APPENDIX S

Removed sections from original guideline

1.1 Pharmacological treatment

1.1.1 Introduction

The evidence base for the newer AEDs (gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, topiramate and vigabatrin) which were the subject of the Institute's Technology Appraisals has not been reviewed in detail, but the resulting recommendations have been incorporated into the guideline where appropriate (see Methods 2.7).

The next section considers, in turn, the questions of when should AED therapy be started and when it should it be discontinued. The issue of monitoring AED blood levels and the use of other blood tests is also considered.

1.1.2 Pharmacological treatment of epilepsy

Adults:

The newer AEDs gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, topiramate and vigabatrin, within their licensed indications, are recommended for the management of epilepsy in people who have not benefited from treatment with the older antiepileptic drugs such as carbamazepine or sodium valproate, or for whom the older antiepileptic drugs are unsuitable because:

- there are contraindications to the drugs
- they could interact with other drugs the person is taking (notably oral contraceptives)
- they are already known to be poorly tolerated by the individual
- the person is a woman of childbearing potential. [**A (NICE)**]

Children:

The newer AEDs gabapentin, lamotrigine, oxcarbazepine, tiagabine, topiramate, and vigabatrin (as an adjunctive therapy for partial seizures), within their licensed indications, are recommended for the management of epilepsy in children who have not benefited from treatment with the older antiepileptic drugs such as carbamazepine or sodium valproate, or for whom the older antiepileptic drugs are unsuitable because:

- there are contraindications to the drugs
- they could interact with other drugs the child is taking (notably oral contraceptives)
- they are already known to be poorly tolerated by the child
- the child is currently of childbearing potential or is likely to need treatment into her childbearing years. [**A (NICE)**]

Vigabatrin is recommended as a first-line therapy for the management of infantile spasms. [**A (NICE)**]

Evidence statements

Evidence from randomised trials comparing newer and older antiepileptic drugs as monotherapy did not suggest differences in their effectiveness in seizure control. There was also insufficient evidence to distinguish between the different newer antiepileptic drugs for seizure control. (Ia NICE)

Evidence was inadequate to support a conclusion that the newer drugs were generally associated with improved quality of life. (Ia NICE)

Clinical effectiveness of individual drugs varies by seizure type and by epilepsy syndrome. (Ia, Ib)

It was not possible to determine whether any one drug was more likely to bring about seizure freedom over the longer term than any other. (Ia NICE)

Different preparations may vary in bioavailability or have different pharmacokinetic profiles. (IV)

1.1.3 Pharmacological treatment in the management of the epilepsies by drug

Two technology appraisals have been published on the use of newer drugs in adults and children with epilepsy. The remit of the evidence reviews produced to inform the guidance was to assess the effectiveness of newer drugs compared with older drugs. The following evidence reviews were produced for the older drugs and other drugs not included in the technology appraisals.

Only high quality systematic reviews of RCTs and high quality RCTs were included in the evidence reviews for this section.

The drugs to be included were taken from the National Society for Epilepsy website (http://www.epilepsynse.org.uk/). Two other drugs were added (felbamate and sulthiame) on the advice of the GDG. It was agreed that remacemide and zonisamide should not be included.

- Acetazolamide (ACZ)
- Carbamazepine (CBZ)
- Clobazam (CLB)
- Clonazepam (CLN)
- Ethosuximide (ESM)
- Felbamate (adults only) (FBM)
- Gabapentin (GBA)
- Lamotrigine (LMG)
- Levetiracetam (LEV)
- Oxcarbazepine (OXC)
- Phenobarbitone (PHB)

- Phenytoin (PHY)
- Piracetam (adults only) (PRC)
- Primidone (PMD)
- Sodium valproate (VPA)
- Sulthiame (children only) (STM)
- Tiagabine (TBG)
- Topiramate (TPM)
- Vigabatrin (VGB)

1.1.3.1 Acetazolamide (ACZ)

No systematic reviews or RCTs were identified that reviewed the effectiveness of acetazolamide in the management of the epilepsies.

1.1.3.2 Carbamazepine (CBZ)

Secondary evidence

Three Cochrane reviews were identified.{Marson, 2003 5164 /id;Tudur Smith, 2002 952 /id;Tudur Smith, 2003 930 /id} Seven papers reporting possible RCTs (published since 1999) were assessed as potentially being relevant. However, on re-examining the abstracts, none of the 7 trials identified compared CBZ with PHB, PHY, or VPA as monotherapy in epilepsy.

Tudur Smith 2003{Tudur Smith, 2003 930 /id}

Tudur Smith and colleagues reviewed the effectiveness of CBZ compared to PHB monotherapy in people with partial onset seizures (simple/complex partial or secondarily generalised tonic-clonic seizures) or generalised tonic-clonic seizures (with or without other generalised seizure types). Randomised or quasi-randomised, blinded or unblinded controlled trials in children or adults were included.

Outcome measures were

a. time to withdrawal of allocated treatment,

b. time to 12 month remission, and

c. time to first seizure.

Individual patient data were available for 684 participants from four trials, representing 59% of the participants recruited into the nine trials that met the inclusion criteria. Of these four trials, two recruited adults only (aged 13 to 82 years), one recruited adults and children (aged 2 to 68 years) and one recruited children only (aged 3 to 16 years).

The main overall results (hazard ratio HR, 95% CI) adjusted for seizure type were,

a. time to withdrawal 1.63 (1.23 to 2.15),
(HR>1 indicates a clinical advantage for CBZ)

b. time to 12 month remission 0.87 (0.65 to 1.17),
(HR>1 indicates a clinical advantage for PHB)

c. time to first seizure 0.85 (0.68 to 1.05)
(HR>1 indicates a clinical advantage for CBZ)

The results showed that time to withdrawal was significantly improved with CBZ compared to PHB, suggesting that CBZ is significantly better tolerated than PHB. No overall difference between drugs was identified for the outcomes 'time to 12 month remission' and 'time to first seizure'. However, subgroup analyses for time to first seizure suggested an advantage with PHB for partial onset seizures (0.71, 0.55 to 0.91) and a clinical advantage with CBZ (1.50, 0.95 to 2.35) for generalized onset tonic-clonic seizures.

Tudur Smith 2002{Tudur Smith, 2002 952 /id}

This Cochrane study reviewed evidence comparing CBZ and PHY when used as monotherapy in people with partial onset (simple/complex partial or secondarily generalised tonic-clonic seizures) or generalised tonic-clonic seizures (with or without other generalised seizure types). Randomised controlled trials in children or adults with partial onset seizures or generalized onset tonic-clonic seizures were included.

Outcomes were

a. time to withdrawal of allocated treatment,

b. time to 12 month remission,

c. time six month remission, and

d. time to first seizure post randomisation.

Individual patient data were available for 551 participants from three trials, representing 63% of the participants recruited into the nine trials that met the inclusion criteria. Two of these trials recruited adults only (aged 13 to 82 years) and one recruited children only (aged 3 to 16 years).

Main results (HR 95% CI) were

a. time to withdrawal of allocated treatment 0.97 (0.74 to 1.28),
(HR>1 indicates a clinical advantage for CBZ)

b. time to 12 month remission 1.00 (0.78 to 1.29)
(HR>1 indicates a clinical advantage for PHY)

c. time to six month remission 1.10 (0.87 to 1.39)
(HR>1 indicates a clinical advantage for PHY)

d. time to first seizure 0.91 (0.74 to 1.12)
(HR>1 indicates a clinical advantage for CBZ)

The results suggested no overall difference between CBZ and PHY for these outcomes. However, the authors commented that confidence intervals were wide and the possibility of the existence of important differences had not been excluded.

Marson 2003{Marson, 2003 5164 /id} and Marson 2002{Marson, 2002 5163 /id}

The objective of this review was to assess the evidence comparing CBZ and VPA monotherapy in adults and children with partial onset seizures (simple/complex partial or secondarily generalised tonic-clonic seizures) or generalised onset tonic-clonic seizures. Randomised controlled trials comparing CBZ and VPA monotherapy for epilepsy were included.

Outcome measures were

a. time to withdrawal of allocated treatment,

b. time to 12 month remission, and

c. time to first seizure post randomisation.

Individual patient data were available for 1265 individuals from five trials, representing 85% of those recruited into the eight trials that met the inclusion criteria. Of these five trials, three recruited adults only (aged 13 to 83 years) and two children only (aged 3 to 16 years).

The main overall results (HR 95% CI) were

a. time to treatment withdrawal 0.97 (0.79 to 1.18)
   (HR>1 indicates a clinical advantage for CBZ),

b. 12 month remission 0.87 (0.74 to 1.02)
   (HR>1 indicates a clinical advantage for VPA),

c. first seizure 1.09 (0.96 to 1.25)
   (HR>1 indicates a clinical advantage for CBZ)

The results showed no overall difference for these outcomes. However, a test for interaction between treatment and epilepsy type was significant for time to first seizure, indicating an advantage for CBZ in the treatment of partial seizures (1.22, 1.04 to 1.44). There was some heterogeneity and age was shown to be significantly linked with treatment effect. The authors suggested that the age distribution of adults classified as having a generalized epilepsy (36% and 44% in two trials had generalised epilepsy with onset over the age of 30 years) indicated that significant numbers of individuals may have had their epilepsy misclassified.{Marson, 2003 5164 /id;Marson, 2002 5163 /id}

Another systematic review of AED (CBZ, PHY, VPA) efficacy and safety was identified.{Ramsay, 1997 322 /id} This was an older review, published in 1997, and there were significant methodological flaws in the analysis. Therefore, only the results of the Cochrane reviews described above have been included.

Primary evidence

No RCTs were identified since the Cochrane reviews above.

1.1.3.3 Clobazam (CLB)

Secondary evidence

No systematic reviews were identified on the effectiveness of clobazam in the management of the epilepsies.

Primary evidence

One RCT of clobazam as monotherapy in children was identified.

Canadian Study Group for Childhood Epilepsy 1998{Canadian Study Group for Childhood Epilepsy, 1998 4634 /id}

The Canadian Study Group for Childhood epilepsy compared the effectiveness of monotherapy clobazam (CLB) to carbamazepine (CBZ) and phenytoin (PHY) in children with epilepsy. Children aged 2-16 years with newly diagnosed epilepsy or previous failure of one drug (for poor efficacy or side effects) were assigned to one of two study arms and then randomised to CLB versus CBZ or CLB versus PHY. Eligible children had partial epilepsies or only generalized tonic-clonic seizures. The study was double blind. An intention to treat analysis assessed the primary endpoint, defined as the length of retention on the initial medication during the year after randomisation.

235 children were included: 159 randomised to CLB versus CBZ and 76 to CLB versus PHY. Altogether, in all study arms, 119 received CLB, 78 CBZ, and 38 PHY. Overall, 56% continued to receive the original medication for 1 year with no difference between CLB and standard therapy (CBZ and PHY). 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 PHY) Seizure control was equivalent for all three medications, as were side effects. PHY and CBZ induced more biologic side effects, such as rash, while CLB induced slightly more behavioural effects. Tolerance developed in 7.5% of children receiving CLB, 4.2% with CBZ and 6.7% with PHY.

In a more detailed analysis of the cognitive and behavioural effects of CLB,{Bawden, 1999 5113 /id} a subset of the children in the above trial underwent neuropsychological assessments at 6 weeks and 12 months after initiation. There were no statistically significant

differences between the CLB and standard monotherapy groups on any of the measures. There was no evidence of deterioration in children who took CLB for the full 12 month period.

Four trials of CLB as adjunctive therapy in both adults and children were identified.

Aucamp 1985{Aucamp, 1985 4683 /id}

Aucamp assessed the efficacy of CLB as add-on therapy in 12 institutionalised adults. All participants had uncontrolled seizures, defined as two or more seizures in the two weeks preceding the study period. The trial was a double blind, randomised cross-over design. Nine of the twelve participants became seizure free when taking CLB.

Keene 1990{Keene, 1990 545 /id}

Keene and colleagues reported the results of a double-blind cross-over study comparing clobazam and placebo in the treatment of refractory childhood epilepsy. Participants were aged between 2 years to 19 years and had more than 4 seizures a month.

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. Only 2/21 children had behavioural changes on the drug sufficiently severe to require the child to drop out of the study prematurely. Drug interactions between clobazam and the other anticonvulsant medicines did not occur.

Koeppen 1987{Koeppen, 1987 4645 /id}

Clobazam was compared with placebo as antiepileptic adjunct medication in 129 therapy-resistant epileptic individuals mainly having complex partial seizures. The study was performed in five European countries according to a double-blind crossover design lasting 7 months and included 129 participants.

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 individual in the placebo group. The most frequent adverse reactions to clobazam were drowsiness and dizziness.

Schmidt 1986{Schmidt, 1986 4666 /id}

The efficacy of CLB as adjunctive therapy was assessed in a double-blind trial in 20 adults with chronic complex partial seizures uncontrolled by maximally tolerable daily dosage of

standard antiepileptic drug therapy. 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%) adults had a seizure reduction by more than 75%, including four (20%) who had complete control. Tolerance to the antiepileptic effect of clobazam was noted in 56% of individuals, and mild transient sedation occurred in 40%.

1.1.3.4 Clonazepam (CLN)

Secondary evidence

No systematic reviews were identified that reviewed the effectiveness of clonazepam in the management of the epilepsies.

Primary evidence

One RCT was identified.

Mikkelsen 1981{Mikkelsen, 1981 4654 /id}

In a double-blind randomised trial of CBZ and CLN in adults and children (age range 6 to 72 years) with newly diagnosed, untreated psychomotor epilepsy, 19 participants were allocated to CBZ, and 17 to CLN.

Five participants were withdrawn from the CBZ group, and 7 from the CLN 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 ($p>0.20$).

For participants treated for at least one month, the median difference in the number of seizures between the two groups was not significant (95% CI – 0.3 to 0.4).

1.1.3.5 Ethosuximide (ESM)

No systematic reviews or RCTs were identified that reviewed the effectiveness of ethosuximide in the management of the epilepsies in adults.

One Cochrane review was identified for the use of ethosuximide in children with absence seizures{Posner, 2003 1430 /id} (Pharmacological treatment in the management of the epilepsies by syndrome).

No other RCTs of ESM in epilepsy were identified.

1.1.3.6 Felbamate (FBM)

Secondary evidence

No Cochrane reviews or protocols were identified that consider the effectiveness of felbamate in the treatment of the epilepsies. One other systematic review was identified.

French 1999{French, 1999 543 /id}

The Quality Standards subcommittee of the American Academy of Neurology and the American Epilepsy Society published a practice advisory on the use of FBM for the treatment of various types of epilepsy. This was based on a review of the literature (only Medline searched – no other details were given). Of the 54 articles assessed as relevant, only nine studies were Class I evidence (defined as well-designed, prospective, blinded, controlled studies), of which seven related to the efficacy of FBM.

The practice advisory summarised the evidence as follows:

- FBM was found to be effective for
  - Partial seizures in adults aged 18 to 65 as adjunctive and monotherapy
  - Lennox-Gastaut syndrome as adjunctive therapy (see Lennox Gastaut syndrome (LGS)).

Primary evidence

No RCTs were identified.

1.1.3.7 Gabapentin (GBA)

The effectiveness of gabapentin is addressed in the Technology Appraisals for adults and children.

1.1.3.8 Lamotrigine (LMG)

The effectiveness of lamotrigine is addressed in the Technology Appraisals for adults and children.

1.1.3.9 Levetiracetam (LEV)

The effectiveness of levetiracetam is addressed in the Technology Appraisals for adults.

1.1.3.10 Oxcarbazepine (OXC)

The effectiveness of oxcarbazepine is addressed in the Technology Appraisals for adults and children.

1.1.3.11 Phenobarbitone (PHB)

Secondary evidence

Two Cochrane reviews were identified.{Taylor, 2003 5188 /id;Tudur Smith, 2003 930 /id}

Tudur Smith 2003{Tudur Smith, 2003 930 /id}

Tudur Smith and colleagues reviewed the effectiveness of CBZ compared to PHB monotherapy in people with partial onset seizures (simple/complex partial or secondarily generalised tonic-clonic seizures) or generalised tonic-clonic seizures (with or without other generalised seizure types). Randomised or quasi-randomised, blinded or unblinded controlled trials in children or adults were included.

Outcome measures were

a. time to withdrawal of allocated treatment,

b. time to 12 month remission, and

c. time to first seizure.

Individual patient data were available for 684 participants from four trials, representing 59% of the participants recruited into the nine trials that met the inclusion criteria. Of these four trials, two recruited adults only (aged 13 to 82 years), one recruited adults and children (aged 2 to 68 years) and one recruited children only (aged 3 to 16 years).

The main overall results (HR 95% CI) adjusted for seizure type were,

a. time to withdrawal 1.63(1.23 to 2.15),
(HR>1 indicates a clinical advantage for CBZ)

b. time to 12 month remission 0.87(0.65 to 1.17),
(HR>1 indicates a clinical advantage for PHB)

c. time to first seizure 0.85(0.68 to 1.05)
(HR>1 indicates a clinical advantage for CBZ)

The results showed that time to withdrawal was significantly improved with CBZ compared to PHB, suggesting that CBZ is significantly better tolerated than PHB. No overall difference between drugs was identified for the outcomes 'time to 12 month remission' and 'time to first seizure'. However, subgroup analyses for time to first seizure suggested an advantage with PHB for partial onset seizures (0.71, 0.55 to 0.91) and a clinical advantage with CBZ (1.50, 0.95 to 2.35) for generalized onset tonic-clonic seizures.

Taylor 2003{Taylor, 2003 5188 /id}

In this Cochrane review, the effects of PHB compared to PHY when used as monotherapy in people with partial onset seizures (simple/complex partial or secondarily generalised tonic-clonic seizures) or generalised tonic-clonic seizures (with or without other generalised seizure types) were assessed. Randomised controlled trials in children or adults were included.

Outcomes were

a. time to withdrawal of allocated treatment,

b. time to 12 month remission, and

c. time to first seizure post randomisation.

Individual patient data were obtained for four of the ten studies meeting the inclusion criteria, amounting to 599 individuals, or approximately 65% of the potential data. Two trials were adults only (aged 14 to 81 years) and two children only (aged 2 to 18 years).

The main overall results were

a. time to treatment withdrawal 1.62 (95% CI 1.22 to 2.14),
(HR>1 indicates a clinical advantage for PHY)

b. time to 12 month remission 0.93 (95% CI 0.70 to 1.23) and
(HR>1 indicates a clinical advantage for PHB)

c. time to first seizure 0.84 (95% CI 0.68 to 1.05)
(HR>1 indicates a clinical advantage for PHY).

These results indicate a statistically significant clinical advantage for PHY in terms of treatment withdrawal and a non-significant advantage in terms of 12 month remission. Results for time to first seizure suggest a non-significant clinical advantage for PHB.

Primary evidence

No further RCTs were identified.

1.1.3.12 Phenytoin (PHY)

Secondary evidence

Three Cochrane reviews were identified.{Taylor, 2003 5188 /id;Tudur Smith, 2003 974 /id;Tudur Smith, 2002 952 /id}

Tudur Smith 2002{Tudur Smith, 2002 952 /id}

This Cochrane reviewed evidence comparing CBZ and PHY when used as monotherapy in people with partial onset (simple/complex partial or secondarily generalised tonic-clonic seizures) or generalised tonic-clonic seizures (with or without other generalised seizure types). Randomised controlled trials in children or adults with partial onset seizures or generalized onset tonic-clonic seizures were included.

Outcomes were

a. time to withdrawal of allocated treatment,
b. time to 12 month remission,
c. time six month remission, and
d. time to first seizure post randomisation.

Individual patient data were available for 551 participants from three trials, representing 63% of the participants recruited into the nine trials that met the inclusion criteria. Two of these trials recruited adults only (aged 13 to 82 years) and one recruited children only (aged 3 to 16 years).

Main results (HR 95% CI) were

a. time to withdrawal of allocated treatment 0.97 (0.74 to 1.28),
   (HR>1 indicates a clinical advantage for CBZ)
b. time to 12 month remission 1.00 (0.78 to 1.29)
   (HR>1 indicates a clinical advantage for PHY)
c. time to six month remission 1.10 (0.87 to 1.39)
   (HR>1 indicates a clinical advantage for PHY)
d. time to first seizure 0.91 (0.74 to 1.12)
   (HR>1 indicates a clinical advantage for CBZ)

The results suggested no overall difference between CBZ and PHY for these outcomes. However, the authors commented that confidence intervals were wide and the possibility of important differences existing had not been excluded.

Taylor 2003{Taylor, 2003 5188 /id}

In this Cochrane review, the effects of PHB compared to PHY when used as monotherapy in people with partial onset seizures (simple/complex partial or secondarily generalised tonic-clonic seizures) or generalised tonic-clonic seizures (with or without other generalised seizure types) were assessed. Randomised controlled trials in children or adults were included.

Outcomes were

a. time to withdrawal of allocated treatment,

b. time to 12 month remission, and

c. time to first seizure post randomisation.

Individual patient data were obtained for four of the ten studies meeting the inclusion criteria, amounting to 599 individuals, or approximately 65% of the potential data. Two trials were adults only (aged 14 to 81 years) and two children only (aged 2 to 18 years).

The main overall results were

a. time to treatment withdrawal 1.62 (95% CI 1.22 to 2.14),
(HR>1 indicates a clinical advantage for PHY)

b. time to 12 month remission 0.93 (95% CI 0.70 to 1.23) and
(HR>1 indicates a clinical advantage for PHB)

c. time to first seizure 0.84 (95% CI 0.68 to 1.05)
(HR>1 indicates a clinical advantage for PHY).

These results indicate a statistically significant clinical advantage for PHY in terms of treatment withdrawal and a non-significant advantage in terms of 12 month remission. Results for time to first seizure suggested a non-significant clinical advantage for PHB.

Tudur Smith 2003{Tudur Smith, 2003 974 /id}

Tudur Smith and colleagues reviewed evidence comparing PHY and VPA when used as monotherapy in people with partial onset seizures (simple/complex partial or secondarily generalised tonic-clonic seizures) or generalised tonic-clonic seizures (with or without other generalised seizure types). Randomised controlled trials in children or adults were included.

Outcomes were

a. time to withdrawal of allocated treatment,
b. time to 12 month remission,
c. time to six month remission and
d. time to first seizure post randomisation.

Data were available for 669 individuals from five trials, representing 60% of the participants recruited into the eleven trials that met our inclusion criteria. Of these five trials, one recruited adults only (aged 14 to 72 years), one recruited children only (aged 3 to 16 years), two recruited both (aged 3 to 64 years) and one recruited older subjects only (aged (61 to 95 years).

One important limitation was that in four of the five trials, for people classified as having generalized onset seizures, tonic-clonic seizures were the only seizure types recorded at follow-up. Hence results applied only to generalized tonic-clonic seizures.

The main overall results were as follows

a. time to withdrawal of allocated treatment 1.10 (0.79 to 1.54)
   (HR>1 indicates a clinical advantage for VPA)
b. time to 12 month remission 1.04 (0.78 to 1.38)
   (HR>1 indicates a clinical advantage for PHY)
c. time to six month remission 0.89 (0.71 to 1.11)
   (HR>1 indicates a clinical advantage for PHY)
d. time to first seizure 0.92 (0.74 to 1.14)
   (HR>1 indicates a clinical advantage for VPA).

The results suggest no overall difference between the drugs for these outcomes. No statistical interaction between treatment and seizure type (partial versus generalized) was found.

Another systematic review of AED (CBZ, PHY, VPA) efficacy and safety was identified.{Ramsay, 1997 322 /id} This was an older review, published in 1997, and there

were significant methodological flaws in the analysis. Therefore, only the results of the Cochrane reviews described above have been included.

Primary evidence

No further RCTs were identified.

1.1.3.13 Piracetam (PRC)

Secondary evidence

No systematic reviews were identified that reviewed the effectiveness of piracetam in the management of the epilepsies in adults.

Primary evidence

One RCT was identified.{Koskiniemi, 1998 4646 /id}

Koskiniemi 1998{Koskiniemi, 1998 4646 /id}

This RCT compared the efficacy, tolerability, and safety of three daily regimens of oral piracetam in adults with progressive myoclonus epilepsy (Unverricht-Lundborg disease).

Twenty adults (12 men, eight women), aged 17 to 43 years, with classical Unverricht-Lundborg disease were enrolled in a multicentre, randomised, double blind trial of crossover design in which the effects of daily doses of 9.6g, 16.8g, and 24g of piracetam, given in two divided doses, were compared with placebo. The crossover design was such that individuals received placebo and two of the three dosage regimens of piracetam, each for two weeks, for a total treatment period of six weeks and thus without wash out between each treatment phase. The primary outcome measure was a sum score representing the adjusted total of the ratings of six components of a myoclonus rating scale in which stimulus sensitivity, motor impairment, functional disability, handwriting, and global assessments by investigators and individuals were scored. Sequential clinical assessments were made by the same neurologist in the same environment at the same time of day.

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 the individual (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. More individuals showed clinically relevant improvement with the highest dosage and, in individuals, increasing the dose improved response. Piracetam was well tolerated and adverse effects were few, mild, and transient.

1.1.3.14 Primidone (PMD)

Secondary evidence

No systematic reviews were identified that reviewed the effectiveness of primidone in the management of the epilepsies.

Primary evidence

One RCT was identified.

Mattson 1985{Mattson, 1985 4651 /id} and Smith 1987{Smith, 1987 24 /id}

A 10-centre, double-blind trial to was conducted to compare the efficacy and toxicity of four antiepileptic drugs in the treatment of partial and secondarily generalized tonic-clonic seizures in 622 adults. Participants were randomly assigned to treatment with carbamazepine, phenobarbital, phenytoin, or primidone and were followed for two years or until the drug failed to control seizures or caused unacceptable side effects. Strict exclusion criteria limited confounding factors such as drug or alcohol abuse. 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 those given primidone. Phenytoin

caused more dysmorphic effects and hypersensitivity. Control of tonic-clonic seizures did not differ significantly with the various drugs. A behavioural toxicity battery was performed whenever possible prior to administration of any antiepileptic drug and at 1, 3, 6, and 12 months after initiation of monotherapy. Significant differences in performance on all subtests of the battery were found between individuals with epilepsy and a control group matched by age, sex, and education. When the differential effects of all four drugs on behavioural toxicity were compared, few statistically significant differences emerged. However, carbamazepine consistently produced fewer adverse effects on tests of attention/concentration and motor performance than did the other three antiepileptic drugs. Both carbamazepine and phenytoin were associated with significantly lower incidences of intolerable side effects than were primidone or phenobarbital.

Overall, carbamazepine and phenytoin were recommended drugs of first choice for single-drug therapy of adults with partial or generalized tonic-clonic seizures or with both.

1.1.3.15 Sodium valproate (VPA)

Secondary evidence

Three Cochrane reviews were identified.{Marson, 2003 5164 /id;Posner, 2003 1430 /id;Tudur Smith, 2003 974 /id}

Marson 2003{Marson, 2003 5164 /id} and Marson 2002{Marson, 2002 5163 /id}

The objective of this review was to assess the evidence comparing CBZ and VPA monotherapy in adults and children with partial onset seizures (simple/complex partial or secondarily generalised tonic-clonic seizures) or generalised onset tonic-clonic seizures. Randomised controlled trials comparing CBZ and VPA monotherapy for epilepsy were included.

Outcome measures were

a. time to withdrawal of allocated treatment,

b. time to 12 month remission, and

c. time to first seizure post randomisation.

Individual patient data were available for 1265 individuals from five trials, representing 85% of those recruited into the eight trials that met the inclusion criteria. Of these five trials, three recruited adults only (aged 13 to 83 years) and two children only (aged 3 to 16 years).

The main overall results (HR 95% CI) were

a. time to treatment withdrawal 0.97 (0.79 to 1.18)
   (HR>1 indicates a clinical advantage for CBZ),

b. 12 month remission 0.87 (0.74 to 1.02)
   (HR>1 indicates a clinical advantage for VPA),

c. first seizure 1.09 (0.96 to 1.25)
   (HR>1 indicates a clinical advantage for CBZ)

The results showed no overall difference for these outcomes. However, a test for interaction between treatment and epilepsy type was significant for time to first seizure, indicating an advantage for CBZ in the treatment of partial seizures (1.22, 1.04 to 1.44). There was some heterogeneity and age was shown to be significantly linked with treatment effect. The authors suggested that the age distribution of adults classified as having a generalized epilepsy (36% and 44% in two trials had generalised epilepsy with onset over the age of 30 years) indicated that significant numbers of individuals may have had their epilepsy misclassified.

Posner 2003{Posner, 2003 1430 /id}

This reviews the use of VPA in childhood absences (see Childhood absence epilepsy (CAE)).

Tudur Smith 2003{Tudur Smith, 2003 974 /id}

Tudur Smith and colleagues reviewed evidence comparing PHY and VPA when used as monotherapy in people with partial onset seizures (simple/complex partial or secondarily generalised tonic-clonic seizures) or generalised tonic-clonic seizures (with or without other generalised seizure types). Randomised controlled trials in children or adults were included.

Outcomes were

a. time to withdrawal of allocated treatment,

b. time to 12 month remission,

c. time to six month remission and

d. time to first seizure post randomisation.

Data were available for 669 individuals from five trials, representing 60% of the participants recruited into the eleven trials that met our inclusion criteria. Of these five trials, one recruited adults only (aged 14 to 72 years), one recruited children only (aged 3 to 16 years), two recruited both (aged 3 to 64 years) and one recruited older subjects only (aged (61 to 95 years).

One important limitation was that in four of the five trials, for people classified as having generalized onset seizures, tonic-clonic seizures were the only seizure types recorded at follow-up. Hence results applied only to generalized tonic-clonic seizures.

The main overall results were as follows

a. time to withdrawal of allocated treatment 1.10 (0.79 to 1.54)
(HR>1 indicates a clinical advantage for VPA)

b. time to 12 month remission 1.04 (0.78 to 1.38)
(HR>1 indicates a clinical advantage for PHY)

c. time to six month remission 0.89 (0.71 to 1.11)
(HR>1 indicates a clinical advantage for PHY)

d. time to first seizure 0.92 (0.74 to 1.14)
(HR>1 indicates a clinical advantage for VPA).

The results suggest no overall difference between the drugs for these outcomes. No statistical interaction between treatment and seizure type (partial versus generalized) was found.

Primary evidence

No RCT evidence was found.

1.1.3.16 Sulthiame (STM)

Secondary evidence

No systematic reviews were identified that reviewed the effectiveness of sulthiame in the management of the epilepsies in children.

Primary evidence

One RCT was identified that assessed sulthiame in the treatment of epilepsy.{Green, 1974 1435 /id} However, only 31% of the recruited participants completed the study. This is well below the accepted level of 80%. The age of the participants was not clear, so this was excluded.

1.1.3.17 Tiagabine (TBG)

The effectiveness of tiagabine is addressed in the Technology Appraisals for adults and children.

1.1.3.18 Topiramate (TPM)

The effectiveness of topiramate is addressed in the Technology Appraisals for adults and children.

1.1.3.19 Vigabatrin (VGB)

The effectiveness of vigabatrin is addressed in the Technology Appraisals for adults and children.

1.1.4 Pharmacological treatment in the management of the epilepsies by syndrome

Two technology appraisals have been published on the use of newer drugs in adults and children with epilepsy. The remit of the evidence reviews produced to inform the guidance was to assess the effectiveness of newer drugs compared with older drugs. The following evidence reviews were produced for effectiveness of drugs in specific epilepsy syndromes.

Only high quality systematic reviews of RCTs, and high quality RCTs were included in the evidence reviews for this section.

The literature was searched for evidence on the treatment of the following syndromes identified by the GDG as being relevant to this guideline:

- Benign epilepsy with occipital spikes (BCOS)
- Benign rolandic epilepsy/benign epilepsy with centrotemporal spikes (BECTS)
- Childhood absence epilepsy (CAE)
- Continuous spike wave of slow sleep (CSWS)
- Infantile spasms
- Juvenile myoclonic epilepsy (JME)
- Landau Kleffner syndrome (LKS)
- Lennox Gastaut syndrome (LGS)
- Myoclonic astatic epilepsy (MAE)
- Severe myoclonic epilepsy of infancy (SMEI)

It should be noted that this list is not exhaustive.

1.1.4.1 Benign epilepsy with occipital spikes (BCOS)

No systematic reviews or RCTs of the treatment for this syndrome were identified.

1.1.4.2 Benign rolandic epilepsy/benign epilepsy with centrotemporal spikes (BECTS)

Secondary evidence

No systematic reviews of the treatment for this syndrome were identified.

Primary evidence

Two RCTs were identified.{Bast, 2003 4626 /id;Rating, 2000 4663 /id}

Rating 2000{Rating, 2000 4663 /id}

Rating and colleagues aimed to evaluate the efficacy and tolerability of sulthiame (STM) as monotherapy in children with benign childhood epilepsy with centrotemporal spikes (BECTS).

Sixty-six BECTS children entered a 6-month double-blind trial and were randomised to receive either STM (5 mg/kg/day) or a placebo. All children had had two or more seizures during the 6 months preceding the trial and were aged 3-11 years.

The primary effectiveness variable was the rate of treatment failure events (TFEs) per group. TFEs consisted of a first seizure after a 7-day run-in period, intolerable adverse events (AEs), development of another epileptic syndrome, or termination of the trial by parents or the child.

Twenty-five of the 31 STM-treated children (81%) and 10 of the 35 placebo-treated children (29%) completed the trial without any TFEs ($p = 0.00002$). Most TFEs were seizures (n=4 for the STM group, n=21 for the placebo group). Parents requested termination of treatment for two placebo-treated children. Treatment was terminated in four children for administrative reasons. No child was withdrawn for AEs. While all children displayed at least one specific focus in either the awake or asleep EEG initially, 11 STM-treated individuals had a normal awake EEG and 10 had a normal asleep one after 6 months. The effects on EEG should be interpreted with caution as the trial was not designed primarily to investigate the effect of STM on EEG discharges (see Bast 2003).

The authors concluded that STM was remarkably effective in preventing seizures in children with BECTS. Children having 2 or more seizures during the past 6 months had a high risk of early recurrence of seizures.

Bast 2003{Bast, 2003 4626 /id}

Using data from the RCT described above, Bast and colleagues evaluated the effects of STM on the EEGs of children with BECTS.

One-hundred seventy-nine sleep EEGs were recorded at screening and after 4 weeks, 3 months, and 6 months. EEGs were analysed by a blinded reviewer using a standard protocol for each EEG. This standard protocol collected data on general changes, specific epileptiform, and nonspecific focal and generalized changes. A classification system was defined depending on rating of pathologic EEG changes. Because of the higher number of treatment-failure events (i.e., seizures) in the placebo group, there was an increasing imbalance between the two groups regarding the number of recorded sleep EEGs over time (STM, 104; placebo, 74). A Wilcoxon-Mann-Whitney U test was used to describe differences in the grade of pathology during individual follow-up between the two groups.

The sleep-EEG was found to be normalized in 21 children treated with STM (12/21 transient) and in five treated with placebo (4/5 transient). In the STM group, the EEG showed a marked improvement during intra-individual course when comparing the classification of follow-up EEGs at each time point with the screening EEG. Comparable improvements were not observed in the placebo group (exact two-tailed p value at 4 weeks, $p<0.0001$; at 3 months, $p=0.0010$; and at 6 months, $p<0.0001$).

STM had marked effects on the EEG in BECTS, which led to normalization in the majority of the children. Most of those whose EEGs were not normalized showed improvement in the grade of EEG pathology. Normalization persisted in >50% of children during the investigation. Spontaneous normalization in the placebo group reflected the wide spectrum of individual courses, which must be considered when analysing drug effects on EEG in BECTS.

1.1.4.3 Childhood absence epilepsy (CAE)

Secondary evidence

One Cochrane review was identified for the use of ESM, VPA or LMG in the treatment of absence seizures.{Posner, 2003 1430 /id}

Posner 2003{Posner, 2003 1430 /id}

The authors reviewed the evidence for the effects of ESM, VPA and LMG as treatments for children and adolescents with absence seizures, when compared with placebo or each other. Randomised parallel group monotherapy or add-on trials were included.

Outcome measures were

a. proportion of individuals seizure free at 1, 6 and 18 months post randomisation;
b. people with a 50% or greater reduction in seizure frequency;
c. normalisation of EEG and/or negative hyperventilation test and
d. adverse effects.

Four small trials were found,{Callaghan, 1982 3602 /id;Frank, 1999 4605 /id;Martinovic, 1983 4896 /id;Sato, 1982 4665 /id} which were of poor methodological quality. No trials were found comparing valproate or ethosuximide versus placebo.

One trial{Frank, 1999 4605 /id} (29 participants) compared LMG with placebo using a response conditional design. Individuals taking LMG were significantly more likely to be seizure free than participants taking placebo during this short trial. A responder enriched design was used where participants responding to lamotrigine during a pre-randomisation baseline phase were randomised to continue lamotrigine or have it withdrawn. This trial therefore compared the effect of continuing versus withdrawing LMG. The results were as follows, in the initial open label dose escalation phase 71% of the participants became seizure free on LMG using a 24-hour EEG/video telemetry recording; in the placebo controlled phase 64% of the participants on LMG remained seizure free versus 21% on the placebo ($p<0.03$).{Frank, 1999 4605 /id}

Three studies compared ESM with VPA,{Callaghan, 1982 3602 /id;Martinovic, 1983 4896 /id;Sato, 1982 4665 /id} but because of diverse study designs and populations studied, a meta-analysis was not undertaken.

For the chosen outcome 'seizure freedom', data at the time points specified (one, 6 and 18 months) were not available. Rather than not present any data for this outcome, results for individual studies were presented.

a. proportion of individuals seizure free at 1, 6 and 18 months post randomisation
   The relative risk (RR) estimates with 95% **c**onfidence **i**ntervals (CI) for seizure freedom (RR<1 favours ESM) were:

   (a) 0.70 (95% CI 0.32 to 1.51);
   (b) 0.88 (95% CI 0.53 to 1.46);
   (c) 1.93 (95% CI 0.87 to 4.25).

Hence none of these trials found a difference for this outcome. However, confidence intervals were all wide and the possibility of important differences was not excluded and equivalence could not be inferred.

b. people with a 80% or greater reduction in seizure frequency
   This outcome was only reported in one trial, and the RR was 0.70 (95% CI 0.19 to 2.59).

Again no difference was found, but the confidence interval was wide and equivalence could not be inferred.

c. people with a 50% or greater reduction in seizure frequency
   This was reported in two trials. In one trial all participants achieved this outcome. For the other trial the RR was 1.02 (95% CI 0.70 to 1.48).

Again no difference was found, but the confidence interval was wide and equivalence could not be inferred.

None of these studies found a difference between VPA and ESM with respect to seizure control, but confidence intervals were wide and the existence of important differences could not be excluded. The authors concluded that although individuals taking LMG were significantly more likely to be seizure free than participants taking placebo, overall there was insufficient evidence to inform clinical practice.{Posner, 2003 1430 /id}

Primary evidence

Only one RCT that was not already included in the Cochrane review on absences was identified.{Trudeau, 1996 4671 /id}

Trudeau 1996{Trudeau, 1996 4671 /id}

The efficacy and safety of GBA monotherapy in newly diagnosed absence epilepsy was evaluated in two identical RCTs. 33 children were randomised to either treatment (n=15, dose range from 9.7 to 19.1 mg/kg/day) or placebo (n=18). No statistically significant baseline differences were found between the two groups. Seizure frequency was determined by baseline 24 hour EEG, which was repeated at the end of the 2 week treatment phase.

In an intention-to-treat analysis, data on two children was 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. The authors suggested that the lack of effect may have been due to the study being underpowered (terminated early due to slow recruitment), the 2-week treatment period being too short, or subtherapeutic doses.

1.1.4.4 Continuous spike wave of slow sleep (CSWS)

No systematic reviews or RCTs of the treatment for this syndrome were identified.

1.1.4.5 Infantile spasms

Secondary evidence

One Cochrane review was identified.{Hancock, 2003 1431 /id}

Hancock 2003{Hancock, 2003 1431 /id}

Hancock and colleagues compared 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. All randomised controlled trials (RCTs) of the administration of drugs to people with infantile spasms were included.

Outcomes included

- cessation of spasms,

- time to cessation of spasms,
- participants with cessation of spasms remaining spasm free,
- reduction in spasms,
- resolution of hypsarrhythmia,
- subsequent epilepsy rates, and
- adverse effects.

Eleven RCTs were included, which in total recruited 514 participants and tested eight different drugs. Overall, methodology of the studies was poor. No study assessed long-term psychomotor development or onset of other seizure types.

One small study{Chiron, 1997 4616 /id} found VGB to be more efficacious than hydrocortisone in stopping infantile spasms in a group of people with tuberous sclerosis. This study compared VGB (150 mg/kg/day) and hydrocortisone (15 mg/kg/day) in 22 infants with infantile spasms due to tuberous sclerosis, and found in the initial phase, all participants (11 infants) treated with VGB to be spasm free as compared to five of 11 infants (45%) treated with hydrocortisone giving a Peto odds ratio of 13.8 (95% CI 2.21 to 86.35). On average the 11 responders to vigabatrin took 4 days (range 0.5 to 14 days, median 2 days) to achieve complete cessation of spasms, whilst the 5 responders to hydrocortisone took an average of 13 days (range 3 to 30 days, median 23.5 days) giving a weighted mean difference of -8.8 (95% CI -19.2 to 1.6). 10 of the 11 infants who responded to vigabatrin remained spasm free; this information was not given for the five responders to hydrocortisone. Other effects were not reported.{Chiron, 1997 4616 /id}

One underpowered study showed a trend for VGB to be more efficacious than placebo in stopping infantile spasms.{Appleton, 1999 4610 /id} Of the 40 participants, 7 of 20 (35%) participants treated with vigabatrin compared with 2 of 20 (10%) treated with placebo showed complete cessation of spasms, giving a Peto odds ratio of 4.1 (95% CI 0.9 to 17.5). Effects on time taken to achieve cessation of spasms was not reported as an outcome in this study. There was a greater than 70% reduction in spasms in 40% of the group treated with VGB compared with 15% in the group treated with placebo. However, it was not clear from the paper to what proportion of the two groups of individuals these figures applied, whether the figures applied to the whole group or just those individuals in whom complete cessation of

spasms was not achieved. Four of the seven participants who responded to vigabatrin relapsed and all the participants successfully treated with placebo relapsed. Overall only three participants treated with vigabatrin and no individual treated with placebo treatment remained spasm free within the four week study period giving a Peto odds ratio of 8.2 (95% CI 0.8 to 84). Effects on time taken to relapse were not reported as an outcome in this study. Five of the seven participants who were spasm free with vigabatrin showed resolution of hypsarrhythmia on EEG, compared with one of the two participants who had become spasm free on placebo, Peto odds ratio 2.4 (95% CI 0.1 to 54.6). Other effects were not reported.{Appleton, 1999 4610 /id}

Two small studies{Baram, 1996 1 /id;Hrachovy, 1983 49 /id} when combined showed ACTH to be more efficacious than low-dose prednisone (2 mg/kg).

Baram et al {Baram, 1996 1 /id} in their study compared ACTH with prednisone and found 7 (~ 50%) participants in both groups to have developed other seizure types over the period of follow up of 2 to 48 months. However, this comparison was confounded by the fact that some infants initially randomised to receive prednisone went on to receive ACTH within the follow up period. They did not report subsequent epilepsy rates at five years of age. Baram and colleagues{Baram, 1996 1 /id} showed ACTH to be superior to prednisone with cessation of spasms in 13 of 15 (87%) participants and 4 of 14 (29%) participants respectively. Hrachovy and colleagues{Hrachovy, 1983 49 /id} compared 12 participants treated with ACTH with 12 participants treated with prednisone. In the initial phase of the trial 5 of 12 (42%) participants treated with ACTH had complete cessation of spasms and resolution of hypsarrhythmia on their EEG compared with 4 of 12 (33%) treated with prednisone. Combining the two studies, ACTH stopped the spasms in 67.5% of participants compared with prednisone in 31% of participants giving a Peto odds ratio of 4.2 (95% CI 1.4 to 12.4). Baram 1996,{Baram, 1996 1 /id} found that, on average, the 13 responders to ACTH took 3.2 days (range 1 to 7 days, median 2 days) to achieve complete cessation of spasms, whilst the 4 responders to prednisone took an average of 4 days (range 2 to 7 days, median 3.5 days) giving a weighted mean difference of -0.8 (95% CI -3.3 to 1.7). In Baram 1996,{Baram, 1996 1 /id} 2 of the 13 participants who responded to ACTH relapsed and none of the 4 responders to prednisone relapsed. Hrachovy 1983{Hrachovy, 1983 49 /id} found three of the five participants who responded to ACTH relapsed and one of the four responders to prednisone also relapsed. Overall, Baram 1996{Baram, 1996 1 /id} found 11 participants who responded to ACTH remained spasm free and the four responders to prednisone also remained spasm free. In Hrachovy 1983,{Hrachovy, 1983 49 /id} two

participants successfully treated with ACTH remained spasm free and three successfully treated with prednisone remained spasm free within the study period. The combined Peto odds ratio for these two studies is 2.6 (95% CI 0.8 to 8.1~). Baram 1996{Baram, 1996 1 /id} showed ACTH to be superior to prednisone with resolution of hypsarrhythmia in 13 of 15 participants treated with ACTH compared to 4 of 14 of participants treated with prednisone giving a Peto odds ratio of 10.1 (95% CI 2.4 to 43.2). In Hrachovy 1983,{Hrachovy, 1983 49 /id} 5 of 12 participants treated with ACTH had resolution of hypsarrhythmia but this was not reported for the group treated with prednisone. Other effects were not reported.

One study also suggested that control of spasms occurred more frequently with high dose VGB as compared to low dose VGB.{Elterman, 2001 4638 /id} 8 of 75 participants treated with low dose vigabatrin became spasm free as compared with 24 of 67 participants treated with high dose vigabatrin, giving a Peto odds ratio of 0.24 (95% CI 0.11 to 0.52). Effects on time taken to achieve cessation of spasms within the initial two week study period were not reported as an outcome in this study. But in an open follow up period of the study, where other treatment could be given (but details not provided) the authors found that the number of responders increased from 8% at 2 weeks, to 42% at 4 weeks, 55% at 2 months and 65% at three months. 8 of 75 participants treated with low dose vigabatrin had no evidence of hypsarrhythmia compared with 24 of 67 participants treated with high dose vigabatrin, giving a Peto odds ratio of 0.24 (95% CI 0.11 to 0.52). Other effects were not reported.

It was not possible to compare reduction in the number of spasms between the different treatments because of differences in methods of analysis. Overall, only 18 individuals were reported to have been withdrawn from the trial treatments due to adverse effects and 4 deaths were reported.

The authors concluded that no single treatment was proven to be more efficacious in treating infantile spasms than any of the others (other than VGB in the treatment of infantile spasms in tuberous sclerosis in one underpowered study).{Hancock, 2003 1431 /id}

Primary evidence

No RCTs were identified since the above reviews.

1.1.4.6 Juvenile myoclonic epilepsy (JME)

No systematic reviews or RCTs of the treatment for this syndrome were identified.

1.1.4.7 Landau Kleffner syndrome (LKS)

No systematic reviews or RCTs of the treatment for this syndrome were identified.

1.1.4.8 Lennox Gastaut syndrome (LGS)

Secondary evidence

One Cochrane review was identified.{Hancock, 2003 1429 /id}

Hancock 2003{Hancock, 2003 1429 /id}

This review compared the effects of pharmaceutical therapies used to treat Lennox-Gastaut syndrome in terms of control of seizures and adverse effects. Many people who have this syndrome will already be receiving other antiepileptic medications at the time of their entry into a trial. However, for the purpose of this review only the effect of the single therapeutic agent being trialled (often as add-on therapy) was considered. All randomised controlled trials (RCTs) of the administration of drug therapy to individuals with Lennox-Gastaut syndrome were included.

Five RCTs were included, but the authors were unable to perform a meta-analysis, primarily because each trial studied a different therapy. However, even if two or more of the trials had considered the same therapy it would still have been difficult to combine the results. The studies had used different entry criteria and definitions (summarised under description studies) leading to heterogeneity between the groups. In addition the studies all used different outcome measures, for example one study only considered cessation or reduction of all seizure types whilst one considered a reduction in the number of absence, tonic and atonic seizures and another reported a reduction in drop attacks, tonic-clonic seizures and all seizure types. Even when studies did report the same outcomes the results were often presented in different ways, for example one study gave the reduction in all seizure types as the percentage

reduction in number of seizures for each participant, whilst another gave an overall reduction for all the participants combined.

The optimum treatment for Lennox-Gastaut syndrome remains uncertain and no study showed any one drug to be highly efficacious; LMG, TPM and FBM may be helpful as add-on therapy.

Primary evidence

No RCTs were identified as having been published since the Cochrane review.

1.1.4.9 Myoclonic astatic epilepsy (MAE)

No systematic reviews or RCTs of the treatment for this syndrome were identified.

1.1.4.10 Severe myoclonic epilepsy of infancy (SMEI)

Secondary evidence

No systematic reviews of the treatment for this syndrome were identified.

Primary evidence

One RCT was identified.{Chiron, 2000 4631 /id}

Chiron 2000{Chiron, 2000 4631 /id}

The efficacy of stiripentol as add-on therapy in severe myoclonic epilepsy in infancy was evaluated in a randomised placebo-controlled trial involving 41 children taking valproate and clobazam. After a one month baseline period, children were assigned to either the treatment group (n=21) or the placebo group (n=20). Children were assessed every month during the two month double blind period. Seizure frequency was based on a diary maintained by

parents and carers, and drug compliance based on the number of capsules returned. Responders were defined as having more than 50% reduction in the frequency of clonic (or tonic-clonic) seizures during the second month of the double blind period compared with baseline.

Table 1 Comparison of stiripentol and placebo groups Modified from Chiron 2000{Chiron, 2000 4631 /id} and reprinted with permission from Elsevier (The Lancet, 2000, 356, 1638-42)

	Stiripentol n=21)	**Placebo (n=20)**	**Difference between groups**
Responders (95% CI)	15 (71%) (52.1% to 90.7%)	1 (5%) (0% to 14.6%)	p<0.0001
Individuals who became seizure free (95% CI)	9 (43%) (21.9% to 65.9%)	0 (0.0% to 13.9%)	p=0.0013
Median (range) monthly seizures in double blind period	5 (0 to 27)	14 (2 to 23)	p=0.0063
Mean change from baseline of seizure frequency (95% CI)	-69% (-50% to -85%)	7% (25% to 11%)	p<0.0001

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%) children on stiripentol but none on placebo became free of clonic (or tonic-clonic) seizures. In each group, one person had status epilepticus. Absolute seizure frequency was significantly lower on stiripentol than placebo (p=0·0063) after a decrease of 69% on stiripentol but an increase of 7% on placebo (p<0·0001). 21 children on stiripentol had moderate side-effects (drowsiness, loss of appetite) compared with eight on placebo, but side-effects disappeared when the dose of co-medication was decreased in 12 of the 21 cases.{Chiron, 2000 4631 /id}

1.1.5 Side effects of antiepileptic drugs

The GDG agreed to use the information on side effects from both the National Society for Epilepsy website (http://www.epilepsynse.org.uk/) and the Summary of Product Characteristics for each drug. The tables are presented alongside the drug tables in Appendix B:

The tables are intended to make the prescriber aware of the side effects that are commonly caused by AEDs.

1.1.6 In adults and children with epilepsy, is the ketogenic diet effective in reducing seizure frequency?

The ketogenic diet should not be recommended for adults with epilepsy. **[C]**

The ketogenic diet may be considered as an adjunctive treatment in children with drug-resistant epilepsy. **[C]**

Evidence statement

There is no RCT evidence on the effectiveness of the ketogenic diet in people with epilepsy. Observational studies suggest a potential benefit effect in children with epilepsy. (III)

Details

Secondary Evidence

One Cochrane review was identified that addressed the use of the ketogenic diet in the management of the epilepsies.{Levy, 2003 4165 /id}

Levy 2003{Levy, 2003 4165 /id}

This review aimed to assess the evidence from RCTs regarding the effects of ketogenic diets for people with epilepsy.

However, no RCTs were found. The majority of reported studies of the effects of ketogenic diets were not randomised or controlled and were predominantly retrospective.

A Medline search for observational studies assessing the effects of ketogenic diets upon seizures was undertaken, and 20 studies were found. These studies indicated a potential beneficial effect, supporting the need for further study in randomised controlled trials.

Table 2 Observational studies of ketogenic diets with at least three months follow-up{Levy, 2003 4165 /id}
Modified from Levy, Issue 3, Cochrane Library 2003. Copyright Cochrane Library, reproduced with permission

Trial	Design	Type of diet an number of recruited	Number with 50% seizure free reduction;			Adverse affects; number
			3 months	6 months	12 months	
Barborka 1927	Retrospective	Classical 100	44;?	43;?	36;8	
Berman 1978	Retrospective	Classical 8 MCT, 18	6;2	6;?		
Caraballo 1998	Prospective	Classical 14	7;0	7;0	7;0	Gastrointestinal;2 Fluid/electrolyte;1 Infection;1
Cusmai 1999	Prospective	Classical 41	13;6	10;3	3;?	
Debakan 1966	Retrospective	Classical 11	4;5	4;5	4;5	
Freeman 1998	Prospective	Classical 150	85;4	72;5	64;11	Gastrointestinal;5 Renal calculi;4
Hassan 1999	Retrospective	Classical 49 MCT,3	20;6			Behavioural;2 Gastrointestinal;1 Fluid/electrolyte;1
Helmholtz 1927	Retrospective	Classical 127	38;56	33;53	23;42	Behavioural;2 Gastrointestinal;4
Hopkins 1970	Retrospective	Classical 34	10;7			Gastrointestinal;1 Fluid/electrolyte;1
Huttenlocher 1971	Retrospective	MCT, 12	6;3	3;2	2;2	Gastrointestinal;5
Kinsman 1992	Retrospective	Classical 58	763;717	?;?	?;?	Fluid/electrolyte;7
Maydell 2001	Retrospective	Classical 143	59;21	60;24	54;23	Behavioural;20 Gastrointestinal;75 Fluid/electrolyte;15
Moreno Villares 2001	Retrospective	Modifiec MCT, 12	9;1	6;2	3;1	
Nordli 2001	Retrospective	Classical 32	4;0	13;6		Gastrointestinal;3 Fluid/electrolyte;1
Panico 2000	Prospective	Classical 13	10;4	8;3	8;4	Gastrointestinal;4 Fluid/electrolyte;1 Anaemia;3
Schwartz 1989	Prospective	Classical MCT, modified MCT total 59	51;?			Behavioural;1 Gastrointestinal;15 Fluid/electrolyte;0
Sirven 1999	Prospective	Classical 11	6;0	6;?		Behavioural;2 Gastrointestinal;11 Menstrual issues;9
Trauner 1985	Retrospective	MCT,17	4;10	4;9	4;7	Gastrointestinal;3
Veggiotti 1999	Retrospective	Classical 10	4;0	4;0	1;0	Behavioural;4 Candida;2 Fluid/electrolyte;2
Wilkins 1937	Retrospective	Classical 34	12;5	13;10	13;12	

Classical = classical ketogenic diet
MCT = medium chain triglyceride.

Primary evidence

No RCTs were identified.

2 Management of acute or prolonged seizures and status epilepticus in adults and children

2.1 Introduction

Prolonged seizures requiring emergency treatment are defined as convulsive seizures lasting 5 or more minutes. Serial seizures are defined as 3 or more seizures in an hour.

Status epilepticus is defined as a condition in which 'epileptic activity persists for 30 minutes or more'.{Shorvon, 1994 5183 /id} Generalised tonic-clonic status is a medical emergency that is associated with significant morbidity and mortality if not treated promptly. Therefore rapid diagnosis and treatment is crucial.

2.2 Are rectal/buccal benzodiazepines effective in the treatment of acute convulsive seizures in the community?

An individual who has prolonged convulsive (lasting 5 minutes or more) or serial seizures (three or more seizures in an hour) in the community should receive urgent care and treatment. **[A]**

Treatment should be administered by trained clinical personnel or, if specified by an individually agreed protocol drawn up with the specialist, by family or carers with appropriate training. **[GPP]**

Rectal diazepam is safe and effective in first-line treatment of prolonged seizures and is recommended in the majority of cases. **[A]**

For many individuals and in many circumstances, buccal midazolam[1] is more acceptable than rectal diazepam and is easier to administer. It should be used according to an agreed protocol drawn up by the specialist and only used following training. **[GPP]**

Healthcare professionals should inform individuals, and their families and/or carers, that buccal midazolam is currently unlicensed. **[GPP]**

Care must be taken to secure the individual's airway and assess his or her respiratory and cardiac function. **[GPP]**

Depending on response and the individual's situation, emergency services should be contacted, particularly if:

- seizures develop into status epilepticus
- there is a high risk of recurrence
- this is the first episode
- there may be difficulties monitoring the individual's condition. **[GPP]**

Evidence statements

Rectal diazepam is effective in terminating prolonged and serial seizures in adults and children in the community. (Ib)

A comparison of buccal midazolam versus rectal diazepam shows similar effectiveness. (Ib)

[1] Buccal midazolam is currently unlicensed for the treatment of prolonged or repeated seizures.

A comparison of intranasal midazolam versus rectal diazepam in children shows midazolam to be more effective (Ib)

Details

The use of IV drugs by paramedics and other trained personnel has been excluded.

Secondary evidence (adults and children)

No systematic reviews of the use of rectal or buccal benzodiazepines in adults were identified.

No systematic reviews of the use of benzodiazepines for acute seizures in children were identified.

Primary evidence

Cereghino 1998{Cereghino, 1998 4776 /id}

Cereghino and colleagues evaluated the effectiveness and safety of a single-dose treatment for acute repetitive seizure (ARS) episodes (e.g., clusters) administered in a nonmedical setting by caregivers. A multicentre, randomised, parallel, double-blind study of a single administration of Diastat (diazepam rectal gel) for treating episodes of ARS was undertaken. ARS episodes and treatment criteria were defined for each individual at the start of the study. Caregivers were taught to determine ARS episode onset, administer a predetermined dose of study medication, monitor outcome, count respirations, and record seizures and adverse events.

158 people were enrolled, of whom 114 had a treated ARS episode (Diastat, n=56; placebo, n=58). Diastat treatment reduced median seizure frequency ($p = 0.029$). More Diastat treated individuals 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.

Dreifuss 1998{Dreifuss, 1998 4777 /id}

Dreifuss and colleagues conducted a randomised, double-blind, parallel-group, placebo-controlled study of home-based treatment for acute repetitive seizures. Individuals were randomly assigned to receive either rectal diazepam gel, at a dosage varying from 0.2 to 0.5 mg per kilogram of body weight on the basis of age, or placebo. Children received one dose at the onset of acute repetitive seizures and a second dose four hours later. Adults received three doses -- one dose at onset, and two more doses 4 and 12 hours after onset. Treatment was administered by a care giver, such as a parent, who had received special training. The number of seizures after the first dose was counted for 12 hours in children and for 24 hours in adults.

Of 125 participants (64 assigned to diazepam and 61 to placebo) with a history of acute repetitive seizures, 91 (47 children and 44 adults) were treated for an exacerbation of seizures during the study period. 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 those receiving diazepam ($p<0.001$). Thirty-five individuals reported at least one adverse effect of treatment; somnolence was the most frequent. Respiratory depression was not reported

Scott 1999{Scott, 1999 4778 /id}

Scott and colleagues aimed to find out whether there are differences in efficacy and adverse events between buccal administration of liquid midazolam and rectal administration of liquid diazepam in the acute treatment of seizures. At a residential school with on-site medical facilities, 42 young people with severe epilepsy were enrolled. Continuous seizures of more than 5 minutes duration were randomly treated with buccal midazolam or rectal diazepam. If the seizure did not stop within 10 minutes, additional medication chosen by the attending physician was administered. Oxygen saturation and blood pressure were monitored for 30 minutes after treatment. The main outcome measures were efficacy, time from arrival of the nurse to drug administration, time from drug administration to end of seizure, and incidence of adverse cardiorespiratory events.

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 minutes. 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. Buccal midazolam was universally acceptable to the nursing and care staff.{Scott, 1999 4778 /id}

Results for the adult participants in two of the RCTs{Cereghino, 1998 4776 /id;Dreifuss, 1998 4777 /id} presented above were re-analysed and published in 2002.{Cereghino, 2002 4779 /id}

Cereghino 2002{Cereghino, 2002 4779 /id}

Cereghino and colleagues evaluated the efficacy and tolerability of rectal diazepam gel in the treatment of acute repetitive seizures in adults.

The results of two multicentre, double-blind, placebo controlled trials (study 001 and study 003) were combined to give a sample size of 96 adults with a history of acute repetitive seizures, were randomised into two groups. Of these 96, 70 experienced acute repetitive seizures and received treatment (n=31) or placebo (n=39). There were no significant baseline differences between the two groups.

There was a significant reduction in seizure frequency in individuals who received rectal diazepam gel compared with the placebo group. The median number of seizures per hour in the rectal diazepam gel treated group was 0.00, vs 0.13 in the placebo group (p=0.002). In addition, significantly more rectal diazepam gel treated individuals remained seizure-free during the 12-- hour observation period (71% [22/31] vs 28% [11/39]). The rectal diazepam gel exerted a prompt therapeutic effect that persisted throughout the observation period. Time to next seizure was significantly longer in rectal diazepam gel treated than placebo-treated individuals (p<0.001). Global assessment as provided by the caregivers was in favour of rectal diazepam gel for both study 001 (p=0.17) and study 003 (p=0.02).

The proportion of people experiencing at least one adverse event was higher (32% [10/31]) in the rectal diazepam gel treated group than in the placebo-treated group (23% [9/39]). Somnolence and dizziness were the only central nervous system adverse events that occurred more frequently in those receiving rectal diazepam gel than in those receiving placebo.

The only serious adverse events occurred in two individuals in the rectal diazepam gel group who inadvertently received more than 180% of the intended doses. These resolved without incident. There were no reports of severe respiratory depression necessitating emergency medical care in either treatment group.{Cereghino, 2002 4779 /id}

Fisgin 2002{Fisgin, 2002 4780 /id}

One RCT was identified that compared the efficacy and side effects of rectal diazepam and intranasal midazolam in the treatment of acute convulsions in children.

In the diazepam group, the seizures of 13 (60%) individuals terminated in 10 minutes; however, 9 (40%) did not respond. In the midazolam group, 20 (87%) individuals responded in 10 minutes, but 3 (13%) 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 ($p<0.05$). No serious complications were observed. However, the treatment was administered by physicians in the emergency room, rather than by caregivers in the community.

2.3 How should status epilepticus be managed in adults and children in the hospital setting?

In hospital, individuals with generalised tonic–clonic status epilepticus should be managed immediately, as follows (with local protocols being in place – see suggested guideline in Appendix C):

- secure airway
- give oxygen
- assess cardiac and respiratory function
- secure intravenous (IV) access in a large vein. **[GPP]**

Lorazepam should be used as a first-line treatment in status epilepticus (see Appendix C). **[D]**

Non-convulsive status is uncommon and management is less urgent. A suggested guideline can be found in Appendix C. **[GPP]**

Evidence statements

Intravenous lorazepam and diazepam are both effective in controlling tonic-clonic status epilepticus. (Ib adults Ia children)

Lorazepam may be more effective than diazepam but the difference does not reach statistical significance. (Ib)

2.3.1 How should convulsive status epilepticus be managed in adults and children in the hospital setting?

Details

There were several primary papers exploring the usefulness of neuron specific enolase as a marker of brain damage, but this was felt to be out of the scope of the guideline.

Secondary evidence

No systematic reviews on the management of status epilepticus in adults were identified.

Appleton 2003{Appleton, 2003 1960 /id}

A recent Cochrane review on drug management for acute tonic-clonic convulsions, including convulsive status epilepticus, reviewed the evidence comparing diazepam, lorazepam, phenobarbitone, phenytoin, and paraldehyde in children. The definition of status epilepticus used was 'a generalized tonic-clonic convulsion lasting 30 minutes or more, or repeated tonic-clonic convulsions occurring over a 30 minute period without recovery of consciousness between each convulsion'. Main outcome measures included cessation of convulsion or episode of status epilepticus, number of additional drugs needed to stop the convulsion, rates of respiratory depression, and hospital admissions due respiratory depression. Only one trial was identified that compared lorazepam and diazepam given either intravenously or rectally, depending on venous access.

The authors concluded that there was no evidence to suggest that intravenous lorazepam should be preferred to diazepam as the first-line drug in treating acute tonic-clonic convulsions including convulsive status epilepticus in children. There was some evidence that rectal lorazepam may be more effective and safer than rectal diazepam, but the data were

insufficient to indicate that lorazepam should replace diazepam as the first choice rectal drug in treating acute tonic-clonic convulsions and convulsive status epilepticus.

Primary evidence

Alldredge 2001{Alldredge, 2001 4792 /id}

Alldredge and colleagues undertook a randomised, double-blind trial to evaluate intravenous benzodiazepines administered by paramedics for the treatment of out-of-hospital status epilepticus. Adults with prolonged (lasting five minutes or more) or repetitive generalized convulsive seizures received intravenous diazepam (5mg), lorazepam (2mg), or placebo. An identical second injection was given if needed.

Of the 205 participants enrolled, 66 received lorazepam, 68 received diazepam, and 71 received placebo. Status epilepticus had been terminated on arrival at the emergency department in more individuals treated with lorazepam (59.1%) or diazepam (42.6%) than those 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).

Leppick 1983{Leppik, 1983 4782 /id}

Leppick and colleagues compared lorazepam with diazepam for the treatment of status epilepticus in a double-blind, randomised trial. Seventy-eight individuals with 81 episodes were enrolled. Participants received one or two doses of either 4 mg of lorazepam or 10 mg of diazepam intravenously.

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 group and in 12% of the diazepam-treated group (assumed to be non-

significant). Respiratory depression and arrest, the most frequent adverse effects, were treated symptomatically; no adverse sequelae were noted.

Treiman 1998{Treiman, 1998 4783 /id}

Treiman and colleagues conducted a five-year randomised, double-blind, multi-centre trial of four intravenous regimens: diazepam followed by phenytoin, lorazepam, phenobarbital, and phenytoin. Individuals were classified as having either overt generalized status epilepticus (defined as easily visible generalized convulsions) or subtle status epilepticus (indicated by coma and ictal discharges on the electroencephalogram, with or without subtle convulsive movements such as rhythmic muscle twitches or tonic eye deviation). Treatment was considered successful when all motor and electroencephalographic seizure activity ceased within 20 minutes after the beginning of the drug infusion and there was no return of seizure activity during the next 40 minutes.

In an intention-to-treat analysis, the differences among treatment groups were not significant, either among those 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.

No RCTs for the management of status epilepticus in children were identified post Cochrane review.

2.3.2 How should non-convulsive status epilepticus be managed in adults and children in the hospital setting?

No systematic reviews or RCTs were identified.

2.4 How should refractory status epilepticus be managed in adults and children in the hospital setting?

Treatment of refractory status epilepticus in secondary care should follow the suggested guidelines (see Appendix C). **[D]**

In adults, propofol or thiopental should be used to control refractory status epilepticus. Adequate monitoring, including blood levels of thiopental, and critical life systems support is required (see Appendix C). **[C]**

In children, midazolam or thiopental should be used to control refractory status epilepticus. Adequate monitoring, including blood levels of thiopental, and critical life systems support is required (see Appendix C). **[C]**

Regular medication should be continued at optimal doses and the reasons for status epilepticus should be investigated. **[GPP]**

As the treatment pathway progresses, the expertise of an anaesthetist/intensivist should be sought. **[GPP]**

If either the whole protocol or intensive care is required the tertiary centre should be consulted. **[GPP]**

An individual treatment pathway should be formulated for people who have recurrent convulsive status epilepticus. **[GPP]**

It should be noted that pentobarbital is not available in the UK for use in humans and so cannot be recommended as a treatment option in status.

Evidence statements

Midazolam and propofol and pentobarbital are all effective in controlling refractory status epilepticus in adults. (III)

Midazolam, diazepam, isoflurane, thiopental and pentobarbital are all effective in controlling refractory status epilepticus in children. (III)

A comparison of midazolam versus diazepam showed similar effectiveness in controlling refractory status epilepticus in children. (Ib)

Differences in costs for 24 hours treatment of benzodiazepines compared to barbiturates are small compared to savings produced by shorter treatment length and quicker return to consciousness. (III)

2.4.1 How should refractory convulsive status epilepticus be managed in adults and children in the hospital setting?

Details

Secondary evidence

No systematic reviews of RCTs were identified.

Primary evidence

Only one RCT on the management of refractory status epilepticus was found. The study population was children aged 2 to 12 years. No RCTs could be found for adults.

Singhi 2002{Singhi, 2002 4784 /id}

One RCT was identified that compared the efficacy of continuous midazolam and diazepam infusion in the control of refractory status epilepticus in children aged 2 to 12 years. Refractory status epilepticus was defined as motor seizures uncontrolled after two doses of diazepam 0.3mg/kg and phenytoin infusion 20mg/kg. Children were randomised to either continuous midazolam (n=21) or diazepam infusion (n=19) in incremental doses.

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 ($0.05>p<0.1$).

No RCT evidence on thiopentone and phenobarbitone was identified.

Other evidence

Claassen 2002{Claassen, 2002 4785 /id}

Claassen and colleagues compared the efficacy of midazolam, propofol, and pentobarbital in terminating seizures and improving outcomes in adults with refractory status epilepticus. Inclusion criteria were peer-reviewed studies of adults with status epilepticus refractory to at least two conventional AEDs. Main outcome measures were the frequency of immediate treatment failure, mortality, and titration goal (seizure suppression vs EEG background suppression). 28 studies were included, but there was no documentation of quality assessment. However, the authors did note limitations of review due to the small numbers of reported cases, publication bias, and the retrospective nature of the included studies. Other limitations noted were the lack of continuous EEG monitoring in many cases, and the changes in intensive care management over the time period of the review (1980 – 2001).

Summary statistics were calculated, but no details of the meta-analysis were given. However, included case series and reports did show that midazolam, propofol and pentobarbital were effective in controlling seizures.

Brown 1998{Brown, 1998 4786 /id}

Brown and Levin reviewed the evidence relating to the mechanism of action, clinical efficacy, adverse effects, and therapeutic considerations of using propofol in the management of individuals with refractory status epilepticus. Most of the evidence described the use of propofol after other treatments failed or were not tolerated. The initiation of propofol usually resulted in termination of seizure activity and/or EEG burst suppression within seconds that was sustained during drug use. Propofol was also well tolerated. The review concluded that although promising results had been seen, controlled clinical trials were necessary to assess the comparative efficacy, adverse effects, and clinical outcomes of propofol in refractory status epilepticus.

The majority of the included papers discussed the use in adults only, but there were two papers that described the use of propofol in children. One case report of a 9 month old child described how seizure activity was reduced within 30 seconds of administration and EEG burst suppression was documented during administration. Another paper described the use of propofol in 5 children aged 19 months to 19 years. Seizure activity resolved in all the

children, and treatment was withdrawn within 20 minutes to 48 hours (from both reports) without a return of seizure activity.

Niermeijer 2003{Niermeijer, 2003 4787 /id}

The evidence on the efficacy and safety of propofol in the treatment of refractory status epilepticus was reviewed. 22 articles were included, of which only two were non-randomised studies comparing treatments, and the rest were case series or reports.

The results of the two studies comparing the effectiveness of propofol with midazolam and high dose barbiturates in adults are shown below:

- Seizure control was achieved in 5 of the 8 (63%) treatments with propofol compared with 9 of 11 (82%) treatments with high dose barbiturates (p=0.60). Only one of the adults treated with propofol survived compared with 4 of the 8 treated with high dose barbiturates (p=0.28).{Stecker, 1998 4788 /id}

- Seizure control was achieved in 9 of the 14 (64%) adults treated with propofol compared with 4 of the 6 (67%) treated with midazolam (p≥0.61). There was no significant difference in mortality rates. However, for individuals with APACHE II scores of 20 or more, propofol was associated with higher mortality than midazolam (p=0.05).{Prasad, 2001 4791 /id}

Gilbert 1999{Gilbert, 1999 4789 /id} and Gilbert 1999{Gilbert, 1999 4790 /id}

Gilbert and colleagues published two systematic reviews of the efficacy and mortality, and the complications and costs of the treatment of refractory generalised status epilepticus in children. Refractory status epilepticus was defined as continued status epilepticus despite receiving at least two anticonvulsants in appropriate doses. The study population was children aged 1 month to 18 years. Included study designs were case reports, and retrospective or prospective studies. 111 children from 12 studies published between 1983 and 1998 met the inclusion criteria.

Although summary statistics were presented, no details of the meta-analysis were reported. However, included studies did show that diazepam, midazolam, thiopental, pentobarbital and isoflurane were effective in controlling seizures.

Health economics

Gilbert 1999{Gilbert, 1999 4790 /id}

The study presented a review of the medical literature on complications and costs of treatment of refractory generalized convulsive status epilepticus in children.

The authors argued that complications and costs as presented in their study appeared to favour continuous infusion of a short-acting benzodiazepine such as midazolam a reasonable first choice. However, there is need for proper randomised trials because the authors believed that the published data included in the review contained non-treatment-related biases that precluded statistical comparisons or evidence based recommendations.

Of the bolus doses described in the literature, midazolam was the most expensive ($9.34), followed by diazepam ($2.80), pentobarbital ($2.35) and thiopental ($1.84). For continuous dosing, costs are presented per 24-hour period. Midazolam was the most expensive ($239), followed by diazepam ($228.69), thiopental ($88.48) and pentobarbital ($11.28).

They found that the differences in costs for 24 hours treatment of benzodiazepines compared to barbiturates were small compared to savings produced by shorter length of treatment and return to consciousness.

2.4.2 How should refractory non-convulsive status epilepticus be managed in adults and children in the hospital setting?

No systematic reviews or RCTs were identified.

2.5 Teratogenic effects of AEDs whilst pregnant or breastfeeding

The evidence relating to the teratogenic effects of AEDs was not reviewed in detail as this area was not a KCQ of the GDG and was addressed by the technology appraisals on the newer AEDs. It should be noted that this is an area where many important questions remain unanswered and further research is needed, notably by using prospective pregnancy registers.

A recent Epilepsy Research Foundation Workshop reviewed the evidence base in relation to AEDs and pregnancy and their findings, together with those of other studies, are summarised here.{Barrett, 2003 2904 /id}

Pregnancy in women with epilepsy is known to be associated with a higher risk of congenital malformations.{Holmes, 2001 5001 /id;Kaneko, 1999 5009 /id;Samren, 1997 3123 /id} However, congenital abnormalities are associated with the use of AEDs rather than the epilepsy itself.{Holmes, 2001 5001 /id;Kaaja, 2003 4980 /id}

The most common major fetal malformations associated with AEDs are: neural tube defects, orofacial defects, congenital heart abnormalities and hypospadias. Minor fetal malformations reported include: hypertelorism, epicanthic folds and digital hypoplasia. 'Fetal anticonvulsant syndromes', comprising typical dysmorphic craniofacial features and a range of musculoskeletal abnormalities have also been described in association with AED treatment in pregnancy.{Clayton-Smith, 1995 3119 /id;Moore, 2000 3122 /id}

Several factors have been identified to account for this increased risk, including the direct teratogenic effects of AED therapy and indirect effects of these drugs by interfering with folate metabolism. Little is known about the psychomotor development of children born to women with epilepsy because few prospective studies have been conducted. Retrospective studies suggest that impaired cognitive development may be associated with maternal drug therapy, notably valproate.{Adab, 2001 3118 /id}

Secondary evidence

NICE{National Institute for Clinical Excellence, 2003 2923 /id}

One technology appraisal of the effects of AED therapy in pregnancy was identified. The evidence base was summarised as follows:

'Few data are available on the use of newer antiepileptic drugs in pregnancy, and it is not yet possible to fully assess the risk of teratogenicity associated with them. Preliminary data from the UK Epilepsy and Pregnancy Register (based on the outcomes of 2028 pregnancies) suggest that the crude rates for risk of major congenital malformation were 4% (95% confidence interval 3.2% to 5.3%) in women taking one antiepileptic drug and 6.3% (95% CI,4.3% to 9.1%) in women taking more than one. There are also data for a small group of women with epilepsy (5.9% of the total) who were not exposed to antiepileptic drugs during pregnancy. The crude malformation rate in this group was 0.9% (95% CI, 0.2% to 4.7%). For the older drugs, the risk in women taking carbamazepine was 2.3% (95% CI, 1.4% to 4.0%), and the risk with sodium valproate was 7.2% (95% CI, 5.2% to 10.0%). The risk with lamotrigine was 3% (95% CI, 1.5% to 5.7%), but no risks were reported for any of the other

newer agents. These data suggest that sodium valproate is associated with a statistically significantly higher risk of malformations than carbamazepine. Although the crude rate for lamotrigine was lower than for sodium valproate, the difference was not statistically significant.'{National Institute for Clinical Excellence, 2003 2923 /id}

No systematic reviews or prospective cohort studies on AEDs and breastfeeding were identified.

2.6 Effectiveness of AEDs whilst pregnant or breastfeeding

Secondary evidence

No systematic reviews of the effectiveness of AED therapy whilst pregnant or breastfeeding were identified. (See Increased risk of seizures)

2.6.1 Which drugs should be avoided in people with learning disabilities and epilepsy?

Details

Secondary evidence

The NICE technology appraisal of newer drugs for adults{2003 2923 /id} with epilepsy concluded that:

- Generally, little evidence was found on the use of these agents in specific subgroups, such as older people or adults with learning disabilities. No monotherapy studies in adults with learning disabilities were found, and only three studies of adjunctive therapy reported results exclusively from this population. There was some evidence from one study that both lamotrigine and gabapentin have some beneficial effects on behaviour in adults with learning disabilities.

- The Committee noted the lack of high-quality evidence on which to base recommendations on the most appropriate treatments for adults with learning disabilities.

- The Committee noted that the importance of regular monitoring of effectiveness and tolerability was the same for adults with learning disabilities as for the general population of people with epilepsy.{2003 2923 /id}

Primary evidence

No further RCT evidence was identified.

Consensus guideline recommendations

Anon 2001{2001 245 /id}

The need to consider the side effect profile of AEDs, notably in relation to cognitive and behavioural effects, was emphasised.

Epileptic seizures are common in older people. In one UK study based on a large primary care computerized database the overall prevalence of epilepsy in people aged over 60 was 11.8 per 1000 and the overall annual incidence in those over 60 was 117 per 100 000.{Tallis, 1991 3621 /id} . The majority of seizures in old age are either focal or focal in origin with secondary generalization. {Sander, 1990 1926 /id}

Cerebrovascular disease is the commonest cause of seizures in old age. Otherwise unexplained epilepsy occurring for the first time in old age may be an early presentation of cerebrovascular disease. {Sander, 1990 1926 /id;Tallis, 2003 3645 /id} As far as provoked seizures are concerned, common causes in this age group include iatrogenic seizures caused by existing drug therapy for other co-morbid conditions and alcohol.

The recommendations on choice of treatment and the importance of regular monitoring of effectiveness and tolerability are the same for older people as for the general population. **[A (NICE)]**

Specific issues in relation to the diagnosis and management of epilepsy in older people are not reviewed here.{Tallis, 2003 3645 /id} The GDG decided that while the issue of epilepsy in older people was important it was not appropriate to include a separate section in the guideline on the diagnosis and management of epilepsy in this group.

The GDG felt strongly that older people with epilepsy should have access to the same range of investigations and treatment as any other group with epilepsy. The emphasis in the *National Service Framework for Older People* on rooting out age-related discrimination is noted here.{2001 3646 /id}

Standard Two of the NSF around person-centred care includes the use of the Single Assessment Process, which will cut red tape and save older people from having to provide the

same personal details and discuss their needs with a range of different agencies. It will also make sure their needs and wishes lie at the heart of the process.{2001 3646 /id}

All aspects of the NSF that are related to medicines management in older people are summarised in an accompanying report.{Department of Health, 2001 3653 /id} All principles outlined in this report should be considered when prescribing for older people with epilepsy. However, as issues around medicines management in this group of individuals are not specific to AEDs, no additional recommendations have been made in this guideline.

There may be particular challenges in providing information and support for this group as there may be occasions where older people with epilepsy cannot make their own decisions due to decreased mental capacity. It is important that decisions are made with appropriate advocacy for the individual, as outlined in recent guidance from the Department of Health.{2001 3632 /id}