these need to be replicated before clear conclusions can be drawn. RCTs with large numbers of patients are a prerequisite to acquiring well-founded knowledge about psychological interventions in patients with relatively well-controlled epilepsy.	Limited literature search

First Author	Year	Title	Description	Search Strategy	N	Included studies	Excluded studies	Results and Conclusions	Quality
Fisher	1999	Reassessment: Vagus nerve stimulation for epilepsy	Report by the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology, of the E05 multicentre RCT on vagus nerve stimulation for epilepsy		1 RCT			Patients receiving high stimulation showed an average reduction in seizure frequency compared to baseline of 28%, versus 15% for those on low stimulation. Degree of improvement in seizure control from VNS remains comparable to that of new AEDs, but is lower that that of mesial temporal lobectomy in suitable surgical resection candidates. However, VNS population studied in pivotal trials was refractory to standard therapy. Efficacy in less severely affected candidates remains to be evaluated. Nevertheless, there is sufficient evidence to suggest that VNS is safe and effective.	
Fowle	2000	Uses and abuses of the EEG in Epilepsy	To indicate clinical situations in epilepsy in which the EEG provides useful information and those in which it is unhelpful and should be avoided.	MEDLINE, Cochrane Library, NHS CRD databases, Effectiveness Healthcare Bulletin, plus various other databases and Internet sites.	3 studies?	Not stated - studies on electroencephalography and electroencephalogram?		The EEG has many uses in epilepsy, but may also be abused. The situations in which the EEG can contribute to the diagnosis of epilepsy are rare. Asking for an EEG in this situation is therefore usually an abuse. Once the diagnosis is established, however, the EEG is probably the most important investigation in helping define the type of epilepsy, the prognosis, and the initial approach to therapy.	Lack of reporting of systematic review process.
French	1999	Practice Advisory: the use of felbamate in the treatment of patients with intractable epilepsy	Advisory, to 1) determine the current role of felbamate for treatment of various types of epilepsy; 2) provide guidelines to ensure maximum safety and effectiveness when the risk/benefit ratio is in favour of the use of felbamate.	MEDLINE search.	54 articles identified, of which 9 were Class I ("well - designed, prospective, blinded, controlled studies"). 7 of these were RCTs.	English language, human studies. Relevant to the topics of efficacy, practice, treatment guidelines, and side effects.	Articles were excluded if they reviewed multiple drugs, discussed only mechanisms of action, consisted of news reports, or summarised previous data without providing new insight or opinion.	Class I evidence found for benefits of felbamate: Effective for partial seizures in adults aged 18 to 65 as adjunctive and monotherapy. Effective for Lennox-Gastaut syndrome as adjunctive therapy	Limited literature search
Gilbert	1999	Complications and costs of treatment of refractory generalised convulsive status epilepticus in children	Review of the literature on treatment of refractory generalised convulsive status epilepticus in children and extract data on treatment complications after applying inclusion criteria to limit patient selection and case severity biases. Aims to provide an evidence-based recommendation for optimal therapy.	MEDLINE search. Bibliographies of identified articles were reviewed for additional relevant studies.	12 articles (with a total of 111 children meeting inclusion criteria)	English language studies. Children included in this study were between ages of 1 month and 18 years, and had convulsive generalised status epilepticus refractory to at least two anticonvulsants administered in appropriate doses.	Papers not meeting inclusion criteria, or whose descriptions in the literature were unclear were excluded.	Benzodiazepines appear to have higher drug costs but lower complications and overall costs than barbiturates.	Clear inclusion and exclusion criteria stated. Costs included, not economic evaluation.

First Author	Year	Title	Description	Search Strategy	N	Included studies	Excluded studies	Results and Conclusions	Quality
Gilbert 1999 (see Gilbert 1999)	1999	Efficacy of mortality in treatment of refractory generalised convulsive status epilepticus in children: a meta-analysis	Investigated the relationship between different pharmacologic therapies for refractory generalised convulsive status epilepticus and two primary outcomes: efficacy, defined as seizure cessation, and mortality.	MEDLINE search. Bibliographies of identified articles were reviewed for additional relevant studies.	12 articles (with a total of 111 children meeting inclusion criteria)	English language studies. Children included in this study were between ages of 1 month and 18 years, and had convulsive generalised status epilepticus refractory to at least two anticonvulsants administered in appropriate doses.	Studies were excluded where: treatment reviews did not present original data, patients were adults or neonates, seizure type (focal only, non-conclusive, or not interpretable), and initial treatment for status epilepticus not clearly described or not adequate. Studies of phenobarbital, lorazepam, and propofol, which are widely referenced but which did not meet criteria, were included only in the discussion.	Number of patients included and the unresolved issues of possible patient selection bias do not permit recommending the use of any anticonvulsant agent over the others on the basis of mortality or efficacy, but support the view that midazolam is a reasonable candidate for first use. The apparent effectiveness of midazolam in children with refractory generalised convulsive status epilepticus, combined with its pharmacokinetic advantages, warrant a clinical trial comparing it to pentobarbital.	Clear inclusion and exclusion criteria stated. Although summary statistics were given, there was no details of the technique used to calculate this.
Gilbert	2000	An EEG should not be obtained routinely after first unprovoked seizure in childhood	to quantify and analyse the value of expected information from an EEG after first unprovoked seizure in childhood.	MEDLINE search. Bibliographies of identified articles were reviewed for additional relevant studies.	4 studies, involving a total of 831 children.	English language, human studies. Studies had to have included seizure recurrence data, with a minimum f-u of 2 years, and had to include some description of what was considered an abnormality. Studies had to have enrolled patients who came to medical attention for their first unprovoked seizure. Only 5 studies of standard interictal, EEG were eligible.	Studies on both children and adults were not used if the results were not presented separately.	The quantity of information from the EEG is too low to affect treatment recommendations in most patients. EEG should be ordered selectively, not routinely, after first unprovoked seizure in childhood.	
Gilbert	2003	Meta-analysis of EEG test performance shows wide variation among studies	To account for variation in test characteristics between studies	MEDLINE 1970 to 2000 and bibliographies of articles	19 relating epileptiform abnormalities and 12 relating abnormal EEGs and seizure recurrence	Standard EEGs. Had to describe threshold for EEG description. Min of 1 year f-u. Single EEG per patient	Case-control studies and studies of neonates and infants only.	There is wide inter-reader interpretation variation and this influences the accuracy of the EEG to discriminate between people who will or will not have further seizures	Limited searching but well-reported. Good description of analysis.
Hancock	CR	Treatment of Lennox-Gastaut syndrome	To compare the effects of pharmaceutical therapies used to treat Lennox-Gastaut syndrome in terms of control of seizures and adverse effects.	Searched: Cochrane Epilepsy Group Trials Register, MEDLINE, EMBASE. Contacted pharmaceutical companies and colleagues in the field to ascertain any unpublished/ongoing studies.	5 RCTs	All RCTs of the administration of drug therapy to patients with Lennox-Gastaut syndrome		The optimum treatment for Lennox-Gastaut syndrome remains uncertain and no study to date has shown any one drug to be highly efficacious; lamotrigine, topiramate and felbamate may be helpful as add-on therapy. Until further research has been undertaken clinicians will need to continue to consider each patient individually, taking into account the potential benefit of each therapy weighed against the risk of adverse effects.	Comprehensive literature search. Clear inclusion and exclusion criteria stated. Meta-analysis was not undertaken, due to the heterogeneity of included studies.

First Author	Year	Title	Description	Search Strategy	N	Included studies	Excluded studies	Results and Conclusions	Quality
Hancock	CR	Treatment of infantile spasms	To compare the effects of single drugs used to treat infantile spasms in terms of long-term psychomotor development, subsequent epilepsy, control of the spasms and adverse effects.	Searched: Cochrane Epilepsy Group Trials Register, MEDLINE, EMBASE. Contacted pharmaceutical companies. Appeals at international conferences.	11 RCTs	All RCTs of the administration of drugs to people with infantile spasms		No single treatment was proven to be more efficacious in treating infantile spasms than any of the others. Few studies considered psychomotor development or subsequent seizure rates as outcomes and none had long-term follow-up. Further trials with larger numbers of participants, and longer follow-up, are required.	
Hirtz	2000	Practice parameter: evaluating a first nonfebrile seizure in children	Review of available evidence on evaluation of the first nonfebrile seizure in children in order to make practice recommendations based on this available evidence	MEDLINE, Current Contents. Additional articles from references of these were included.	66	References were reviewed pertaining to adults with first seizures only, to both children and adults with first seizures, and to children with both new and established seizures.	Articles were excluded if they contained only data on adults with established epilepsy.	Routine EEG as part of the diagnostic evaluation was recommended. Further studies are needed using large, well-characterised samples and standardized data collection instruments.	Linked recommendations and evidence
Hirtz	2003	Practice parameter: treatment of the child with a first unprovoked seizure	Reviews available data on the decision to begin treatment after a child or adolescent experiences a first unprovoked seizure and presents evidence-based practice recommendations.	MEDLINE, BIOSIS, Current Contents. Additional articles from references of these were included.	unclear - 30? studies, of which 11 Class I	Articles pertaining to children with both first seizures and established epilepsy were included.	Articles were excluded if they did not report data from either children or adults who had experienced only a single seizure.	Treatment with AEDs is not indicated for the prevention of the development of epilepsy. Treatment with AEDs may be considered in circumstances where the benefits of reducing the risk of a second seizure outweigh the risks of pharmacologic and psychosocial side effects. Further research is needed on the efficacy and side effects of the new AEDs in children.	Linked recommendations and evidence
Levy	CR	Ketogenic diet for epilepsy	To overview the evidence from RCTs regarding the effects of ketogenic diets	Searched: Cochrane Epilepsy Group Trials Register, Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE.	No RCTs found	RCTs of ketogenic diets in people with epilepsy		There is no reliable evidence from RCTs to support the use of ketogenic diets for people with epilepsy. There are large observational studies, some prospective, suggesting an effect on seizures. These effects need validating in randomised controlled trials. For those with a difficult epilepsy on multiple antiepileptic drugs, we consider the ketogenic diet a possible option.	Comprehensive literature search. Presented summary of observational studies for limited evidence.
Linzer	1997	Clinical guideline: diagnosing syncope: Part 1: Value of history, physical examination, and electrocardiography	To review the literature on diagnostic testing in syncope and provide recommendations for a comprehensive, cost-effective approach to establishing its cause.	MEDLINE search and manual review of bibliographies of identified articles.	Most electrophysiologic studies identified were referral studies or case series. Paucity of data from RCTs.	Articles were included if they addressed diagnostic testing in syncope or near syncope and reported results for at least 10 patients.		Many tests for syncope have a low diagnostic yield. A careful history, physical examination, and electrocardiography will provide a diagnosis or determine whether testing is necessary in most patients.	

First Author	Year	Title	Description	Search Strategy	N	Included studies	Excluded studies	Results and Conclusions	Quality
Marson	2002	Carbamazepine versus valproate monotherapy for epilepsy: a meta-analysis	To provide an overview of the evidence comparing carbamazepine (CBZ) and valproate (VPA) monotherapy for epilepsy, investigating whether existing data support the current practice of preferring CBZ for partial-onset and VPA for generalised seizures. Meta-analysis of RCTs by using individual patient data.	Searched MEDLINE, the Cochrane Library. Pharmaceutical industry (manufacturers of CBZ and VPA) consulted regarding reports of any unpublished trials they were aware of. Original investigators of relevant trials found were asked whether they were aware of any trials missed by the searches.	8 studies meeting inclusion criteria were identified	Included studies were: (a) randomised monotherapy studies comparing CBZ and VPA, (b) double, single or unblinded; and (c) either quasi-randomised or used adequate methods of randomisation concealment. Children or adults with partial-onset seizures or generalised onset tonic-clonic seizures.		Found some evidence to support the preference of CBZ for partial-onset seizures, but no evidence to support the preference of VPA over CBZ for generalised-onset seizures. Results of this meta-analysis do not provide unequivocal evidence on which a choice between these drugs can be made for the global outcome Time to treatment discontinuation.	Misclassification may have confounded results.
Marson	CR	Carbamazepine versus sodium valproate monotherapy for epilepsy	To overview the best evidence comparing carbamazepine and valproate monotherapy	Searched MEDLINE, the Cochrane Library, Cochrane Epilepsy Group Trials Register, pharmaceutical industry.	5 trials, including 1265 patients	RCTs comparing carbamazepine and valproate monotherapy for epilepsy		For time to 12 month remission and time to first seizure, results support the policy of using carbamazepine as the treatment of first choice in patients with a partial epilepsy. The belief that valproate is superior to carbamazepine for generalised tonic-clinic seizures as part of a generalised epilepsy is not supported by this data.	Significant numbers of patients may have had their epilepsy misclassified.
Meads	2002	Systematic reviews of specialist epilepsy services	To systematically review the current evidence on specialist epilepsy clinics compared to general neurology clinics and specialist epilepsy nurses compared to usual care	MEDLINE, PsycLit, EMBASE, GEARS, BIDS, ISI, UKCHHO, International HTA websites, InterTASC databases and The Cochrane Library. Experts contacted. No language restriction.	1 RCT and 2 other studies on epilepsy clinics, and 4 RCTs and a controlled trial on epilepsy nurses.	Any studies comparing specialist epilepsy clinics or nurses to generalist services or usual care, reporting physical health, costs or generic quality-of-life (QOL) outcomes were included.	Studies were excluded if they did not distinguish between patients attending specialist or generalist health clinics or if they reported results of patient satisfaction surveys only.	Data synthesis was inappropriate. Epilepsy clinics showed no evidence of reduced seizure frequency or severity, no QOL information and were more expensive. Epilepsy nurse services showed no evidence of reduced seizure frequency or severity, no effect on QOL but were less expensive. Little reliable empirical evidence found to suggest that one model of care is superior to any other.	Comprehensive literature search. Health economic information included.

First Author	Year	Title	Description	Search Strategy	N	Included studies	Excluded studies	Results and Conclusions	Quality
NICE TA	TA	Technology Assessment Report - Newer drugs for epilepsy in adults	To examine the clinical effectiveness, tolerability, and cost effectiveness of newer drugs for epilepsy in adults	Searched MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, National Research Register, PREMEDLINE, PsycINFO. Also Conference Papers Index. No language restriction.	The report identified: 142 clinical effectiveness studies, 77 studies of serious, rare and long-term adverse events, 21 cost effectiveness studies	Please refer to Technology Assessment Report, pg.41 (clinical effectiveness studies), pg.46 (rare and long-term adverse events), and pg.48 (cost effectiveness studies)		There is little good quality evidence from clinical trials to support the use of newer monotherapy ad adjunctive AEDs over older drugs or to support the use of one newer AED over another. In general the available data relating to clinical effectiveness, safety and tolerability failed to demonstrate consistent and statistically significant differences between the drugs. The exception was comparisons between newer adjunctive AEDs and placebo, where significant differences favoured the newer AEDs. However, trials often only had relatively short-term treatment durations and often failed to limit recruitment to either partial or generalised onset seizures, thus limiting the applicability of the data.	Comprehensive literature search.
NICE TA	TA	Technology Assessment Report - Newer drugs for epilepsy in children	To examine the clinical effectiveness, tolerability, and cost effectiveness of newer drugs for epilepsy in children	Searched MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, National Research Register, PREMEDLINE, Science Citation Index. Also bibliographies of relevant studies and contacted experts. No language or date restriction.	The report identified: 20 clinical effectiveness studies	Please refer to Technology Assessment Report, pg.39 (clinical effectiveness studies)	Individuals with single seizure, status epilepticus, seizures following surgery, febrile convulsions, trigeminal neuralgia, cortical myoclonus	There is some evidence from placebo-controlled trials that each of the newer agents tested are of some value in the epilepsy sub-types under investigation. Where active controls have been used, the newer agents appear no more effective, but have better tolerability.	Comprehensive literature search.
Niermeijer	2003	Propofol in status epilepticus: little evidence, many dangers?	Review the effectiveness and safety of propofol in status epilepticus	MEDLINE 1987-2001	2 non-randomised studies, 12 case reports and 7 case series.	Any study that reported primary data		Both non-randomised studies reported higher risk of mortality associated with propofol.	Limited review.
Posner	CR	Ethosuximide, sodium valproate or lamotrigine for absence seizures in children and adolescents	to review the evidence for the effects of ethosuximide, valproate and lamotrigine as treatments for children and adolescents with absence seizures, when compared with placebo or each other	Searched MEDLINE, EMBASE, the Cochrane Library. Study bibliographies examined. No language restriction. Contacted manufacturers of sodium valproate, lamotrigine and ethosuximide regarding reports of any unpublished trials.	4 small trials identified, of poor methodological quality	Randomised parallel group monotherapy or add-on trials which include a comparison of any of the following in children or adolescents with absence seizures: ethosuximide, sodium valproate, lamotrigine and ethosuximide or placebo.		None of the studies found a difference between valproate and ethosuximide with respect to seizure control, but confidence intervals were wide and the existence of important differences could not be excluded.	Comprehensive literature search.

First Author	Year	Title	Description	Search Strategy	N	Included studies	Excluded studies	Results and Conclusions	Quality
Privitera	CR	Vagus nerve stimulation for partial seizures	to determine the effects of VNS high-level stimulation compared to low-level (presumed subtherapeutic doses) stimulation	Searched MEDLINE, EMBASE, Cochrane Epilepsy Group Trials Register, Cochrane Central Register of Controlled Trials.	2 studies met inclusion criteria	RCTs using an adequate method of allocation concealment. Double blind trials. Individuals of any age with drug-resistant partial epilepsy. Vagus nerve stimulation using any paradigm, compared to: a) low intensity VNS stimulation, or b) no stimulation.		VNS for partial seizures appears to be an effective and well tolerated treatment. Results of the efficacy analysis show that VNS stimulation using the high stimulation paradigm was significantly better than low stimulation. Results for the outcome "withdrawal of allocated treatment" suggest that VNS is well tolerated as no significant difference was found between the high and low stimulation groups, and withdrawals were rare. Typical nervous system adverse effects of anti-epileptic drugs such as ataxia, dizziness, fatigue, nausea, and somnolence were not statistically significantly associated with VNS treatment.	
Ramaratnam	CR	Psychological treatments for epilepsy	To assess whether the treatment of epilepsy with psychological methods is effective in reducing seizure frequency and/or leads to a better QOL	Searched MEDLINE, Cochrane Epilepsy Group Trials Register, Cochrane Central Register of Controlled Trials. Cross references from identified publications.	3 small trials identified, of poor methodological quality	RCTs or quasi-randomised studies assessing one or more types of psychological or behaviour modification techniques for people with epilepsy.		No study found a significant effect of relaxation therapy on seizure frequency. One trial found cognitive behaviour therapy to be effective in reducing depression, among people with epilepsy with a depressed affect, whilst another did not. In view of methodological deficiencies and limited number of individuals studied, reviewers found no reliable evidence to support the use of these treatments and further trials are needed.	Comprehensive literature search.
Sirven	CR	Early versus late antiepileptic drug withdrawal for people with epilepsy in remission	To quantify seizure relapse risk after early (less than two seizure free years) versus late (more than two seizure free years) AED withdrawal in adult and paediatric epilepsy patients.	Searched MEDLINE, EMBASE, Cochrane Epilepsy Group Trials Register, Cochrane Central Register of Controlled Trials, Index Medicus, CINAHL and handsearched relevant journals.	7 controlled trials. No eligible trials evaluating seizure-free adults.	RCTs that evaluate withdrawal of AEDs after varying periods of seizure remission in adults and children with epilepsy. Included studies compared an early versus late antiepileptic drug discontinuation.	Non randomised trials. Studies on highly specific patient samples (e.g. neonates).	There is evidence to support waiting for at least two or more seizure free years before discontinuing AEDs in children, particularly if individuals have an abnormal EEG and partial seizures. There is insufficient evidence to establish when to withdraw AEDs in children with generalised seizures. There is no evidence to guide the timing of withdrawal of AEDs in seizure free adults. Further blinded RCTs are needed to identify the optimal timing of AED withdrawal and risk factors predictive of relapse.	Comprehensive literature search.

First Author	Year	Title	Description	Search Strategy	N	Included studies	Excluded studies	Results and Conclusions	Quality
Swedish Council on Technology Assessment in Healthcare (SBU)	1998	Therapeutic drug monitoring in epilepsy treatment - Findings by SBU Alert	To identify studies showing the extent to which drug monitoring contributes toward greater effectiveness in epilepsy treatment as measured by better seizure control.	Details of literature search not specified.	1 prospective randomised study	RCTs to assess the benefits of therapeutic drug monitoring, where treatment results are compared among patient groups who either received or did not receive data on concentrations in treatment.		The findings show that there is currently poor evidence to demonstrate the benefits of the method for patients.	
Taylor	CR	Phenobarbitone versus phenytoin monotherapy for partial onset seizures and generalised onset tonic-clonic seizures	To review the effects of phenobarbitone compared to phenytoin when used as monotherapy in patients with partial onset seizures or generalised tonic-clonic seizures with or without other generalised seizure types.	Searched MEDLINE, Cochrane Epilepsy Group Trials Register, Cochrane Central Register of Controlled Trials. Handsearched relevant journals, contacted pharmaceutical companies and researchers in the field to seek any ongoing or unpublished studies.	Data obtained for 4 of 10 studies meeting the inclusion criteria.	RCTs in children or adults with partial onset seizures or generalised tonic-clonic seizures. Trials must have included a comparison of phenobarbitone monotherapy with phenytoin monotherapy.		The results of this review favour phenytoin over phenobarbitone, as phenobarbitone was significantly more likely to be withdrawn than phenytoin. Given that no significant differences for seizure outcomes were found, the higher withdrawal rate with phenobarbitone may be due to adverse effects.	Comprehensive literature search.
Tudur Smith	CR	Carbamazepine versus phenytoin monotherapy for epilepsy	To review the best evidence comparing carbamazepine and phenytoin when used as monotherapy in people with partial onset seizures, or generalised onset tonic-clonic seizures with or without other generalised seizure types.	Searched MEDLINE, Cochrane Epilepsy Group Trials Register, Cochrane Central Register of Controlled Trials. Handsearched relevant journals, contacted pharmaceutical companies and researchers in the field to seek any ongoing or unpublished studies.	3 trials. Individual patient data available for 551 participants.	RCTs in children or adults with partial onset seizures or generalised onset tonic-clonic seizures. Trials must have included a comparison of carbamazepine monotherapy and phenytoin monotherapy.		No evidence found of a significant difference between carbamazepine and phenytoin for the outcomes examined in this review. Confidence intervals were wide and the possibility of important differences existing cannot be excluded.	Comprehensive literature search.
Tudur Smith	CR	Carbamazepine versus phenobarbitone monotherapy for epilepsy	To review the effects of phenobarbitone compared to phenytoin monotherapy for people with partial onset seizures or generalised onset tonic-clonic seizures.	Searched MEDLINE, EMBASE, Cochrane Controlled Trials Register. Handsearched relevant journals, contacted manufacturers of carbamazepine, experts in the field and original trial investigators.	4 trials. Data available for 684 seizures.	RCTs or quasi-randomised, blinded or unblinded controlled trials in children or adults with partial onset seizures or generalised onset tonic-clonic seizures.		No overall difference between carbamazepine and phenobarbitone for time to 12 month remission or time to first seizure, however, subgroup analyses for time to first seizure suggest an advantage with phenobarbitone for partial onset seizures and a clinical advantage with carbamazepine for generalised onset tonic-clonic seizures. Phenobarbitone is significantly more likely to be withdrawn, indicating that it is less well tolerated than carbamazepine.	Comprehensive literature search.
Tudur Smith	CR	Phenytoin versus valproate monotherapy for partial onset seizures and generalised onset tonic-clonic seizures	To review the best evidence comparing phenytoin and valproate when used as monotherapy in people with partial onset seizures, or generalised onset tonic-clonic seizures with or without other generalised seizure types.	MEDLINE, Cochrane Epilepsy Group Trials Register, handsearched relevant journals. Contacted pharmaceutical industry and researchers in the field.	5 trials (669 participants)	RCTs in children or adults with partial onset seizures or generalised onset tonic-clonic seizures. Trials must have included a comparison of valproate monotherapy with phenytoin monotherapy.		No evidence found of a significant difference between valproate and phenytoin for the outcomes examined in this review. No unequivocal evidence to overthrow or support the policy of using valproate in generalised onset tonic-clonic seizures and phenytoin in partial onset seizures.	Comprehensive literature search.

1.2 Randomised controlled trials

First Author	Year	Title	Setting	Description	Methodology	N	Inclusions	Exclusions	Outcomes	Results	Quality and Comments
Alldredge	2001	A comparison of lorazepam, diazepam, and placebo for the treatment of out-of-hospital status epilepticus	Emergency care by paramedics - US	RCT to assess effectiveness of benzodiazepines as an out-of-hospital treatment	Randomisation by computer. Double blind. Sample size calculation done.	205. 66 randomised to lorazepam, 68 to diazepam, and 71 to placebo. Some baseline differences - race and ethnic groups. Slightly longer time to treatment in the placebo group. None of the differences were associated with outcome.	Aged 18 years and over. Out-of-hospital diagnosis of status epilepticus.	Pulse of less than 60 beats per minute. Systolic blood pressure of less than 100mmHg. Second or third degree atrioventricular block. Sustained ventricular tachyarrhythmia. Asthma or chronic obstructive pulmonary disease. History of long-term use of benzodiazepines, or sensitivity to benzodiazepines. Pregnancy. IV access could not be established. Transported by private ambulance or in police custody.	Termination of status epilepticus. Out-of-hospital complications. Complications at transfer. Duration of status epilepticus before arrival at hospital. Neurologic outcome at discharge. Disposition from the emergency department.	Status epilepticus had been terminated on arrival at the emergency department in more patients treated with lorazepam (59.1%) or diazepam (42.6%) than patients given placebo (21.1%) (p=0.001). After adjustment for covariates, the odds ratio for termination of status epilepticus by the time of arrival in the lorazepam group as compared with the placebo group was 4.8 (95% CI, 1.9 to 13.0). The odds ratio was 1.9 (95% CI, 0.8 to 4.4) in the lorazepam group as compared with the diazepam group and 2.3 (95% CI, 1.0 to 5.9) in the diazepam group as compared with the placebo group. The rates of respiratory or circulatory complications (indicated by bag valve-mask ventilation or an attempt at intubation, hypotension, or cardiac dysrhythmia) after the study treatment was administered were 10.6% for the lorazepam group, 10.3% for the diazepam group, and 22.5% for the placebo group (p=0.08)	Slightly underpowered. Large study. Well reported. Well cited.
Anon	1991	Randomised study of antiepileptic drug withdrawal in patients in remission	40 (epilepsy?) centres in the UK and 5 elsewhere in Europe	Pragmatic multi-centre RCT to compare seizure control using slow withdrawal vs routine maintenance of drug therapy	No blinding as placebo not used. Blinding of EEG. Central randomisation.	1013 - 49% M. 510 allocated to withdrawal group, 503 to continued medication group. Some differences at baseline.	History of two or more definite seizures, had been free of all seizures for at least 2 years, and were taking AEDs.	Progressive neurological disorder or other condition likely to reduce follow-up to below 2 years.	Seizure freedom	By 2 years after randomisation, 78% of patients in the treatment group and 59% of those in the withdrawal group remained seizure free, but thereafter the differences between the two groups diminished.	Large study. Well cited. Some pharma involvement.
Anon	1993	Prognostic index for recurrence of seizures after remission of epilepsy	(see Anon 1991)								EEG and generalised seizures were added as 'clinical judgement' rather than evidence based variables

First Author	Year	Title	Setting	Description	Methodology	N	Inclusions	Exclusions	Outcomes	Results	Quality and Comments
Anon	1998	Clobazam has equivalent efficacy to carbamazepine and phenytoin as monotherapy for childhood epilepsy	15 paediatric epilepsy centres - Canada	RCT to compare the effectiveness of monotherapy clobazam with carbamazepine and phenytoin	Double blind. Permuted block design randomisation. Sample size calculation done.	235 - 119 randomised to clobazam, 116 to standard therapy. No baseline differences.	Aged 6 months to 17 years. Diagnosis of epilepsy (two or more unprovoked seizures) by a child neurologist. Seizure types of partial, partial with generalisation, primary generalised tonic-clonic.	Generalised absence, atonic, tonic, or myoclonic seizures. Progressive neurologic disease. Other serious chronic illness. Previous history of poor compliance with AED medication.	Retention on study medication for 12 months or discontinuation of medication for any reason.	56% continued to receive the original medication for 1 year with no difference between CLB and standard therapy (CBZ and PHT). Of these 131 children, 39% (n=51) were seizure free for the 12 month period of the trial (23% of those taking CLB, 25% CBZ, and 11% taking PHT) Seizure control was equivalent for all three medications, as were side effects. There were no statistically significant differences between the CLB and standard monotherapy groups on any of the measures of neuropsychological functioning.	Reasonable study - well reported methodology, large sample.
Aucamp	1985	Clobazam as adjunctive therapy in uncontrolled epileptic patients	No details (institutions?)- South Africa	RCT to assess the efficacy of clobazm as adjunctive therapy in uncontrolled epilepsy	No details of randomisation. Double blind. Selected group of participants.	12 - 50%M. All were institutionalised. Aged 17 to 53 years.	No details.		Frequency, severity, and duration of seizures (assessed by trained staff).	Nine (75%) of the participants became seizure free when taking clobazam.	Small study with selected group. Methodology poorly reported.
Bast	2003	The influence of sulthiame on EEG in children with benign childhood epilepsy with centrotemporal spikes (BECTS)	(see Rating 2000)								
Bawden	1999	The cognitive and behavioural effects of clobazam and standard monotherapy are comparable	(see Anon 1998)								
Cereghino	1998	Treating repetitive seizures with a rectal diazepam formulation: a randomized study. The North American Diastat Study Group	Community (non-medical) - US	RCT of effectiveness and safety of a single-dose treatment for acute repetitive seizures administered in a nonmedical setting by caregivers	Double blind. Block randomisation. Dispensing pharmacist not blind. Sample size calculation done.	114 - 57M. 56% aged 12 years or older. 56 randomised to rectal diazepam, and 58 to placebo. Some baseline differences, authors argued that these did not affect the results.	Outpatients or institionalised individuals aged 2 years or older with a documented history of acute repetitive seizures. At least two episodes of acute repetitive seizures must have occurred within I year, and one episode within 6 months of study entry.	Received other investigational drug or device within 30 days of study entry. History of progressing habitually to status epilepticus. No clinically signficant abnormality.	Seizure count. Time to next seizure. Time from administration to next seizure.	Diastat treatment reduced median seizure frequency (p = 0.029). More Diastat patients were seizure free post-treatment (Diastat, 55%; placebo, 34%; p=0.031). Analysis of the time to the next seizure favoured Diastat treatment (p<0.007). The most common adverse event was somnolence	Pharma sponsored.
Cereghino	2002	Rectal diazepam gel for treatment of acute repetitive seizures in adults	(see Cereghino 1998 and Dreifuss 1998)								

First Author	Year	Title	Setting	Description	Methodology	N	Inclusions	Exclusions	Outcomes	Results	Quality and Comments
Chiron	2000	Stiripentol in severe myoclonic epilepsy in infancy: A randomised placebo-controlled syndrome-dedicated trial	15 (epilepsy?) centres - France	RCT trial of stiripentol as an add-on therapy for SMEI	Randomisation by computer generated list. Double blind. Sample size calculation done.	42 - 17M. 22 randomised to treatment, and 20 to placebo. No baseline differences.	Aged 3 years or older. Diagnosis of SMEI. Appearance of myoclonia after 1 years of age. Atypical absences. Generalised spikes and waves on EEG. Mental delay. At least 4 clonic (or tonic-clonic seizures) per month. Taking valproate or clobazam as ongoing AED therapy.	Receiving drugs other than valproate or clobazam (except progabide). Parents who were unable to comply regularly with drug delivery and daily seizure diary.	Percentage of responders on treatment (50% reduction in seizures). Absolute count of seizures compared with baseline.	The frequency of responders was greater on stiripentol (71%, 95% CI 52.1 to 90·7) than on placebo (5%, 95% CI 0 to14·6) with a high significance (p<0·0001). During the double-blind period, nine (43%) patients on stiripentol but none on placebo became free of clonic (or tonic-clonic) seizures	Small study and slightly underpowered (needed 40 in the trial) due to drop outs on placebo. Pharma sponsored.
Dreifuss	1998	A comparison of rectal diazepam gel and placebo for acute repetitive seizures	Home based - US?	RCT of rectal diazepam gel for acute repetitive seizures	Double blind. Randomisation by block design. Sample size calculation done.	91 - 51M. 45 randomised to diazepam, and 46 to placebo. Baseline differences in race.	Aged 2 to 60 years of age. Maximal weight of 100 kg. Had at least four episodes of acute repetitive seizures during preceding year and at least one in the preceding three months. On stable AED regimen for at least 4 weeks. No treatable cause of seizures. Women who used contraception and were not pregnant.	Plasma phenobarbital levels greater than 30mg per litre. Current treatment with drugs other than AEDs. Long term benzodiazepine use. Use of CNS depressants, or drugs interacting with diazepam. More than one previous with rectal diazepam. Nonepileptic seizures in past 5 years. Habitual progression to status epilepticus. Clinically significant psychiatric disorder. Lack of suitable care giver. Use of other investigational drug or device in preceding 5 months.	Seizure frequency and global assessment of treatment outcome by caregiver.	Diazepam treatment was superior to placebo with regard to the outcome variables related to efficacy: reduced seizure frequency (p<0.001) and improved global assessment of treatment outcome by the care giver (frequency and severity of seizures and drug toxicity) (p<0.001). Post hoc analysis showed diazepam to be superior to placebo in reducing seizure frequency in both children (p<0.001) and adults (p=0.02), but only in children was it superior with regard to improvement in global outcome (p<0.001). The time to the first recurrence of seizures after initial treatment was longer for the patients receiving diazepam (p<0.001). Thirty-five patients reported at least one adverse effect of treatment; somnolence was the most frequent	Pharma sponsored. Underpowered.

First Author	Year	Title	Setting	Description	Methodology	N	Inclusions	Exclusions	Outcomes	Results	Quality and Comments
Fisgin	2002	Effects of intranasal midazolam and rectal diazepam on acute convulsions in children: prospective randomized study	Emergency room - Turkey	RCT to compare rectal diazepam and intranasal midazolam in acute convulsions in children	Quasi-randomised (odd/even days). Not blinded. No sample size calculation reported.	45 - 19M. 22 allocated to diazepam, and 23 to midazolam. Possible baseline differences.	Children admitted to the emergency room.		Termination of seizures. Time to response.	In the diazepam group, the seizures of 13 (60%) patients terminated in 10 minutes; however, 9 (40%) patients did not respond. In the midazolam group, 20 (87%) patients responded in 10 minutes, but 3 (13%) patients did not respond. Midazolam was found to be more effective than diazepam, and the difference was statistically significant ($p<0.05$). The necessity of a second drug for the seizures that did not stop with the first drug was higher in the diazepam group than the midazolam group, and the difference was statistically significant ($p<0.05$)	Small study. Quasi-randomised. Not blinded.
Froscher	1981	A prospective randomised trial on the effect of monitoring plasma anticonvulsant levels in epilepsy	Outpatient clinic? - Germany	RCT to assess whether routine AED plasma level monitoring influenced care	Physicians not blinded. No details of randomisation.	114 - aged between 11 and 74 years. 58 randomised to monitoring, and 56 to usual care. No baseline differences.	Minimum of 3 seizures of one seizure type during last 12 months.	Evidence of non-compliance. Alcohol abuse. Pregnancy.	Frequency of seizures. Frequency of side-effects.	Seizure control improved to a similar degree in both groups. Therapeutic results were not significantly different between groups.	Poorly reported. Not sure how often drug levels were measured. Lack of blinding.
Helgeson	1990	Sepulveda Epilepsy Education: the efficacy of a psychoeducational treatment program in treating medical and psychosocial aspects of epilepsy	Weekend training programme - US	RCT to assess effectiveness of the programme	Not blinded. Waiting list control. No details of randomisation. No sample size calculation reported.	38 - 10M. 20 randomised to programme, and 18 to waiting list. Some baseline differences.	Adults with epilepsy.	Learning disability. Dementia. Presence of psychosis.	Measures of anxiety and depression. Psychological and social problems with epilepsy. Coping. Self-efficacy. Knowledge and medical management.	The treatment group showed a significant increase in overall understanding of epilepsy ($F(1,36)=39.74$, $p<0.0001$), a significant decrease in fear of seizures ($F(1,36)=7.49$, $p<0.009$), and a significant decrease in hazardous self-management practices ($F(1,36)=29.67$, $p<0.0001$). The treatment group also showed a significant increase in medication compliance ($F(1,24)=4.18$, $p<0.05$).	Small study with several possibilities for bias: baseline differences (control group had higher levels of depression and anxiety), most outcomes were not objectively measured (patient self-reported), measurement of blood AED levels was not done for all participants, significant loss to follow up. Other possible biases may be due to poor reporting (for example, there were no details of randomisation, concealment of allocation, or levels of blinding

First Author	Year	Title	Setting	Description	Methodology	N	Inclusions	Exclusions	Outcomes	Results	Quality and Comments
Jannuzzi	2000	A multicentre randomized controlled trial on the clinical impact of therapeutic drug monitoring in patients with newly diagnosed epilepsy	Centres (no details of type or numbers) - Italy	Multicentre, randomised parallel-group trial to assess the clinical impact of monitoring serum levels of AEDs in people with newly diagnosed epilepsy.	Treating physician not blinded. Central randomisation. Sample size calculation done.	180. 93 randomised to monitoring, and 87 to usual care. 50%M and 55%M of the groups respectively. No significant baseline differences.	Aged between 6 and 65 years. Diagnosis of untreated partial or idiopathic generalised epilepsy. History of at least 2 seizures in past 4 moths. Clinical indication to initiate treatment with carbamazepine, phenytoin, valproate, phenobarbital, or primidone. Ability to comply with the study procedures.	Diagnosis of benign rolandic epilepsy, absence epilepsy, or epileptic enephalopathy. Presence of known progressive disease. Pregnancy. Severe hepatic or renal insufficiency. History of drug or alcohol abuse. Treatment with AED.	Proportion reaching complete seizure remission in last 12 months of follow-up. Proportion seizure free since initiation of treatment. Time to first seizure. Time to reach 12-month seizure remission.	There were no significant differences between the monitored group and the control group with respect to patients achieving 12-month remission (60% vs. 61%), patients remaining seizure free since initiation of treatment (38% vs. 41%), and time to first seizure or 12-month remission	Underpowered - needed 180 but only 116 completed the study. Well reported.
Keene	1990	Clobazam as an add-on drug in the treatment of refractory epilepsy of childhood	Paediatric neurology department? - Canada	RCT to assess the effectiveness of clobazam as add-on therapy in children	Double blind crossover. Sample size calculation done.	21 - 10M. Aged from 2 to 19 years. 10 randomised to placebo then clobazam, and 11 to clobazam then placebo. No baseline differences.	Aged between 6 months and 18 years. More than 4 seizures per month.	Diagnosis of degenerative central nervous system disorder, brain tumour. Past history of poor compliance.	Rate of drug success - 50% or more reduction in seizures.	52% (n=11/21) of children had greater than 50% reduction in their seizure frequency when taking the clobazam. During the placebo phase no child recorded a greater than 50% reduction in seizure frequency.	Small study.
Koeppen	1987	Clobazam in therapy-resistant patients with partial epilepsy: A double-blind placebo-controlled crossover study	9 centres (no details of type) - Europe	Multicentre trial to assess the effectiveness of clobazam in refractory partial seizures	Double blind crossover design. Randomisation done by centre.	129 - 56M. 63 randomised to clobazam then placebo, and 66 to placebo then clobazam. Some baseline differences may exist - no statistics given.	Diagnosis of partial epilepsy who were refractory to treatment, and still receiving basic AED medication.		Seizure frequency. EEG findings. Measures of mood states, global ratings of efficacy and safety and side effects.	19% (n=20/129) of those receiving clobazam became seizure-free during the maintenance dose period. In contrast, freedom from seizures was not observed in any placebo patient. The most frequent adverse reactions to clobazam were drowsiness and dizziness	Large sample. Multicentre.
Koskiniemi	1998	Piracetam relieves symptoms in progressive myoclonus epilepsy: A multicentre, randomised, double blind, crossover study comparing the efficacy and safety of three dosages of oral piracetam with placebo	4 (epilepsy?) centres - Finland	RCT to compare three daily dosage regimes of piracetam	Double blind, placebo controlled crossover trial. No details of randomisation. Sample size calculation reported.	32 - 12M. Aged from 17 to 43 years. Allocated randomly to one of the nine sequences of treatment.	Diagosis of Unverricht-Lundborg disease with onset between ages 6 and 15 years.	Diagnosis of mild Unverricht-Lundborg disease. Pregnant or lactating women. Women of childbearing age who were not using adequate contraception. Clinically relevant abnormalities in lab tests. Participation in a drug trial during three months before enrolment. Participation of a third member of the family in the study.	Stimulus sensitivity. Motor impairment. Functional disability. Handwriting. Global assessment by investigator and participant.	Treatment with 24g/day piracetam produced significant and clinically relevant improvement in the primary outcome measure of mean sum score (p=0.005) and in the means of its subtests of motor impairment (p=0.02), functional disability (p=0.003), and in global assessments by both investigator (p=0.002) and patient (p=0.01). Significant improvement in functional disability was also found with daily doses of 9.6g and 16.8g. The dose-effect relation was linear and significant	Small study. Defined group of participants. Pharma sponsored.

First Author	Year	Title	Setting	Description	Methodology	N	Inclusions	Exclusions	Outcomes	Results	Quality and Comments
Leppik	1983	Double-blind study of lorazepam and diazepam in status epilepticus	3 emergency centres - US	RCT to compare lorazepam and diazepam in the treatment of status epilepticus	Double blind. No details of randomisation, other than done by assembler of the drug kits. No sample size calculation reported.	70 episodes. 37 randomised to lorazepam and 33 to diazepam. Possible baseline differences.	Adults with convulsive status epilepticus.	Presence of terminal illness. Cardiac arrhythmia. Hypotension. Acute metabolic disorder causing status epilepticus. History of sensitivity to benzodiazepines. Childbearing potential. Received diazepam or other treatment prior to referral to study.	Termination of seizures. Time to response.	Seizures were controlled in 89% of the episodes treated with lorazepam and in 76% treated with diazepam although this difference was not statistically significant. The times for onset of action of the medications did not differ significantly. Adverse effects occurred in 13% of the lorazepam-treated patients and in 12% of the diazepam-treated patients (assumed to be non-significant). Respiratory depression and arrest, the most frequent adverse effects, were treated symptomatically; no adverse sequelae were noted.	Reasonable sample. Some reporting problems.

First Author	Year	Title	Setting	Description	Methodology	N	Inclusions	Exclusions	Outcomes	Results	Quality and Comments
Lewis	1990	Randomized trial of a program to enhance the competencies of children with epilepsy	Child-parent education at epilepsy centre - Chile	RCT to assess effectiveness of the programme	Not blinded. Traditional lectures given to control. Randomisation by number. No sample size calculation reported.	236 children. 123 randomised to education, and 113 to control. Some baseline differences.	Children aged 7 to 14 years who attended epilepsy centre.		Knowledge. Perceived competencies. Self-reported gains. Parental knowledge. Parental anxiety. Perceptions of the programme's efficacy.	Increase in knowledge in both groups of children, but the knowledge of children in the intervention group increased significantly compared to the control group in areas related to management of seizures. There was a significant increase in the self-perception of social competency ($p<0.05$) in the intervention group (n=106) than the control group (n=92) and they also reported significantly better behaviour ($p<0.002$). There was an increase in knowledge for both groups of parents. However, there was a significant decrease in knowledge related to seizure management in the intervention group (n=185) compared to the control group (n=180). Parents in the intervention group (n=175), and mothers particularly, were more likely to report that they were less anxious ($p<0.001$) and the levels of anxiety were decreased ($p<0.01$) when compared to the control group (n=176)	Large study of reasonable quality. The groups were treated equally, and most outcomes were measures in a reliable, standard and valid way. There were some possibilities of bias that may have been due to lack of reporting (no details were given of the randomisation and concealment of allocation, or levels of blinding)
Lewis	1991	Impact of the children's epilepsy program on parents	(see Lewis 1990)								

First Author	Year	Title	Setting	Description	Methodology	N	Inclusions	Exclusions	Outcomes	Results	Quality and Comments
Mattson	1985	Comparison of carbamazepine, phenobarbital, phenytoin, and primidone in partial and secondarily generalized tonic-clonic seizures	10 veterans administration medical centres - US	Multicentre RCT to compare the efficacy and toxicity of carbamazepine, phenobarbital, phenytoin, and primidone in partial and secondarily generalized tonic-clonic seizures	Different randomisation schedules for different seizure types. Not sure if treating physician was blinded.	622 - 87%M. Mean age 41 years. 101 randomised to carbamazepine, 101 to phenobarbital, 110 to phenytoin, and 109 to primidone. No baseline differences.	Aged 18 to 70 years. Simple or complex partial or secondary generalised tonic-clonic seizures.	Documented previous failure with, or hypersensitivity to, any of the four study groups. Alcohol or drug abuse. Known non-compliance. Severe psychiatric problems. Low intelligence. Progressive neurologic disorder. Unstable medical disorder. Alcohol related seizures.	Retention on study medication. Composite scores, total seizure control, seizure rate, incidence of side effects.	Seizure freedom for tonic-clonic seizures was similar for all drugs (CBZ 48%, PHB 43%, PHY 43%, PMD 45%). Carbamazepine provided complete control of partial seizures (43%) more often than primidone (15%) or phenobarbital (16%) ($p<0.03$). Differences in failure rates of the drugs were explained primarily by the fact that primidone caused more intolerable acute toxic effects, such as nausea, vomiting, dizziness, and sedation. Decreased libido and impotence were more common in patients given primidone. Phenytoin caused more dysmorphic effects and hypersensitivity. Control of tonic-clonic seizures did not differ significantly with the various drugs.	
May	2002	The efficacy of an educational treatment program for patients with epilepsy (MOSES): Results of a controlled, randomized study	22 epilepsy centres - Germany, Austria and Switzerland	RCT to assess educational programme	Not blinded. Waiting list control. No details of randomisation. No sample size calculation reported.	242 - aged 16 to 80 years of age. 113 randomised to education, and 129 to waiting list. Some baseline differences.	Individuals attending clinics.	Learning disability. Acute psychiatric illness. Nonepileptic seizures only. Under 16 years of age.	Health related quality of life. Self-esteem. Depression. Restrictions in daily life. Epilepsy related fear. Stigma, Mobility and leisure.	Although both groups showed improvements, the participants in MOSES showed significant improvements in knowledge ($p<0.001$), coping with epilepsy ($p=0.004$), seizure outcome ($p=0.041$), and were more satisfied with the therapy (better tolerability of AEDs, fewer side effects $p=0.014$) compared with the control group. The participants were also highly satisfied with the programme. However, there were many aspects of epilepsy measures that were not improved by the programme, including unnecessary restriction of activities, and epilepsy-related fears.	large study, with some possibilities of bias; the control group had a longer duration of epilepsy than the intervention group, the control group were given no 'passive' education, significant loss to follow up. Again, there was a lack of reporting of the randomisation and blinding.

First Author	Year	Title	Setting	Description	Methodology	N	Inclusions	Exclusions	Outcomes	Results	Quality and Comments
Mikkelsen	1981	Clonazepam (Rivotril(TM)) and carbamazepine (Tegretol(TM)) in psychomotor epilepsy: A randomized multicentre trial	No details - Denmark?	Multicentre RCT to compare the effectiveness of clonazepam and carbamazepine in psychomotor epilepsy	Double blind. No details of randomisation.	36 - 14M. Age range 6 to 72 years. 17 randomised to clonazepam, and 19 to carbamazepine. Stated that groups were comparable, but appears to be more tonic-clonic seizures in the clonazepam group.	Previously untreated with recently diagnosed psychomotor epilepsy (complex partial seizures).	Progressive brain diseases. Presenile dementia. Liver and kidney diseases. Pregnancy.	Number of withdrawals from treatment. Time to withdrawal. Number of seizures until withdrawal. Side effects.	Five participants were withdrawn from the carbamazepine group, and 7 from the clonazepam group, and there was no significant differences between the groups in terms of number of withdrawals, timing of withdrawals, number of seizures to withdrawal, and side effects (p>0.20).	Small study. Possible baseline differences. Large age range.
Rating	2000	Sulthiame as monotherapy in children with benign childhood epilepsy with centrotemporal spikes: A 6-month randomized, double-blind, placebo-controlled study	26 (epilepsy?) centres - Europe	Multicentre study to assess the efficacy of sulthiame as monotherapy in BECTS	Randomisation concealed. Double blind. Sample calculation done (needed 140, or 60 at interim analysis).	66 - 40M. Aged between 3 and 10 years of age. 31 randomised to treatment group,. 35 to placebo. No baseline differences.	Children with a diagnosis of BECTS who had had two or more seizures during the past 6 months.	Children with severe organic diseases, acute porphyria, history of mental illness, relevant hypersensitivity, somatic signs of puberty, or relevant renal, thyroid, or hepatic dysfunction. Children pre-treated with AEDs after 6 months of age (unless intervention lasted less than 1 week).	Rate of treatment failure events (TFE). Change in EEG recordings over time.	Twenty-five of the 31 sulthiame-treated patients (81%) and 10 of the 35 placebo-treated patients (29%) completed the trial without any TFEs (p=0.00002). Most TFEs were seizures (n=4 for the STM patients, n=21 for the placebo group). While all patients displayed at least one specific focus in either the awake or asleep EEG initially, 11 sulthiame-treated patients had a normal awake EEG and 10 had a normal asleep one after 6 months	Small sample. Stopped at interim analysis due to superiority of sulthiame. Authors urged caution with the EEG results as the trail was not designed to assess the effect of sulthiame on the EEG.
Schmidt	1986	Clobazam for refractory focal epilepsy. A controlled trial	Seizure clinic - Germany?	Randomised crossover trial of add-on clobazam in refractory partial seizures	No details of randomisation. Double blind.	20 - 9M. Age range 18 to 54 years. 9 randomised to clobazam then placebo, 11 to placebo then clobazam. No baseline comparison reported.	Aged 18 to 55 years. Complex partial seizures. More than three seizures per month during 12 months preceding trial despite maximally tolerated AED treatment.	Progressive brain lesion. Impaired capacity.	Mean number of seizures and frequency. Plasma AED levels. Side effects.	The mean number of seizures was statistically significantly lower during the three months of active treatment as compared with placebo. At the end of the third month, eight (40%) of the patients had a seizure reduction by more than 75%, including four patients (20%) who had complete control. Tolerance to the antiepileptic effect of clobazam was noted in 56% of the patients, and mild transient sedation occurred in 40% of the patients	Small study. No details of randomisation.

First Author	Year	Title	Setting	Description	Methodology	N	Inclusions	Exclusions	Outcomes	Results	Quality and Comments
Scott	1999	Buccal midazolam and rectal diazepam for treatment of prolonged seizures in childhood and adolescence: a randomised trial	Residential school - UK	RCT to assess efficacy and safety of buccal midazolam and rectal diazepam	Randomisation by envelope. Not blinded. Sample size calculation done.	42 - of whom 28 had episodes. Aged 5 to 19 years. 40 episodes randomised to midazolam, and 39 to rectal diazepam. No baseline differences.	Individuals who had been previously treated with rectal diazepam for acute seizures.		Termination of seizures. Time to response. Seizure duration. Oxygen saturation and blood pressure.	Buccal midazolam was used to treat 40 seizures in 14 students, and rectal diazepam 39 seizures in 14 students. Midazolam stopped 30 (75%) of 40 seizures and diazepam 23 (59%) of 39 (p=0.16). The median time from arrival of the nurse to administration of medication was 2 min. Time from administration to end of seizure did not differ significantly between the two treatments. No clinically important adverse cardiorespiratory events were identified in the two groups	Small study. Pragmatic trial. Lack of concealment of allocation.
Singhi	2002	Continuous midazolam versus diazepam infusion for refractory convulsive status epilepticus	Paediatric emergency and intensive care unit - India	RCT to compare efficacy of diazepam and midazolam in refractory status epilepticus	Randomisation done centrally. Physician not blinded. No sample size calculation reported.	40 - age range 2 to 138 months. No baseline differences. 21 randomised to midazolam, and 19 to diazepam.	Consecutive admissions of children aged 2 months to 12 years of age.	Neonates. Children with primary cardiac or respiratory diseases. Any other chronic illnesses.	Seizure control. Seizure recurrence. Development of hypotension. Neurologic outcome.	Refractory status epilepticus was controlled in 18 (86%) and 17 (89%) in the midazolam and diazepam groups respectively. The difference was not significant. Median time to seizure control was 16 minutes in both groups, but seizures recurred significantly more often in the midazolam group (57% vs 16% in the diazepam group, p<0.05). Approximately half the children needed mechanical ventilation, and 40% had hypotension in both groups. The mortality was higher in the midazolam group (38% vs 10.5%) but the difference was not highly significant (0.05>p<0.1)	Small study. Not blinded.
Smith	1987		(see Mattson 1985)								

First Author	Year	Title	Setting	Description	Methodology	N	Inclusions	Exclusions	Outcomes	Results	Quality and Comments
Tennison	1994	Discontinuing antiepileptic drugs in children with epilepsy - A comparison of a six-week and a nine-month taper period	2 paediatric epilepsy clinics - US?	RCT to compare a relatively short (six week) period and relatively long (nine month) period of drug tapering in children	Unblinded. Concealment of allocation was unclear.	149 - 79M. 81 randomised to 6 week taper, and 68 to 9 months taper.	No seizures for approximately 18 months.	Single seizure. Febrile seizures only. Neonatal seizures or infantile spasms only.	Seizure recurrence.	Seizures recurred in 53 patients (40%). The mean duration of follow-up was 39 months (range, 11 to 105) for the patients who did not have a recurrence of seizures. Neither the length of the taper period (six weeks vs. nine months, p=0.38) nor the length of time the patients were free of seizures before the taper period was begun (two years vs. four years, p=0.20) significantly influenced the risk of seizure recurrence.	Concealment of allocation was unclear. Unblinded. Possible baseline differences that may have affected the results, but no statistical comparisons were done. The length of follow-up was statistically longer for the 6 week taper group compared with the 9 month group (44 months vs 33 months, p=0.07). If more than one drug was tapered, this was done sequentially. No analysis of whether tapering more than one drug correlated with recurrence.

First Author	Year	Title	Setting	Description	Methodology	N	Inclusions	Exclusions	Outcomes	Results	Quality and Comments
Tieffenberg	2000	A randomized field trial of ACINDES: A child-centered training model for children with chronic illnesses (asthma and epilepsy)	Community - Argentina	RCT to assess effectiveness of programme	Cluster analysis. No details of randomisation. Control was usual care.	167. 103 to education, and 64 to control.	Children with normal IQ scores. No developmental delays. Diagnosis of epilepsy that required permanent medication. Diagnosis confirmed by EEG at least 5 months before study.		Locus of control. Knowledge. Visits for healthcare (routine and emergency). School absenteeism.	Children in the intervention group showed significant improvements in knowledge, belief, attitudes, and behaviours compared with the control group (probability of experimental gain over control =0.69, s2=0.007). Parents of the children also had improved knowledge of epilepsy (increased from 22% to 56% c.f. control 8% to 15%, probability of experimental gain over control =0.62, s2=0.0026) and decreased fear of the child's death (decreased from 69% to 30% c.f. control 74% to 65%, probability of experimental gain over control =0.63, s2=0.0026). The parents in the intervention group allowed their children to sleep at friend's homes more often (probability of experimental gain over control =0.59, s2=0.0026). Rates of seizures (p=0.026), emergency visits (p=0.046), and school absenteeism (p=0.011) decreased significantly in the intervention group compared with the control group	High loss to follow-up in control group (29.7%). Large RCT, and several important methodological issues were not reported (including randomisation, blinding). The use of the probability of gain statistic is unusual
Treiman	1998	A comparison of four treatments for generalized convulsive status epilepticus. Veterans Affairs Status Epilepticus Cooperative Study Group	16 Veterans Affairs medical centres and 6 university hospitals - US	RCT to compare efficacy of phenobarbital, phenytoin, diazepam and phenytoin, and lorazepam in generalised convulsive status epilepticus	Double blind. No details of randomisation	518. 136 randomised to lorazepam, 124 to phenobarbital, 131 to diazepam and phenytoin, 101 to phenytoin only. No baseline difference between treatment groups.	Evidence of generalised status epilepticus at evaluation.	Received treatment. Seizures stopped. Status epilepticus other than generalised. Aged under 18 years. Pregnancy. Neurologic emergency. Contraindication to therapy.	Seizure termination. Outcome 30 days after treatment. Side effects.	In an intention-to-treat analysis, the differences among treatment groups were not significant, either among the patients with overt status epilepticus (p=0.12) or among those with subtle status epilepticus (p=0.91). There were no differences among the treatments with respect to recurrence during the 12-hour study period, the incidence of adverse reactions, or the outcome at 30 days.	Lack of reporting (randomisation, concealment of allocation, sample size). Large study.

First Author	Year	Title	Setting	Description	Methodology	N	Inclusions	Exclusions	Outcomes	Results	Quality and Comments
Trudeau	1996	Gabapentin in naive childhood absence epilepsy: results from two double-blind, placebo-controlled, multicentre studies	8 centres (no details of type) - US and 5 centres (no details of type) - Europe	2 RCTs to compare the efficacy and safety of gabapentin in children with newly diagnosed absence epilepsy	Double blind. No details of randomisation.	33 - 15M. Age range 4 to 12 years. 15 randomised to gabapentin, and 18 to placebo.	Aged 4 to 16 years. Weighing 15 to 70 kilograms. Recent diagnosis of childhood absence epilepsy. At least four observed absence seizures per day during 2 week baseline assessment. Not receiving any AED treatment. Never received treatment for generalised epilepsy. Females were premenarchal or using reliable contraception. No history of serious medical or psychiatric disease. No history of hematologic, hepatic, renal or progressive neurologic disease. No other investigational drug within 1 month of study entry. No history of drug or alcohol abuse in previous 3 years.		Change in seizure frequency.	In an intention-to-treat analysis, data on two children were excluded due to a lack of a baseline EEG because of equipment malfunction. No statistically treatment differences (response ratio, p=0.141 or responder rate, p=0.344) were found between GBA and placebo. GBA did not decrease or increase absence seizures compared with placebo.	Only 2 week trial period. Small sample. Pharma sponsored. Underpowered (needed 20 per group).
Wiebe	2001	A randomized, controlled trial of surgery for temporal-lobe epilepsy	Medical centre - Canada	RCT to compare medical treatment with surgical treatment of temporal lobe epilepsy	Reviewer blinded. Randomisation done by numbered envelopes.	80. 40 assigned to surgery and 40 to medication. Some baseline differences. Lower QoL in medication group.	Aged 16 years or older. Seizures with strong temporal lobe semiology for more than one year. Seizure occurred monthly on average during preceding year despite the use of two or more AEDs, one of which was phenytoin, carbamazepine, or valproate.	Brain lesions that required urgent surgery. Progressive CNS disorders. Active psychosis. Pseudoseizures. IQ lower than 70. Previous surgery for epilepsy. Focal extratemporal spikes or MRI evidence of extratemporal lesions or epileptogenic lesions.	Seizure freedom. Seizure rate. Severity of seizures. Quality of life. Employment or school attendance.	Of the 36 who underwent surgery, 58% were free from seizures that impaired awareness at 12 months, compared with 8% in the medical group ($p<0.001$). 38% of those in the surgical group compared with 3% in the medical group were seizure free, including auras, at 12 months ($p<0.001$). One individual died of SUDEP in the medical group. No deaths occurred in the surgical group.	Small study. Only RCT of surgery compared with medication. Does not evaluate timing of surgery.

1.3 Cohort studies

First Author	Year	Title	Description	Aim	Retro/Prospective	N	Variables	Results	Quality and Comments
Airaksinen	2000	A population-based study on epilepsy in mentally retarded children	Birth cohorts of children born from 1969 to 1972 in a defined geographical area - Finland	Longitudinal study of the cumulative risk and severity of epilepsy in mildly and severely learning disabled children	Prospective	12,882 children, of whom 178 had learning disabilities.	Risk of epilepsy. Classification of seizure type. Onset and cause of epilepsy. Additional disabilities. Mortality. Remission of seizures.	By the age of 22 years, 32 (21%) of the children had defined epilepsy. Four patients with epilepsy had died by age 22, but the causes of death were not directly related to epilepsy. The cumulative probability of remission from seizures (defined as for 5 or more years) at the ages of 10, 17, and 22 years was 8, 25, and 32%. In addition to the 8 (29%) children in remission, 14% of the living 28 children had been seizure free for at least 1 year. So, although 71% of the children had active epilepsy (defined as having seizures in the past 5 years) at age 22 years, 43% had been seizure-free for at least 12 months	Large, population based prospective study.
Annegers	1979	Remission of seizures and relapse in patients with epilepsy	Community sample of individuals in a defined geographical area - US	Longitudinal study to assess the probability of remission upto 20 years after diagnosis	Prospective	618 individuals with a diagnosis of epilepsy (at least two seizures with no apparent cause),	Remission of seizures (seizure free for at least 5 years).	Prognosis for remission of epilepsy is poor in patients with associated neurologic dysfunction identified from birth. Patients with idiopathic seizures and survivors of postnatally acquired epilepsy have better prospects for eventual remission. The probability of remission is highest in patients with generalized-onset seizures diagnosed before 10 years of age. Prognosis is less favourable for those with partial complex seizures and adult-onset epilepsy	Large, population based prospective study.
Bardy	1987	Incidence of seizures during pregnancy, labor and puerperium in epileptic women: a prospective study	Pregnancies in women with epilepsy over a 4 year period - Finland	To investigate changes in seizure frequency, the distribution of seizures over time, and to identify prognostic factors associated with increased seizure frequency.	Prospective	154 pregnancies in 140 women with epilepsy.	Seizure rate. Distribution of seizures over time.	An increase in the number of seizures was noticed in 32% of the cases, a decrease in 14% and unchanged frequency in 23% of the cases, 31% being seizure-free during the study period. The highest incidence of major convulsive seizures occurred during the last trimester of pregnancy, while the incidence of complex partial seizures was highest during puerperium. No factors were found which predict the seizure increase	Prospective.

First Author	Year	Title	Description	Aim	Retro/Prospective	N	Variables	Results	Quality and Comments
Brorson	1987	Long-term prognosis in childhood epilepsy: survival and seizure prognosis	Children who had active epilepsy living in a defined geographical area - Sweden	Follow-up study of prognosis of epilepsy	Prospective	195 children with active epilepsy in original cohort - minimum of two seizures, with at least one during the 3 years prior to enrolment.	Mortality. Seizure prognosis. AED treatment.	Of the 194 children that agreed to participate, 74 had neurodeficit. After 12 years, 29 of the 74 children (39%) were in remission, defined as being seizure free for 3 consecutive years. The annual remission rate was high (12%) only in the first few years after onset, but then fell to 3%	Population based, prospective
Fairgrieve	2000	Population based, prospective study of the care of women with epilepsy in pregnancy	Pregnancies in women with epilepsy in a defined geographical area - UK	Assess the proportion of pregnant women with epilepsy, the care process, and clinical outcomes.	Prospective	400 pregnancies in 300 women with epilepsy	Care process - management, counselling, medication. Pregnancy outcomes - maternal and child mortality, complications	Of the 359 (90%) known pregnancy outcomes, the obstetric complication rate was similar to that of the background population, except for an excess of premature deliveries (8.2%). No statistical significance was given	
Forsgren	1996	Influence of epilepsy on mortality in mental retardation: an epidemiologic study	Cohort of all known individuals with learning disabilities in defined geographical area - Sweden	To study mortality in people with learning disabilities	Prospective	1,478 individuals, of whom 296 had epilepsy.	Mortality.	During the 7 year observation period, 124 people died, of whom 30 (10.1%) had epilepsy. The increased death rate was highly significant for people with MR and epilepsy, (SMR 5.0, 95% CI 3.3 to 7.5) and people with MR, epilepsy and CP (SMR 5.8, 95% CI 3.4 to 9.8). Epilepsy was reported as the cause of death in 1 of the 30 cases, and as a contributing cause in 6. Examination of medical files, death certificates, and necropsy (11 cases) found two deaths to be probably seizure related (one after a fall probably after a seizure, one found dead in bed with no obvious cause) and 28 deaths not related to the epilepsy	Population based, prospective
Forssman	1970	Mortality of the mentally deficient: a study of 12,903 institutionalised subjects	Cohort of all individuals cared for in institutions for people with learning disabilities - Sweden	Analysis of mortality in institutionalised individuals with learning disabilities	Prospective	12,903 individuals, of whom 1,682 had epilepsy.	Mortality	12,873 patients (99.8%) were followed-up until they died or to January 1st 1968. Standard mortality was calculated from the life tables for the standard population in 1960-1965. 1,784 people died during the period of observation, of whom 445 had epilepsy. The overall reduction in life expectancy was 5% compared with 14% for people with epilepsy. Of the 1,682 patients with epilepsy, 26% (445) died and the relative mortality rate was 7.9 times the standard (compared with 3.2 overall)	'Population based, prospective

First Author	Year	Title	Description	Aim	Retro/Prospective	N	Variables	Results	Quality and Comments
Gjerde	1988	The course of epilepsy during pregnancy: a study of 78 cases	Pregnancies in women with epilepsy attending a clinic - Norway	To assess seizure frequency and severity during pregnancy. To assess the influence of drug levels and clinical monitoring on seizure rate.	Prospective	78 pregnancies in 66 women	Seizure frequency. Drugs and drug levels.	No statistically significant differences between frequency before and during pregnancy were found. Cases with seizures before pregnancy tended to have seizures during pregnancy, but there was no association between occurrence of seizures prior to pregnancy and increased frequency during pregnancy. There was no evidence that seizures became more severe during pregnancy. No relationship was found between type of epilepsy and change in seizure frequency during pregnancy.	
Goulden	1991	Epilepsy in children with mental retardation: a cohort study	Birth cohort of children born between 1951 and 1955 in defined geographical area - UK	Longitudinal study of the cumulative risk of epilepsy and to determine risk factors	Prospective	13,842, of whom 221 were receiving special services for learning disabilities.	Risk of epilepsy. Febrile seizures. Remission from epilepsy.	By age 22 years, 33 (15%) had repeated, unprovoked seizures. 39% of these were in remission (defined as seizure free for 5 years). Rates of remission differed by group: 56% MR only, 47% MR and cerebral palsy, 11% postnatal injury	'Population based, prospective
Hart	1990	National General Practice Study of Epilepsy: recurrence after a first seizure	Individuals with epilepsy registered with general practices - UK	To investigate the prognosis of newly diagnosis epilepsy	Prospective	564 individuals with epilepsy	Time from index seizure to seizure recurrence, death or last available follow-up	67% (95% confidence interval 63-71%) had a recurrence within 12 months of the first seizure, and 78% (74-81%) had a recurrence within 36 months. Seizures associated with a neurological deficit presumed present at birth had a high rate of recurrence (100% by 12 months), whereas seizures that occurred within 3 months of an acute insult to the brain, such as head injury or stroke, or in the context of an acute precipitant such as alcohol, carried a much lower risk of recurrence (40% [29-51%] by 12 months). Other factors affecting the risk of recurrence were age-the highest risk being for patients under the age of 16 (83% [77-89%] by 36 months) or over the age of 59 (83% [76-90%] by 36 months-and type of first seizure-the risk of recurrence being much higher for patients with simple partial or complex partial seizures (94% [90-99%] by 36 months) than for those with generalised tonic clonic seizures (72% [67-77%] by 36 months)	

First Author	Year	Title	Description	Aim	Retro/Prospective	N	Variables	Results	Quality and Comments
Kaaja	2002	Enzyme-inducing antiepileptic drugs in pregnancy and the risk of bleeding in the neonate	Cohort of pregnant women with epilepsy at one hospital from 1980 to 1998 - Finland	To determine the occurrence of bleeding complications in newborns exposed to maternal enzyme-inducing AEDs	Prospective	975 pregnancies of at least 22 weeks duration in women diagnosed with epilepsy before pregnancy	Bleeding complications in the child	A group of 1,324 pregnancies (1,334 neonates) served as the control group. None of the exposed group or the control received vitamin K supplementation during pregnancy or labour. All newborns of mothers with epilepsy and control newborns received a standard dose of 1mg vitamin K intramuscularly at birth. 5 exposed (0.7%) and 5 control (0.4%) newborns suffered a bleeding complication. Bleeding was associated with birth at less than 32 weeks (OR=13, 95%CI 2.7-64) and alcohol abuse (OR=17, 95%CI 1.8 to 162). No association was found with exposure to enzyme-inducing AEDs (OR=1.1, 95%CI 0.3-4.6, p=0.8).	
MacDonald	2000	Factors predicting prognosis of epilepsy after presentation with seizures	Cohort of individuals with newly diagnosed epilepsy registered in primary care - UK	To describe clinical features, prognosis and various aspects of care	Prospective	792 individuals with new diagnosis of epilepsy	Prognosis of epilepsy and seizure remission	The dominant clinical feature predicting remission was the number of seizures in the 6-month diagnostic assessment period. Thus, the chance of entering 1 year of remission by 6 years for a patient who had 2 seizures during this initial 6 months was 95%; for 5 years of remission, it was 47% as opposed to 75% for 1 year of remission and 24% for 5 years of remission if there had been 10 or more seizures during this period. The number of seizures in the early phase of epilepsy (here, taken as the first 6 months after presentation) is the single most important predictive factor for both early and long-term remission of seizures	
Nashef	1995	Sudden death in epilepsy: A study of incidence in a young cohort with epilepsy and learning difficulty	Cohort of individuals with epilepsy who attended a school for learning disabilities - UK	Analysis of mortality and sudden death	Prospective	310 - 103 boys and 207 girls.	Mortality. Sudden death.	Total duration of follow-up was 4,135 person years. There were 28 deaths (mean age 19 years, range 10 to 28); 14 were classified as sudden death	Selected population
Olafsson	1998	Pregnancies of women with epilepsy: a population-based study in Iceland	All women with epilepsy treated with AEDs during pregnancy or during a 5 year period preceding the pregnancy - Iceland	To determine the proportion of all pregnancies in women with active epilepsy and compare complication rates, delivery, and outcomes	Retrospective	82,483 live births from 81,473 pregnancies. 266 pregnancies were to 157 women with active epilepsy.	Prevalence of pregnancy in women with epilepsy. Pregnancy and delivery complications. Mortality and malformations.	Caesarean section was performed twice as frequently in women with active epilepsy (13%, 35 of 266 compared with 8.8%, 7,139 of 81,473). Perinatal mortality (11.2 in 1000 compared with 8,7 in 1000, OR=1.5, 95% CI 0.3-4.1) and mean birth weight (3,601g compared with 3,647g, p=0.2) were not significantly different for the offspring of women with active epilepsy.	

First Author	Year	Title	Description	Aim	Retro/Prospective	N	Variables	Results	Quality and Comments
Scheepers	1998	The misdiagnosis of epilepsy: Findings of a population study	Review of patient and audit of care - UK	To assess the standards of epilepsy care in relation to diagnosis, seizure management, and quality of life	Prospective	214 individuals with a diagnosis of epilepsy	N/A	Forty-nine of 214 patients with a primary diagnosis of epilepsy were subsequently found to have been misdiagnosed following a specialist review and investigations. All except two have been withdrawn from antiepileptic medication. The diagnosis of epilepsy was disputed in a further 26 patients	
Schmidt	1983	Change of seizure frequency in pregnant epileptic women	Women referred to two centres for pregnancy planning and during early pregnancy - Germany and Italy	To investigate changes in seizure frequency, the distribution of seizures over time, and to analyse clinical and pharmacological factors associated with seizure relapse	Prospective	136 pregnancies in 122 women with epilepsy	Seizure frequency. Reasons for seizure increases.	Pregnancy did not influence the seizure frequency in 68 pregnancies (50%). In 50 pregnancies (37%) the number of seizures increased during pregnancy or puerperium. The seizure frequency decreased in 18 pregnancies (13%). In 34 out of 50 pregnancies (68%) the increase was associated with non-compliance with the drug regimen or sleep deprivation. In seven out of 18 pregnancies (39%) improvement was related to correction of non-compliance or sleep deprivation during the pregestational nine months. Insufficiently low plasma concentrations of antiepileptic drugs were found in 47% of the women with uncontrolled epilepsy during pregnancy	
Schreiner	2003	Value of the early electroencephalogram after a first unprovoked seizure	Adults admitted to hospital after a certain first unprovoked seizure	To evaluate the predictive value of standard EEG and sleep deprived EEG for seizure recurrence	Prospective	157 adults	Seizure recurrence	The standard EEG was abnormal in 70.7% and significantly associated with an increased risk of seizure recurrence [risk ratio 4.5, 95% confidence interval (CI) 1.8; 11.3, p=0.001]. Subgroup analysis revealed the highest recurrence rates for patients with focal epileptiform activity (risk ratio 2.2, CI 1.2; 4.2, p=0.01). EEGs with sleep deprivation were abnormal in 48.3% of all cases and revealed epileptiform discharges in 13.3% of the patients who had no epileptiform activity in the standard EEG. Routine EEG revealed abnormalities in 60 of 94 patients who presented with normal neurologic status on admission.	

First Author	Year	Title	Description	Aim	Retro/Prospective	N	Variables	Results	Quality and Comments
Sheldon	2002	Historical criteria that distinguish syncope from seizures	Individuals with one or more losses of consciousness - Canada?	To identify historic features that most accurately correspond with the diagnosis	Prospective	671 individuals with loss of consciousness	N/A	The causes of loss of consciousness were known satisfactorily in 539 patients and included seizures (n = 102; complex partial epilepsy [50 patients] and primary generalized epilepsy [52 patients]) and syncope (n = 437; tilt-positive vasovagal syncope [267 patients], ventricular tachycardia [90 patients] and other diagnoses such as complete heart block and supraventricular tachycardias [80 patients]). The point score based on symptoms alone correctly classified 94% of patients, diagnosing seizures with 94% sensitivity and 94% specificity. Including symptom burden did not significantly improve accuracy, indicating that the symptoms surrounding the loss of consciousness accurately discriminate between seizures and syncope	
Sillanpaa	1975	The significance of motor handicap in the prognosis of childhood epilepsy	Cohort of children with epilepsy, admitted to hospital for treatment for epilepsy, and lived in a defined geographical area - Finland	To assess how the severity of epilepsy varies with different degrees of motor handicap	Prospective	244 children - 133 males and 11 females.	Prognosis of epilepsy. Results of medical treatment.	94 patients (28%) were classified as having some degree of motor handicap (clumsiness, cerebral palsy, severe secondary hypotonia). The risk of persistent seizures was 2 times, five times, and ten times that for patients with no motor handicap for people with clumsiness, CP, and severe secondary hypotonia respectively	
Smith	1999	The misdiagnosis of epilepsy and the management of refractory epilepsy in a specialist clinic	Retrospective analysis of case records of 324 patients referred to a single consultant during a 12 month period - UK	To assess the frequency, causes, and consequences of erroneous diagnosis of epilepsy. To evaluate the effectiveness of a specialist clinic in terms of the outcome of patients referred with 'refractory epilepsy'.	Retrospective	324 patients referred to a single consultant in a 12 month period.	N/A	The overall misdiagnosis rate was 46/184 (26.1%). Of the 46 misdiagnoses identified, the sources were as follows: GP 10, physician 24, neurologist 4, neurosurgeon 1, paediatrician 4, and psychiatrist 3.	Only rated as misdiagnosed by one reviewer

First Author	Year	Title	Description	Aim	Retro/Prospective	N	Variables	Results	Quality and Comments
Stroink	2003	The accuracy of the diagnosis of paroxysmal events in children	Children referred to hospital	To assess the accuracy of the initial diagnosis	Prospective	760 children referred to a neurology department	Final diagnosis	In 170 of 224 children seen after a single event, the incident was classified initially as epileptic, in 54 as unclear. In none of the 170 children did the diagnosis prove to be wrong. In four of the 54 children, recurrent episodes enabled a definite diagnosis of epilepsy. In 412 of the 536 children seen with multiple events, an initial diagnosis of epilepsy was made. After follow-up, this initial diagnosis was probably incorrect in 19. In contrast, seven of 124 children with multiple unclear episodes at intake later received the diagnosis epilepsy.	Large, prospective, multi-site study.
Tanganelli	1992	Epilepsy, pregnancy, and major birth anomalies: an Italian prospective, controlled study	Women with epilepsy attending an epilepsy centre - Italy	To compare pregnancies in women with epilepsy to a control group of women without epilepsy	Prospective	138 pregnancies in 97 women compared with 140 pregnancies in 88 women without epilepsy	Seizure rate. Complications.	No change in seizure frequency during pregnancy was seen in 79.7% of cases. Pregnancy complications and incidence of major congenital malformations were only slightly higher in women with epilepsy than in women without epilepsy. No single AED used as monotherapy correlated with increased risk of malformations, but polypharmacy with phenobarbital and phenytoin seemed to represent a risk factor	
Tomsom	1994	Epilepsy and pregnancy: A prospective study of seizure control in relation to free and total plasma concentrations of carbamazepine and phenytoin	Women with epilepsy referred to hospital department - Sweden	To report seizure control and the relation between seizure control and AED levels	Prospective	93 pregnancies in 70 women with epilepsy	Seizure rate. Blood levels of AEDs	Seizure frequency during pregnancy for the group as a whole was not different as compared with the 9 pregestational months and was unaltered or improved in 85% of cases. Total CBZ concentration was slightly lower during the third trimester as compared with baseline, whereas free concentration was unchanged. In contrast, PHT levels decreased steadily as pregnancy progressed. Total plasma concentration was 39% of baseline during the third trimester, whereas free PHT concentration decreased far less, being 82% of baseline level during the third trimester. No clear-cut relation could be demonstrated between seizure control and plasma concentrations,	

1.4 Diagnostic studies

First Author	Year	Title	Setting	Description	Retro/Prospective	N	Inclusions	Exclusions	Tests	Diagnosis	Blinding	Reference Standard	Results	Quality
Alving	1998	Serum prolactin levels are elevated also after pseudo-epileptic seizures	Unclear but "routine clinical setting" - Denmark	Observational study - data from blood tests and evaluation on admission	Prospective	58 - 12M 46F. Median age 28 years (range 13-68). 38 with epileptic seizures and 20 with pseudo-epileptic seizures.	No details given	33 excluded because of uncertain diagnosis, insufficient seizure description, uncertainty about time from previous seizure to index seizure, neuroepileptic drugs, pregnancy.	Serum prolactin (magnetic immuno-assay technique Serono Diagnostics)		Not stated	Clinical assessment with EEG component. Diagnostic evaluation done independently of serum prolactin result	Sensitivity for the maximal rise in pseudoseizures (5.5x) was only 20% and the negative predictive value 40%. For the cut-off in absolute level, (1025 µU/ml), the figures were 34% and 44% respectively.	Low - prospective, but blinding not stated, and small (selected?) sample
Anzola	1993	Predictivity of plasma prolactin levels in differentiating epilepsy from pseudoseizures: a prospective study	Neurological clinic - Italy	Observational study - data from blood tests and evaluation on admission	Prospective	59 - 35M 24F. 40 with seizures (mean age 43.6) and 19 with syncope (mean age 34.8).	Patients with a diagnosis of epileptic seizure or noncardiac syncope, and normal results on EKS, ECG, Holter monitoring, chest radiograph, tests for autonomic dysfunction.	Patients taking medication liable to affect prolactin levels	Plasma prolactin levels (radioimmunoassay)	Epileptic seizures - sudden generalised tonic-clonic, seizure of focal onset with subsequent generalisation	Not stated	Final diagnosis was discussed with colleagues blinded for the study	Levels were significantly increased in patients who had a seizure when P1 was sampled within 60 minutes of an attack, In patients who had a syncopal attack, plasma levels did not increase. For those assessed within 60 minutes of the attack, the positive predictive value of the cut-off (P1 exceeding by +3 s.d. of the mean of P2, P3,P4) was 89% and the negative predictive value was 61%.	Low - prospective, blinding not stated , and small sample
Atakli	1998	Misdiagnosis and treatment in juvenile myoclonic epilepsy	Outpatient clinic - Turkey	Observational study - record review?	Retrospective	76 - 27F, 49M	Diagnosis of JME (76 from 1300 patients) as assessed by the published diagnostic criteria of Panayiotopoulos 1989		CT, MRI	JME: published diagnostic criteria of Panayiotopoulos 1989	Not stated		All CT (n=33) and MRI (n=3) scans were normal	Low quality - biases may exist due to lack of blinding/retrospective design/patient choice. Cited 7 times & AHCPR review.
Benbadis	2000	Induction of psychogenic nonepileptic seizures without placebo	EEG-video monitoring unit - US	Observational study - case series of consecutive patients	Prospective	21 - 52% M. Mean age 36 years (range 19 to 66 years). Duration of PNES ranged from 5 months to 12 years (mean 3.5 years).	Suspected PNES		Induction		Not stated	Psychogenic nonepileptic seizures diagnosed as having no associated evidence of epilepsy	Of 19 inductions performed, 16 (16/19, 84%) were successful in inducing the habitual episode.	Low - prospective, but blinding not stated, no induction of patients with epilepsy, very small sample.

First Author	Year	Title	Setting	Description	Retro/Prospective	N	Inclusions	Exclusions	Tests	Diagnosis	Blinding	Reference Standard	Results	Quality
Berg	2000	Neuroimaging in children with newly diagnosed epilepsy: a community based study	Community based - US	Cohort study - record review and interviews with parents.	Prospective	613 children. Median age at onset=5.3 years. 50% M.	First diagnosis of epilepsy. First unprovoked seizure at age 1 month to 15 years.		MRI, CT	Epilepsy: at least 2 unprovoked seizures occurring one or more days apart	Not stated (but prospective study…)		488 (79.6%) had imaging: 388 (63.3%) magnetic resonance imaging, 197 (32.1%) computed tomography scans, and 97 (15.8%) both. Half of children with idiopathic generalized epilepsy had imaging studies compared with 70% to 100% of children with other forms of epilepsy, depending on the specific type. Etiologically relevant abnormalities were found in 62 (12.7% of those imaged). Fourteen of these children had otherwise completely normal presentations and histories. Their abnormalities included tuberous sclerosis (N = 4), tumours (N = 2), an arteriovenous malformation later diagnosed as a tumour, a cavernous angioma, cerebral malformations (N = 3), and other abnormalities (N = 3). Thirteen of the 14 had partial seizures and 12 had focal electroencephalographic (EEG) findings. Only 1 had neither.	Medium quality - large, prospective study. Cited 3 times.
Bhatia	1997	Usefulness of short-term video EEG recording with saline induction in pseudoseizures	Neurology outpatients - India	Observational study	Prospective	50 - 10M 40F. 24 with pseudoseizure, and 26 with uncertain diagnosis. Age range 7 to 51 years (mean 22.7 years).	Patients with suspected pseudoseizure		Video EEG, saline induction		Not stated	Clinical assessment	Fifteen patients (15/50, 30%) had a spontaneous event during VEEG. A further 15 patients (15/45, 33%) had an event only on placebo induction.	Low - prospective, but blinding not stated, small(ish) sample

First Author	Year	Title	Setting	Description	Retro/Prospective	N	Inclusions	Exclusions	Tests	Diagnosis	Blinding	Reference Standard	Results	Quality
Bunn	2002	How has imaging of the head, neck, and spine changed over 5 years in a district general hospital?	Secondary care - UK	Observational study - case note review	Retrospective	1992-1992 74 scans. 1996-1997 104 scans.	Results for all patients aged 18 years or under who had a CT/MRI scan of the head, neck, or spine requested by a paediatrician		CT, MRI	No definition of seizures	Not done	Definitive diagnosis	A definitive diagnosis was made with CT in 12% of children who presented with seizures, and in 27% with MRI.	Low quality (authors accept that there are limitations of retrospective studies but do little to compensate e.g. dual independent assessment) - Clinical benefit assessed by only one investigator. Diagnosis was not checked, but only assessed as definitive or not. No citations found.
Bye	1990	Commencement of a paediatric EEG-video telemetry service	Secondary care (child neurology) - Australia	Observational study	Prospective?	82 - 42M 40F. Age range 2 months to 16 years (median age 6 years).	Patients referred for telemetry. Reasons for referral were to determine whether the event was ictal or not (76%), localize the seizure onset (4 children), ascertain the frequency of seizures (2 children), classification (1 child), pseudoseizures in addition to epilepsy (2 children) and unresponsive to treatment (1 child).		Video EEG		Not stated		Events occurred during the recording in 80% (66/82) of subjects. Of these, 35% (23/66) were judged to be ictal and the seizure type identified.	Low - probably prospective design, no blinding stated, no reference standard for diagnosis (badly reported?)

First Author	Year	Title	Setting	Description	Retro/Prospective	N	Inclusions	Exclusions	Tests	Diagnosis	Blinding	Reference Standard	Results	Quality
Camfield	2000	How often does routine paediatric EEG have an important unexpected result?	Tertiary paediatric centre - Canada	Observational study - review of consecutive EEG requisitions	Retrospective	250 in 1993, 250 in 1996	Results for children undergoing EEG tests		EEG		Only first EEG was reviewed to avoid bias, and if investigators knew the child then the record was excluded. Predictor blind to EEG result.	Not relevant	Overall, EEG results were correctly predicted in 81%. Prediction for all non-epilepsy reasons was accurate in 91% (n=320). The highest rate of correct prediction was in the group with non-epileptic paroxysmal disorders. Children in this category were almost always ((96%, 157/158) predicted to have a normal EEG. In contrast, for children clinically suspected as having epilepsy the correct EEG findings were correctly predicted in 59% of cases (n=141) (comparison of prediction for paroxysmal vs epileptic disorders, p<0 0001 chi squared).	Medium - blinded, retrospective, large sample, prediction made by one investigator, any difference between prediction and results discussed by two investigators.
Carpay	1997	The diagnostic yield of a second EEG after partial sleep deprivation: a prospective study in children with newly diagnosed seizures	Secondary care (child neurology and clinical neurophysiology) - The Netherlands	Observational study - cohort of children	Prospective	560 but standard EEGs only available for 552. 48% M. Mean age 6.0 years (s.d. 4.1 years).	Children with newly diagnosed seizures aged 1 month to 16 years seen between Aug 1988 and Aug 1992.	Children with neonatal or acute symptomatic seizures, referred from another hospital, history of epilepsy, seen after only one seizures, interval between seizure and first clinic of over 3 months	Standard interictal EEG (STDEEG) , age-dependent sleep deprivation EEG (REPEEG)	Newly diagnosed seizures - idiopathic or remote symptomatic	All EEGs were assessed by experienced clinical neurophysiologists blind to clinical data	Clinical judgement of committee of child neurologists and predefined diagnostic criteria	Fifty six percent (309/552) of sample had a positive STD-EEG and 44% (243/552) had an EEG without epileptiform activity. In 177 (73% of all eligible children) of these negative cases SD-EEGs were recorded. SD-EEGs added 11% (61/552) more diagnoses to the 56% of children with epileptiform activity on the STD-EEG (67% in total).	Medium/High - prospective, blinding, large sample
Dam	1985	Late-onset epilepsy: etiologies, types of seizure, and value of clinical investigation, EEG, and computerised tomography scan	University clinic - Denmark	Cohort study - record review?	Retrospective? - not stated	221 - 114M, 107F. Median age of onset 49 years (range 25-75)	Onset of epilepsy at 25 years of age or older		EEG, CT	No definition of epilepsy	Not stated		Brain tumour, as diagnosed by the CT scan, was the cause of epilepsy in 16% (n=36). The cause (using history, neurological examination, and CT) could not be identified in 38% of patients (n=84).	Low quality - little detail of methods, but quite large. Cited 65 times & AHCPR review.

First Author	Year	Title	Setting	Description	Retro/Prospective	N	Inclusions	Exclusions	Tests	Diagnosis	Blinding	Reference Standard	Results	Quality
Dericioglu	1999	The value of provocation methods in patients suspected of having non-epileptic seizures	Secondary care (EEG laboratory) - Turkey	Observational study - case series using patient records and results of investigations	Retrospective	72 - 22M 50F.	Patients referred to EEG lab with a diagnosis of probable non-epileptic seizures		Induction using IV saline or verbal suggestion		Not stated	Clinical assessment and long-term video EEG monitoring	Non-epileptic seizures were observed in 52 (72.2%) patients. Thirteen of these patients still had risk factors for epilepsy. The authors could not decide whether all of their previous attacks were non-epileptic because 10-30% of the patients with NES also have epileptic seizures. For a more accurate diagnosis the authors decided that these 13 patients, together with the 20 patients who did not have seizures with induction, needed video-EEG monitoring. Thirty-nine patients who had NES and no risk factors for epilepsy were thought to have pure non-epileptic seizures.	Low quality - retrospective, blinding not stated, small sample
Fein	1997	Using age-appropriate prolactin levels to diagnose children with seizures in the emergency department	Children's hospital (emergency department) - US	Observational study - convenience sample with matched control group	Prospective	83 children - 35 with seizures and 48 controls. Age range 3 months to 15 years (2.1+-2.0 years for seizure group, 3.8+-5.0 years for control, p=0.07). Core body temperature 38.8+-15 degrees C, 38.0+-1.0 degrees C, p=0.09).	Patients under the age of 19 years presenting with a generalised tonic-clonic seizure as described by reliable care-takers or health care professionals. Control group had not experienced a seizure, but otherwise required a lumbar puncture.	Patients known to have endocrinologic disorders, suspected ingestion of nonprescribed medication, receiving benzodiazepines, barbiturates, or opiates prior to blood sample.	Serum prolactin levels (microparticle enzyme immunoassay kit - IMX System, Abbott Laboratories)		Laboratory technician blinded to subject group		The positive predictive value of age-adjusted dichotomous levels (elevated and normal) of serum prolactin was 68% (95% CI 47-85%) and the negative predictive value was 76% (95% CI 61-87%).	Medium/High - prospective, blinding of subject group, power calculation done, but small sample.
Goodin	1984	Does the interictal EEG have a role in the diagnosis of epilepsy?	EEG laboratory - US	Observational study - EEG report review	Retrospective	948 patients with various non-epileptic neurological and psychiatric disorders referred for EEG and 764 patients with epilepsy			EEG		Not stated	Clinical assessment	In patients with a diagnosis of non-epileptic neurological and psychiatric disorders only 4% (38/948) had epileptiform activity on the initial EEG. In patients with a clinical diagnosis of epilepsy 52% (397/764) had epileptiform activity on the initial EEG.	Low - retrospective, blinding not stated, no definitive inclusions/exclusions, but very large sample

First Author	Year	Title	Setting	Description	Retro/Prospective	N	Inclusions	Exclusions	Tests	Diagnosis	Blinding	Reference Standard	Results	Quality
Harvey	1997	Temporal lobe epilepsy in childhood: clinical, EEG, and neuroimaging findings and syndrome classification in a cohort with new-onset seizures	Community based - Australia	Observational study - record review followed by medical interview, neurologic examination, and investigation where indicated	Retrospective and prospective (?)	63 (out of 318 with suspected partial seizures) - 29 M 34 F. Ages 3 months to 16 years at enrolment (mean 7.5 years). Age at onset 2 months to 14 years (mean 6.3 years). For boys, mean age at onset was 5.0 years and for girls 7.4 years (p=0.02).	2 or more unprovoked partial seizures of temporal lobe origin with onset before age 15 years		EEG (interictal and ictal), MRI, CT		Not stated	Ictal video-EEG for diagnosis or exclusion of partial seizures of temporal lobe origin	MRI was performed in 58 of the 63 (92%) children and CT in 48 of the 63 (76%). 5 children did not undergo MRI because the CT was normal and their parents did not wish them to undergo MRI. MRI revealed structural abnormalities of the temporal lobe in 24 of the 63 children (38%).	Medium quality - reviewed by 3 investigators. Cited 26 times & AHCPR.

First Author	Year	Title	Setting	Description	Retro/Prospective	N	Inclusions	Exclusions	Tests	Diagnosis	Blinding	Reference Standard	Results	Quality
Hoefnagels	1991	Syncope or seizure? The diagnostic value of the EEG and hyperventilation test in transient loss of consciousness	Neurological department - The Netherlands	Observational study - patient interviews with follow-up	Prospective	119 - 63M 56 F.	Patients 15 years or over referred with one or more episodes of transient loss of consciousness.	Patients with loss of consciousness due to trauma, subarachnoid haemorrhage, patients with epilepsy	EEG and hyperventilation	Transient loss of consciousness - episode of less than one hour with inability to maintain posture and to recall events during the episode	Interpretation of EEG blinded	Assessment according to specific criteria	The authors were able to classify all patients on clinical grounds as having had either an epileptic seizure (38%) or syncope (62%). Their findings for the test characteristics of interictal EEG are presented in Paper 1. A) Results of interictal EEG Seizure (n=45) Syncope (n=73) Normal 15 55 Localised epileptiform activity 10 4 Generalised epileptiform activity 8 0 Localised slow activity 12 14 B) Diagnostic value of epileptiform activity for a seizure Sensitivity 0.40 (18/45)0.95 (69/73)7.3 (2.6 – 20.3)0.6 (0.5 – 0.8) Specificity Likelihood ratio for positive test (CI) Likelihood ratio for negative test (CI)	Medium/High - prospective, blinding, large sample
Holt-Seitz	1999	Seizures in the elderly: aetiology and prognosis	Community based - Canada	Observational study - record review and interviews with patients and carers, physicians, witnesses etc.	Retrospective	84 - 54% M.	Patients who had an EEG for first possible seizure. Aged 60 or over with new onset seizures.	EEG for reasons other than seizures. Onset of seizures before 60 years of age.	EEG, CT, MRI		Not stated		The initial EEG was abnormal in 61 patients (73%). CT was performed in all patients and were abnormal in 57 (68%). Only 11 patients underwent MRI scanning and abnormalities were detected in 7, three of whom had no abnormality detected in CT.	Low quality. Cited 2 times & AHCPR

First Author	Year	Title	Setting	Description	Retro/Prospective	N	Inclusions	Exclusions	Tests	Diagnosis	Blinding	Reference Standard	Results	Quality
Jallon	2001	Newly diagnosed unprovoked epileptic seizures: presentation at diagnosis in CAROLE study	Community based - France	Cohort study - structured questionnaire of patients presenting	Prospective	1,942 patients. Age range 1 month to 95 years	Patients older than 1 month with at least one unprovoked seizure first diagnosed between May 1 1995 and June 30 1996, likely to be followed up for a minimum of 2 years	Patients with a previous clear diagnosis of unprovoked epileptic seizures, acute symptomatic seizures, unlikely to comply with the follow-up.	EEG, CT, MRI				One or more imaging studies were performed in 1,418 patients (73.0%). In the first-seizure group (n=926), a neuroimaging study was performed in 78.2% of the patients (CT scan only 57.9%; MRI only 6.5%; CT scan + MRI 13.8%). This rate varied according to the epileptic syndrome: 55.0% for idiopathic localization-related, 63.5% for idiopathic generalized, 82.1% for isolated seizures, 86.0% for cryptogenic localization-related, and 88.6% for symptomatic localization-related. For patients with newly-diagnosed epilepsy (n=1,016), a neuroimaging study was performed in 68.3% of the patients (CT scan only 42.9%; MRI only 12.2%; CT scan + MRI 13.2%). This rate varied according to the epileptic syndrome: 40.3% for idiopathic generalized, 60.4% for idiopathic localization-related, 65.4% for symptomatic generalized, 74.4% for cryptogenic or symptomatic generalized, 78.0% for undetermined whether focal or generalized, 78.1% for cryptogenic localization-related, and 94.2% for symptomatic localization-related. These high rates of imaging permitted classification of seizures in 78.1% of the first-seizure group and 88.0% of the newly-diagnosed-epilepsy group; classification of syndromes in all the first seizures and 98.6% of those with newly diagnosed epilepsy; and classification of aetiology in all the first seizures and 98.8% of those with newly diagnosed epilepsy, with a reasonably high degree of certainty at the time of initial diagnosis.	Medium - prospective, large sample, classification done independently by four experts with consensus reached

First Author	Year	Title	Setting	Description	Retro/Prospective	N	Inclusions	Exclusions	Tests	Diagnosis	Blinding	Reference Standard	Results	Quality
Jallon	1997	Incidence of first epileptic seizures in the canton of Geneva, Switzerland	Community based - Switzerland	Cohort study - record review	Retrospective	273	Patients presenting with first (provoked or unprovoked) epileptic seizure who underwent an EEG	Incomplete/unsatisfactory/unclear chart data. Unclear diagnosis of epileptic seizure. Not living in Geneva.	EEG, CT, MRI		Not stated		All patients by definition had an EEG recording. 199 patients (67%) underwent CT scanning of which 61 (32%) were normal. 56 patients (19.7%) underwent MRI scanning, which was normal in 30.4%. MRI was normal in 16% of patients with normal CT scans.	Low quality - only one investigator reviewed records, but large cohort. Cited 18 times & AHCPR.
Jan	2002	Assessment of the utility of paediatric electroencephalography	Neurophysiology laboratory - Saudi Arabia	Observational study - record and EEG review	Prospective	439 consecutive paediatric EEGs. Age range 3 days - 17 years (mean 5 years, s.d. 4.2 years)			EEG		One EEGer reviewed both EEG and requisitions, but not concurrently		The first EEG was studied in 65% of cases. Overall, 55% of the EEGs were abnormal. Repeat EEGs were twice as likely to be abnormal (95% CI 1.3-3, P = 0.001). Established epilepsy, using antiepileptic drugs, and sleep record, highly correlated with an abnormal result (P < 0.0001). The EEGer predicted 26% of the EEGs to be normal. A normal EEG was correctly predicted in 98% of non-epileptic paroxysmal events, however, epileptiform activity on the EEG (see table below) was correctly predicted in only 26% of children with seizures. EEGs of 15 (3.4%) children with established epilepsy revealed unexpected findings that completely changed their management. The results have been extracted from the paper and tabulated in Paper 1 (only subgroups of seizure versus non-epileptic paroxysmal event included: 44%, 194/438 of all EEG requests).	Medium/High - prospective, pragmatic blinding, large sample

First Author	Year	Title	Setting	Description	Retro/Prospective	N	Inclusions	Exclusions	Tests	Diagnosis	Blinding	Reference Standard	Results	Quality
Kilpatrick	1991	Magnetic resonance imaging and late-onset epilepsy	Neurology department - Australia	Observational study - case series with age-sex matched group	Prospective	50 patients - 28M 32F (age range 26 to 79 years with a mean of 52 years) with 20 age-sex matches	Patients with late-onset epilepsy in whom the CT was normal, did not allow a definitive diagnosis to be made, showed a lesion believed to be irrelevant to the seizure disorder		CT, MRI	Late-onset epilepsy - seizures beginning after 25 years of age	Yes		Of the 32 patients with normal CT, MRI was normal in 20, showed irrelevant lesions in 8, and showed the cause of seizures in 4. In the 12 patients with non-diagnostic CT, MRI clarified the diagnosis in 5 patients and was normal in 2 patients. The incidence of MRI detected lesions was no greater than in the age-sex matched group of patients without seizures. MRI was diagnostic in 32% (10/31) of patients with partial seizures and/or focal EEG findings as compared with 0% (0/19) of patients without focal seizures.	Medium - prospective, blinding, but small sample

First Author	Year	Title	Setting	Description	Retro/Prospective	N	Inclusions	Exclusions	Tests	Diagnosis	Blinding	Reference Standard	Results	Quality
King	1998	Epileptology of the first-seizure presentation: a clinical, electroencephalographic, and magnetic resonance imaging study of 300 consecutive patients	Tertiary referral hospital - Australia	Cohort study - patient history and results of investigations	Prospective	300 - 170M 130F. Age range 5 to 83 years (mean 31.2 years, s.d. 18.7 years). 20% were under 16 years.	Patients who presented for the first time with an unprovoked seizure with no readily apparent cause. Patients were included with a history of seizure only if they had no previous diagnosis or treatment of epileptic seizures.	Patients with non-epileptic events, seizures provoked by metabolic derangements or poisonings, cerebral palsy, stroke, head injury, encephalitis, cancer, history of drug or alcohol addiction.	EEG, CT, MRI	Unprovoked seizure - included those that occurred in the setting of sleep deprivation, fever, photic stimulation	Not stated	Stepwise diagnosis	A generalised or partial (focal) epilepsy syndrome was clinically diagnosed in 141 (47%) patients with 159 (53%) of cases unclassified. Subsequent analysis showed that only three of these clinical diagnoses were incorrect. Addition of the EEG data enabled the authors to diagnose an epilepsy syndrome in the majority of cases (77%, 232/300); with only 68 (23%) remaining unclassified. Neuroimaging was done for 277 patients (92%); 263 MRI and 14CT alone. 49 of the 50 patients with generalized epilepsy had normal MRI scans. Among the 154 patients with partial epilepsy, MRI revealed 26 (17%) epileptogenic lesions. For the 61 unclassified patients, 9 lesions were revealed by MRI and 2 lesions by CT scan, giving a total of 11/61 (18%). CT was done in 28 of the 38 cases with lesions on MRI, but the lesion was only detected in 12 patients. After MRI, one diagnosis was revised from generalised to partial epilepsy. 11 unclassified patients with focal lesions were reclassified as having partial epilepsy. A final diagnosis of epilepsy was made in 243 (81%) of the initial group.	Medium - prospective, blinding not stated (but testing addition of test results), large sample. Selection bias may exist. Not randomised.

First Author	Year	Title	Setting	Description	Retro/Prospective	N	Inclusions	Exclusions	Tests	Diagnosis	Blinding	Reference Standard	Results	Quality
Lee	2002	Syndromic diagnosis at the Epilepsy Clinic: Role of MRI in lobar epilepsies	Epilepsy clinic - Korea	Observational study - 300 consecutive registered patients	Retrospective	300 - of which 249 were included. Mean age 25 +-11.4 years. Mean duration of epilepsy 9.8 +-8.4 years. 129 M. 38 patients newly diagnosed or previously untreated.		Patients who did not have epilepsy, had a single seizure, had epilepsy but did not undergo EEG or MRI	CBC, blood chemistry, urinalysis, EEG, MRI	Epilepsy - two or more spontaneous seizures	Not stated	Stepwise diagnosis	MRI revealed structural lesions in 106 (43%) of the 249 patients. Lesions were found in 47 (38%) of 125 patients with negative EEGs and in 59 (48%) of 124 patients with positive interictal epileptiform discharges. Both EEG and MRI were negative in 78 (31%) patients, and positive in 59 (24%) patients. The incidence of MRI lesions in different syndromes of the second step diagnosis were 47% in localization related epilepsy, 6% in generalised epilepsy, and 31% in undetermined epilepsy. Among the 199 patients with a second step diagnosis, MRI changed the diagnosis in 30 (12%) patients, however none of these patients had a second step diagnosis of generalised epilepsy. MRI also decreased the proportion of patients in non-specific categories from 37% to 29%.	Low - retrospective, blinding not stated, but reasonable sample
Linzer	1997	Diagnosing syncope. Part 1: Value of history, physical examination, and electrocardiography		Review of the literature on diagnostic testing in syncope										Semi-systematic - Medline only, no quality appraisal
Lusic	1999	Serum prolactin levels after seizure and syncopal attacks	Department of neurology - Croatia	Observational study - case series of attending patients	Prospective	33 - all female. Mean age 28.2+-5.8 years for CPS group and 32.4+-5.5 years for the VVS group.	Patients experiencing complex partial seizures, and those experiencing vaso-vagal syncopal attacks.	Patients with suspected or proven cardiac aetiology for syncope, or autonomic failure	Serum prolactin (Prolactin-IRMA)		Not stated	Established diagnosis of epilepsy, clinical assessment	Mean values of prolactin levels in both groups were increased immediately after the event (CPS: 1142±305 mIU/l, VVS: 874±208 mIU/l). Elevated levels immediately after the event were found in 78% of in the CPS group, and 60% of the VVS group.	Low - prospective, but blinding not stated, very small sample

First Author	Year	Title	Setting	Description	Retro/Prospective	N	Inclusions	Exclusions	Tests	Diagnosis	Blinding	Reference Standard	Results	Quality
McGonigal	2002	Outpatient video EEG recording in the diagnosis of non-epileptic seizures: a randomised controlled trial of simple suggestion techniques	Epilepsy service (tertiary care) - UK	Randomised controlled trial -	Prospective	33 - 8M 22F.	Clinical diagnosis of probable non-epileptic seizures, ability to give informed consent, aged over 16 years.	More than one attack type, suspected coexisting epilepsy, nocturnal attacks only	Suggestion techniques - hyperventilation and photic stimulation		Not stated	Video EEG	Ten out of 15 patients had habitual non-epileptic seizures with suggestion; 5/15 had non-epileptic seizures with no suggestion (p = 0.058; NS); 8/9 patients with a history of previous events in medical settings had non-epileptic seizures recorded during study. Logistic regression analysis with an interaction clause showed a significant effect of suggestion in patients with a history of previous events in medical settings (p = 0.003). An additional inpatient video-EEG was avoided in 14 of the 30 patients (47%).	Medium - RCT, underpowered (post-test calculation), small sample
Neufeld	1997	Sequential serum creatine kinase determination differentiates vaso-vagal syncope from generalized tonic-clonic seizures	Department of neurology - Israel	Observational study - details from family members, ER personnel, other observers	Prospective	33 - 17M 16F. Ages 31+-11 years in the GTCS group, and 32+-13 years in the VVS group. Weight was 62+-12 kg GTCS and 68+-9kg in VVS	Patients with first ever loss of consciousness	Aged over 70 years, overweight, trauma during the event.	serum creatine kinase		Not stated	Clinical assessment and EKG, EEG in VVS group	Using the criteria of CK levels > 200mU/ml (3.33µkat/l) (on either admission or 24-26 hours later) and/or the elevation from the first to the second measurement of >=15mU/ml (0.25µkat/l), there were only 12% false negatives and 12% false positives.	Low - prospective, but blinding not stated and small sample

First Author	Year	Title	Setting	Description	Retro/Prospective	N	Inclusions	Exclusions	Tests	Diagnosis	Blinding	Reference Standard	Results	Quality
Parra	1998	When should induction protocols be used in the diagnostic evaluation of patients with paroxysmal events?	Inpatient video-EEG unit - US	Observational study - consecutive patients admitted to unit	Prospective	100 - 75F 25M. Mean age 31+-16.2 years, range 2 to 72 years. Mean duration of video-EEG was 74+-54.1 hours (median 9 hours).	Patients admitted for a diagnostic monitoring study of paroxysmal spells of undetermined origin		Video EEG with/without induction		Not stated	Video-EEG	The time to the first diagnostic spontaneous event, identified by the patient or a family member as typical, was recorded. Episodes were classified as PNEE, physiologic non-epileptic events (PhysNEE), and epileptic seizures (ES). The mean duration of VEEG was 74+/-SD 54.1 hours. In 82 patients, a diagnostic event occurred spontaneously. The first event was an ES in 22 patients, a PNEE in 53, and a PhysNEE in 7. The time to first diagnostic event was significantly shorter for PNEE than for ES [15.0+/-SD 16.3 hours (range 5 min to 58 hours) vs. 28.6+/-SD 34.0 hours (range 1-110 hours) F=15.621, p < 0.0001]. In the first 24 h, 77.4% of the patients with PNEE had an event. By 48 hours, all but 2 (96.2%) had had diagnostic events. After the first 58 hours of monitoring, all patients with PNEE experienced a spontaneous diagnostic event.	Medium - prospective, blinding not stated but reasonable sample size
Ramirez-Lassepas	1984	Value of computed tomographic scan in the evaluation of adult patients after their first seizure	Neurology service - US	Observational study - record review of patients hospitalised for evaluation of a first acute seizure	Retrospective	148 - 94M aged 16 to 84 years, median 47 years and 54F aged 17 to 90, median 57 years.95 patients had a single seizure, 16 had two, 14 had 3, 3 had 4, and 20 were in SE.	Had a complete neurological exam by a qualified neurologist, complete metabolic workup, screening for toxic substances, EEG performed by a certified technologist.	Patients with a history of seizures or blackouts, alcohol/drug intoxication or withdrawal, known brain tumour, craniotomy or open skull fracture, and those admitted to another hospital service	EEG and CT	Acute seizure - singles seizure or series of seizures occurring within a 48 hour period	Not stated - but confirmed by two reviewers	Clinical assessment and test results	Aetiology was determined in 71 patients (48%), with a structural lesion identified by CT in 55 (37%) and 16 (11%) had metabolic seizures. CT findings agreed with the results of the neurological exam in 82% of cases. CT revealed structural lesions in 14 (15%) patients with non-focal findings and in 12 (22%) patients with generalised EEG abnormalities.	Low - retrospective, blinding not stated, but reasonable sample size

First Author	Year	Title	Setting	Description	Retro/Prospective	N	Inclusions	Exclusions	Tests	Diagnosis	Blinding	Reference Standard	Results	Quality
Roberts	1988	Clinically unsuspected cerebral infarction revealed by computed tomography scanning in late onset epilepsy	Outpatient neurology department - UK	Observational study - consecutive new outpatients referred to clinic	Prospective	132 (88M, 44F) compared with a 132 age-sex matched control group (88M, 44F).	New outpatients with a history of one or more epileptic seizures with age of onset 40 years or older	Patients were excluded if there were other neurological symptoms or there was doubt about the diagnosis	CT		Done	Clinical assessment and CT results	15 of the patients with epilepsy had infarcts on CT compared with 2 of the controls (p=0.003). However, there was no difference between the groups in the presence of relevant clinical features of systemic vascular and cardiac disease. The CT evidence of cerebral atrophy was the same in both groups.	Medium/High - prospective, blinded, age-sex matched control, reasonably large sample
Shah	2001	Peripheral WBC count and serum prolactin level in various seizure types and nonepileptic events	Epilepsy monitoring unit - US	Observational study - patients admitted to epilepsy monitoring unit	Prospective with data analysed retrospectively	340 events in 89 patients - seizure classification and baseline plus both post-event white blood count and prolactin levels were available for 174 events.		Where seizures lasted less than 10 seconds, or where there was a delay for over 120 minutes between the seizure and the blood sample. Brief generalised seizures were excluded to avoid inclusion of brief myoclonic seizures.	Serum prolactin and white blood count		Not stated	Clinical assessment and test results	Serum prolactin level increased above twice the level at baseline after a complex partial seizure or a generalized seizure. Peripheral WBC count was elevated above the upper limit of normal in 36% of cases after a generalized seizure. In generalized seizures, the length of a seizure is positively associated, whereas the lapse time between the seizure onset and blood draw is negatively correlated with the increase in WBC count	Medium - prospective, blinding not stated, but large sample of events

First Author	Year	Title	Setting	Description	Retro/Prospective	N	Inclusions	Exclusions	Tests	Diagnosis	Blinding	Reference Standard	Results	Quality
Sundaram	1990	Factors affecting interictal spike discharges in adults with epilepsy	EEG laboratory - Canada	Observational study - adults referred with definite or suspected seizures	Prospective	203 EEGs from 203 consecutive adults - 107M, 96F age range of 16 to 85 years.	Adults referred for EEG with definite or suspected seizures.	Adults with history suggesting non-specific blackouts, syncope, pseudoseizures or alcohol withdrawal seizures, undergoing telemetry for possible surgery, and those who had any form of surgery for epilepsy.	EEG		Not stated		94 EEGs (46%) showed ISDs. Yield was maximum (68%) when recordings were done within 2 days of a seizure; beyond this period, incidence of ISD did not change with time from the last seizure. EEGs of patients having greater than 12 seizures/year were more likely to contain ISD (68%) than the records of cases with less than 12 attacks/year (37-41%; P less than 0.001). Age and neurological status at the time of EEG, aetiology and anticonvulsants did not influence the frequency of ISD. Analysis of serial EEGs (n = 512) from the study group showed that if initial 3 EEGs lacked ISD, yield from further standard EEGs is small	Medium - large sample, but clinic based. Blinding not stated. Only one reviewer assessed the EEGs.
Tumani	1999	Kinetics of serum neuron-specific enolase and prolactin in patients after single epileptic seizures	Neurology department - Germany	Observational study - patients admitted for continuous EEG monitoring	Prospective	21 patients - 11 with CPS (6M) and 10 with Secondary GTCS (4M). 5 patients without epilepsy used to determine normal ranges	Epilepsy surgery candidates with intractable localisation-related epilepsy syndromes admitted for continuous video-EEG monitoring		Serum neuron-specific enolase		Not stated	Clinical assessment, EEG and additional invasive recordings, MRI and SPECT, neurophysiological testing	There was a significant decrease of NSE and prolactin levels over time (p<0.001). At one hour after the event, only 38%* of patients had increased NSE compared with abnormal prolactin levels in 81%	Low - prospective, but blinding not stated, small sample. Are the results generalisable for diagnosis of epilepsy?

1.5 Economic evaluations

Reference ID	Aim of the study	Study design	Location	Population description	Method	Cost components included	Time horizon & discount rate	Currency and cost year	Results - cost per patient	Results - effectiveness per patient	Results - incremental cost effectiveness	Comments on quality
Boon 2000	To assess cost effectiveness of VNS	Cost effectiveness analysis (using seizure frequency, AEDs dosage, side effects as measure of effectiveness).Before and after study.	Belgium	Patients with medically refractory epilepsy who are unsuitable for surgery.n=20	Effectiveness and resource use data correspond to patients treated between 1995 and 1999.Costing was conducted retrospectively on the same patient.	All hospital costs, cost of AEDs, cost of clinic visits, costs of laboratory tests.	Seizure frequency assessment two years before implantation.The mean follow-up time was 26 months.No discount rate given.	US dollars ($)	Cost results: The mean yearly epilepsy related direct medical costs dropped from an average of $6,682 in the period implantation to $3,635 after the VNS implantation.(t test used)	Mean seizure frequency decreased from 14 seizures per month in the before implantation period to 9 seizures per month after VNS (p=0.0003)Mean number and dosage of AEDs remained unchanged.(t test used)	Costs and benefits were not combined since comparator was do nothing option.	Small sample size.No unique measure of health benefit.No sensitivity analysis included.