REVIEW ARTICLE

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Adverse Reactions to New Anticonvulsant Drugs

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Contents

Abstract

A lack of systematic pharmacoepidemiological studies investigating adverse drug reactions (ADRs) to anticonvulsants makes it difficult to assess accurately the incidence of anticonvulsant-related ADRs. Most of the available information in this regard stems from clinical trial experience, case reports and postmarketing surveillance, sources that are not, by any means, structured to provide precise data on adverse event epidemiology. For various ethical, statistical and logistical reasons, the organisation of structured clinical trials that are likely to provide substantial data on ADRs is extremely difficult.

This review concentrates on current literature concerning serious and life-threatening ADRs. As with the older anticonvulsants, the majority of ADRs to newer anticonvulsants are CNS-related, although there are several that are apparently unique to some of these new drugs. Gabapentin has been reported to cause aggravation of seizures, movement disorders and psychiatric disturbances. Felbamate should only be prescribed under close medical supervision because of aplastic anaemia and hepatotoxicity. Lamotrigine causes hypersensitivity reactions that range from simple morbilliform rashes to multi-organ failure. Psychiatric ADRs and deterioration of seizure control have also been reported with lamotrigine treatment. Oxcarbazepine has a safety profile similar to that of carbamazepine. Hyponatraemia associated with oxcarbazepine is also a problem; however, it is less likely to cause rash than carbamazepine. Nonconvulsive status epilepticus has been reported frequently with tiagabine, although there are insufficient data at present to identify risk factors for this ADR. Topiramate frequently causes cognitive ADRs and, in addition, also appears to cause word-finding difficulties, renal calculi and bodyweight loss. Vigabatrin has been reported to cause seizure aggravation, especially in myoclonic seizures. There have been rare reports of other neurological ADRs to vigabatrin, such as encephalopathy, aphasia and motor disturbances. Vigabatrin-induced visual field constriction is the latest and most worrying ADR. Many questions regarding the nature of this potentially serious ADR remain unanswered, as no prospective controlled study examining the phenomenon has been published. Rare cases of behavioural ADRs and IgA and IgG2 deficiency associated with the use of zonisamide have been reported. However, relatively few patients so far have been exposed to this drug, and therefore more postmarketing information is required.

The relatively late establishment of aplastic anaemia and hepatic failure as potentially fatal ADRs of felbamate, and of visual field constriction with vigabatrin, should serve as ample reminders that ADRs can appear at any time.

Strangely enough, properly controlled observations of the side effects of drug therapy seem to be lacking. . .
- Lennox (1942)[1]

Various authors have continued to make similar comments when reviewing adverse drug reactions (ADRs) to anticonvulsants,[2,3] a reflection of the inadequacy of the present ADR monitoring systems. Although double-blind, placebo-controlled drug trials provide substantial information on short term adverse events, they have severe limitations where long term ADR profiles are concerned. The time limit imposed on anticonvulsant drug clinical trials prevents the early discovery of many ADRs, as the case of aplastic anaemia with felbamate illustrates. Patient numbers in these trials are relatively small and thus limit the meaningfulness of statistical conclusions. For ethical and other considerations, selection criteria for clinical trials often exclude female patients on inadequate contraception, as they also do the elderly and the very young, who may

respond to new drugs differently. Initial clinical trials invariably involve the use of trial drugs as adjunctive therapy. Used as monotherapy, the incidence and nature of adverse drug reactions due to a given drug may be different.

While recognising these shortcomings in the available literature, this review concentrates on ADR profiles of drugs already in clinical usage.

1. Gabapentin

Gabapentin is licensed as add-on therapy for partial seizures with or without secondary generalisation in patients who have not achieved satisfactory control with standard anticonvulsants.[4] Several modes of action have been postulated, including blockade of voltage-dependent sodium ion channels,[5] increased release of γ-aminobutyric acid (GABA),[6] specific binding to a novel site, possibly the neutral L-amino acid transport carrier,[7] and possible modulation of a voltage dependent calcium channel.[8] Gabapentin is excreted unmetabolised via the kidneys and therefore does not cause pharmacokinetic interactions with other anticonvulsants.[4] Indeed, in all the clinical trials reported there were no statistically significant changes in the plasma concentration of other anticonvulsants.[9-12]

1.1 Adverse Events in Clinical Trials

The most common adverse events reported during add-on placebo-controlled clinical trials[13] are shown in table I. Adverse events reported during these clinical trials were mainly CNS-related and tended to be mild. Although occasional serious adverse events such as diminished white blood counts have been reported, the causal relationship is not clear.[12] Overall, no changes in haematological and other laboratory findings have been observed during gabapentin treatment. In a monotherapy study, the reported adverse events of gabapentin were very similar to those in the add-on studies, such as dizziness, headache, fatigue, nausea, vomiting and somnolence. Furthermore, the adverse events were similar to those with carbamazepine monotherapy.[14]

Table I. Most frequently occurring adverse events during placebo-controlled add-on studies with gabapentin (reproduced from Parke-Davis,[13] with permission)

Adverse event	Patients experiencing event (%)	
	gabapentin + anticonvulsants (n = 543)	placebo + anticonvulsants (n = 378)
Somnolence	19.3	8.7
Dizziness	17.1	6.9
Ataxia	12.5	5.6
Fatigue	11.0	5.0
Nystagmus	8.3	4.0
Headache	8.1	9.0
Tremor	6.8	3.2
Nausea and/or vomiting	6.1	7.1
Diplopia	5.9	1.9
Any adverse event	75.1	56.6
Withdrawal due to adverse events	5.0	3.7

1.2 Adverse Events from Clinical Observations

1.2.1 CNS Adverse Events

Psychiatric

Hypomania[15] has been reported in a patient with a past history of probable hypomania, 2 days after the dosage of gabapentin was increased to 900 mg/day. This improved transiently after gabapentin dosage reduction, but full recovery only occurred after cessation of therapy. It has been suggested that cognitively impaired patients with a prior history of behavioural disturbance are more likely to experience aggressiveness and irritability.[16] It has also been suggested that aggression-related adverse effects seem to be dosage-related, and become a significant problem at dosages of 1000 to 1200 mg/day.[17] Childers and Holland[18] also reported that 2 patients experienced heightened anxiety and restlessness, which resolved on withdrawal of the drug.

Gabapentin is not currently licensed for use in children. However, 3 case reports on psychiatric/behavioural ADRs in children have been published. Two children, 1 with learning difficulties and another with attention deficit hyperactivity disorder, developed aggressive behaviour but returned to normal after drug discontinuation.[19] Another

report of 7 children who received gabapentin as add-on medication and subsequently developed behavioural ADRs noted that all behavioural changes were reversible and manageable by dosage reduction or discontinuation of gabapentin. Notably, all patients had baseline attention deficit hyperactivity disorder and developmental delays.[20] A similar report of 3 children draws comparable conclusions.[21]

It is possible that patients with a previous history of psychiatric or behavioural problems and learning disabilities may be predisposed to gabapentin-associated psychiatric or behavioural adverse events. Alternatively, these reports may be a reflection of the initial use of gabapentin in patients with severe epilepsy, in whom learning disabilities, behavioural disturbance and psychiatric disorders commonly coexist.[3] Pharmacoepidemiological studies providing definitive answers are currently unavailable. Although the exact incidence of psychiatric adverse effects occurring in association with gabapentin is unknown, preliminary data do not suggest that they are common.

Seizure Worsening

There have been several reports that gabapentin may exacerbate absence seizures and cause myoclonus. An audit of gabapentin usage in a tertiary referral centre for epilepsy showed that 15% of 263 consecutive patients experienced seizure worsening, and this was in fact the commonest reason for drug withdrawal.[22] Gabapentin has also been reported to cause seizure exacerbation in up to 15% of patients with learning disabilities.[17] A case report of a 14-year-old boy with Lennox-Gastaut syndrome mentions severe seizure worsening after gabapentin was commenced, and he returned to his usual state after gabapentin was stopped.[23] A computer record search in one epilepsy centre showed that 7% of patients experienced seizure deterioration after starting gabapentin.[24] A few cases of gabapentin-induced myoclonus have been reported,[25-27] although it is not possible to ascertain whether these are epileptic phenomenon or movement disorders.[28-30]

Therefore, there is some evidence to conclude that gabapentin can sometimes aggravate seizures, especially in patients with myoclonic and absence seizures. It must be emphasised that gabapentin is not recommended for the treatment of the generalised epilepsies.

Movement Disorders

Three patients with learning difficulties developed choreoathetotic movements after receiving gabapentin for the treatment of epilepsy. All patients recovered after gabapentin was withdrawn.[31,32] Oculogyric crisis was reported to develop in 1 patient receiving gabapentin 1800 mg/day. The patient recovered after a single dose of lorazepam and withdrawal of gabapentin.[27] There is good temporal correlation to suggest that gabapentin was the agent responsible for these movement disorders although, considering the wide usage of gabapentin, these are rare instances.

Polyneuropathy

Polyneuropathy has been reported in a 58-year-old man with neuropathic pain who had initially discontinued therapy with gabapentin due to a rash 5 months after starting gabapentin.[33] Gabapentin was restarted for intractable pain after the rash disappeared. However, it returned along with a burning sensation in the lower extremities that extended to the hips. A toxic polyneuropathy associated with gabapentin was suspected and treatment discontinued, after which he gradually improved. Other causes of polyneuropathy were excluded although, as a single case report, it is difficult to rule out coincidence.

1.2.2 Mortality and Sudden Unexplained Death

In the UK, 361 patients receiving gabapentin in 5 tertiary epilepsy centres had a reported standardised mortality ratio (ratio to general population mortality rate after adjusted for age and gender) of 7.79 [95% confidence interval (CI) 2.69 to 12.89]. Although high, this was thought to be due to the severity of the epilepsy in the patients studied rather than the toxicity of gabapentin.[34]

According to the manufacturer's information, 8 sudden unexplained deaths were recorded among a cohort of 2203 patients treated (2103 patient-years of exposure). This represents an incidence of 3.8

per 1000 patient-years. It is within the range of estimates for the incidence of such events in epilepsy patients not receiving gabapentin.[13]

1.2.3 Overdose

A 16-year-old girl (the daughter of a patient with epilepsy) took an overdose of 48.9g of gabapentin. Six hours later, her only complaints were dizziness and a small amount of liquid stool that had occurred involuntarily during sleep. Upon admission, she was lethargic but arousable. Her ECG was normal and liver function tests, urea and electrolytes, blood count and urinalysis were all normal. She was treated with 1000ml gastric lavage and 50g charcoal with 70% sorbitol. Laboratory studies at 3 and 6 weeks were all normal.[35] The absorption of gabapentin depends on the carrier-mediated L-amino acid transport system. This system can be saturated by a large dose of gabapentin[36] and may therefore minimise the risk of toxicity.[13] A further report of gabapentin overdose also showed no serious ADRs.[37]

2. Felbamate

Felbamate is another newer anticonvulsant drug that has no apparent effect on GABA or benzodiazepine binding but is thought to act through the *N*-methyl-D-aspartate (NMDA) receptor complex[38] and may have an additional sodium channel blocking function. Felbamate was thought to be a very promising anticonvulsant and had a favourable safety profile in animal studies.[39] Median lethal doses remained undetermined because of the physical difficulty in administering large doses to rodents.[39] In clinical trials, felbamate showed wide-spectrum anticonvulsant activity and a lower neurotoxic potential compared with many conventional anticonvulsants. It was therefore approved on 30 July 1993 by the US Food and Drug Administration (FDA) for monotherapy treatment in adults with partial and generalised seizures and for children with Lennox-Gastaut syndrome.[40] In August 1994, with over 100 000 patient-years of exposure, 10 cases of aplastic anaemia (2 fatal) associated with felbamate were reported to the FDA who then, along with the manufacturers, recommended immediate withdrawal of felbamate therapy from all patients.[41] On 1 August 1995, the postmarketing data showed that 32 patients (22 female) had been reported to develop aplastic anaemia; 10 of these cases were fatal.[42] The probable incidence of aplastic anaemia is approximately 127 per million.[43] A recent review suggested that the majority of patients had a history of anticonvulsant allergy/toxicity, cytopenia and immune disease (table II);[44] these conditions may be the risk factors for felbamate-induced aplastic anaemia.

A total of 18 cases of hepatic toxicity have also been reported in association with felbamate, although only 7 cases were classified as causally likely by an independent panel of hepatologists.[45] Using the 130 000 to 170 000 exposed persons as a denominator and 7 likely cases, the estimated incidence is between 1 : 18 500 and 1 : 25 000.[45]

As the true incidence and specific cause(s) of aplastic anaemia and hepatotoxicity are still unclear,[44] felbamate should only be prescribed to patients with intractable epilepsy under close monitoring. The risks for toxicity with felbamate should be evaluated before starting treatment. In addition, liver function tests and full blood count should be performed prior to therapy and at regular intervals. Patients must be educated in the likely prodromal symptoms of potential marrow/liver toxicity. With monitoring, patient education and continued research to further elucidate risk factors, felbamate can be a viable therapeutic agent for patients with epilepsy.[44] Felbamate is now available in the US

Table II. Patient risk factors for developing aplastic anaemia with felbamate.[44] The analysis includes all reported cases, regardless of a definitive diagnosis of aplastic anaemia

Potential risk factor	Percentage of patients (%) [n = 33]
Age >17 years	97
Female gender	67
Concomitant medications	79
Concomitant anticonvulsants	55
History of anticonvulsant toxicity/allergy	52
History of cytopenia	42
History of immune disease	33

for refractory Lennox-Gastaut syndrome and on a 'named basis' in the UK.

With hindsight, it was probably a mistake to market felbamate with no requirement for laboratory control, on the basis that a very small number of people had been exposed to it (approximately 4000) at the time of release.[46] Nevertheless, a costly lesson has been learnt and a more cautious attitude should be adopted for marketing new anticonvulsants.

3. Lamotrigine

Lamotrigine is licensed in the UK as monotherapy of partial seizures with or without secondary generalised tonic-clonic seizures for those over 12 years of age and add-on therapy for children over 2 years of age.[47] In the US, it is licensed for adjunctive therapy in adults with partial seizures as well as conversion to monotherapy in adults who are receiving treatment with a single enzyme-inducing antiepileptic drug. Lamotrigine is also licensed in the US as adjunctive therapy for the generalised seizures of Lennox-Gastaut syndrome in paediatric and adult patients. Increasing experience with lamotrigine suggests that it is effective in the treatment of generalised epilepsies, including idiopathic generalised epilepsies.[48-50] The anticonvulsant effects of lamotrigine are likely to be due to the inhibition of sodium currents by interacting with the inactivated channel[51] and inhibitory effects on the release of glutamate.[52]

3.1 Adverse Events in Clinical Trials

Similar to gabapentin, the most frequently reported adverse events in add-on studies were CNS-related (table III).[53] Although the incidence of such events was high, the effect of pharmacodynamic interactions in the add-on trials is likely to have been significant. Although efforts were made to control pharmacokinetic interactions, the add-on trials were unable to control pharmacodynamic interactions. In the monotherapy clinical trial, most of the adverse events were CNS-related (table IV),[54] and their lower frequency may be due to the removal of possible pharmacodynamic interactions. Rash is the most common reason (in about 2 to 3% of recipients)[53] leading to the discontinuation of the drug. More detailed discussion of this ADR can be found in section 3.2.3.

Table III. Adverse events reported in ≥10% of patients in US placebo-controlled studies of lamotrigine (reproduced from Richens,[53] with permission)

Adverse event	Patients experiencing event (%)	
	lamotrigine (n = 334)	placebo (n = 112)
Dizziness	50	18
Headache	37	36
Diplopia	33	11
Ataxia	24	5
Blurred vision	23	9
Nausea	22	15
Rhinitis	17	19
Somnolence	14	7
Pharyngitis	13	12
Coordination abnormality	12	6
'Flu' syndrome	11	9
Cough	10	8
Rash	10	5
Dyspepsia	10	5
Vomiting	10	9

3.2 Adverse Events from Clinical Observations

3.2.1 CNS Adverse Reactions

Psychiatric

The data from nonblind and double-blind placebo-controlled trials (1920 patients) suggest that the rates of psychosis and depression leading to the discontinuation of lamotrigine are 0.2 and 0.26%, respectively. Adverse events such as aggression, irritability, agitation, confusion and hallucinations have also been reported,[55-57] although it is unclear whether they represent a true association or merely constitute a background incidence.[53] Nevertheless, a case of psychosis has been reported that bears all the hallmarks of 'forced normalisation'. The patient became seizure free with a normal EEG; recovery occurred after lamotrigine was discontinued and antipsychotic treatment was started.[58]

A case of reversible encephalopathy associated with high lamotrigine blood concentration has been reported.[59] The patient improved with serial reduction of the lamotrigine dosage. The authors suggested that the dosage of lamotrigine was too high. However, the patient had been stabilised on his anticonvulsants for several months before encephalopathy developed, and a concurrent urinary tract infection may have played an important role in this adverse event. The exact cause of the problem has not been established.[3]

Seizure Worsening

In one study, 16 of 20 patients with severe myoclonic epilepsy developed seizure worsening, in most cases within 3 months of treatment, and improved after lamotrigine was discontinued.[60] Seizure exacerbation associated with worsening of interictal EEG changes and occurring at various stages of severe myoclonic epilepsy has also been reported.[61]

3.2.2 Overdose

Overdoses of between 1.35 and 4g of lamotrigine have been reported in a few patients. Apart from ataxia, dizziness, headache, nystagmus, somnolence and vomiting, no serious clinical consequences have been noted. A patient who ingested between 4 and 5g was admitted to hospital in a coma lasting 8 to 12 hours, followed by recovery over the next 2 to 3 days. Another patient who ingested 5.6g was found unconscious and, following treatment with charcoal, the patient recovered after sleeping for 16 hours.[62]

Although no serious clinical consequences were reported in the above cases, in one patient (overdose 1.35g) the ECG showed QRS width of 110ms. The ECG changes were possibly caused by the arrhythmogenic effect of the 2-*N*-methyl metabolite of lamotrigine. This metabolite was found to prolong the PR interval in beagle dogs in a dose dependent fashion. Only small amounts of this metabolite are found in human urine, and none in the blood.[62] Whether a large overdose of lamotrigine will produce more of this metabolite in humans remains unknown.

3.2.3 Hypersensitivity Reactions

Hypersensitivity reactions to lamotrigine are of major concern. Stevens-Johnson syndrome, toxic epidermal necrolysis, multi-organ failure, hepatic failure, renal failure and leucopenia have all been reported.

Rash

The major ADR leading to lamotrigine discontinuation is skin rash. The percentage of reported rash varies between 5 and 10%.[55,56,63-66] In clinical trials, the lamotrigine-related rash has most often been limited to a simple morbilliform rash without evidence of systemic involvement, and typically occurs within the first 8 weeks of treatment. The incidence of Stevens-Johnson syndrome in clinical trials is reported to be approximately 1 in 1000 patients.[55,56,66] A few cases of toxic epidermal necrolysis have also been reported.[67-73] It is recognised that concurrent treatment with valproic acid (sodium valproate), a high starting dosage and rapid dosage titration are well recognised risk factors for lamotrigine-related rash.[55,56,74] Children are also more likely to experience a serious rash than adults.[55] This topic has been extensively re-

Table IV. Adverse events reported in >5% of patients during a study of monotherapy with lamotrigine or carbamazepine (reproduced from Brodie et al.,[54] with permission)

Adverse event	Number (%) of patients experiencing event	
	lamotrigine (n = 131)	carbamazepine (n = 129)
Headache	39 (30)	32 (25)
Asthenia	28 (21)	37 (29)
Rash	25 (19)	25 (19)
Nausea	23 (15)	16 (12)
Dizziness	16 (12)	22 (17)
Sleepiness	16 (12)	29 (22)*
'Flu-like' illness	15 (11)	10 (8)
Pharyngitis	12 (9)	9 (7)
Vomiting	12 (9)	9 (7)
Rhinitis	11 (8)	6 (5)
Amnesia	8 (6)	4 (3)
Infection	8 (6)	6 (5)
Back pain	7 (5)	2 (3)
Depression	6 (5)	11 (9)
Ataxia	4 (3)	11 (9)

***** indicates statistically significant significance ($p < 0.05$).

viewed,[55,56,63,66] and the more recent observations are discussed below.

In an observational study conducted in 5 UK tertiary referral centres (1050 patients), females were noted to be twice as likely to experience lamotrigine rash (relative risk 1.83, 95% CI 1.20 to 2.81). The reasons for this are unclear and further study is required to confirm this finding.[75]

Multi-Organ Failure and Disseminated Intravascular Coagulation

In 1992, a review article on lamotrigine mentioned 3 cases of disseminated intravascular coagulation (DIC) and multi-organ failure that had been reported in patients receiving lamotrigine.[76] A later analysis of 28 cases proposed excessive muscular activity caused by convulsive seizures and subsequent rhabdomyolysis as the pathophysiology behind multi-organ failure and DIC.[77] There are indications that this may not be true of every case. We have previously compared data from the UK Committee on Safety of Medicines (CSM) for vigabatrin and lamotrigine (with permission from the UK Medicines Control Agency).[78] Until August 1994, 6 cases of DIC had been reported in patients receiving lamotrigine, whereas no cases of DIC associated with vigabatrin had been reported to the CSM. The usage and indications of vigabatrin are comparable to those of lamotrigine, and vigabatrin has in fact been on the market 2 years longer than lamotrigine. One would expect a similar frequency of this adverse event in the case of vigabatrin, and it is reasonable to conclude that the CSM data generate a hypothesis that lamotrigine may cause DIC.[78]

Stronger evidence to support this view is available in 2 case reports[79,80] where patients have had no generalised seizures at any time before the development of DIC and multi-organ failure. In the absence of other probable causes, lamotrigine was thought to be directly responsible. A later, systematic observational study also reported a 27-year-old female patient who developed asymptomatic DIC 1 month after she commenced lamotrigine. *In summary,* the available literature suggests that many of the reported patients with this ADR probably developed complications secondary to severe convulsions and rhabdomyolysis, although lamotrigine appears to induce similar adverse reactions independently.[81]

Another life-threatening ADR, fulminant hepatic failure, has also been reported.[82] A 22-year-old woman developed a maculopapular rash and hepatic failure. Lamotrigine was stopped and liver function gradually improved after admission to hospital. However, she died unexpectedly of a massive pulmonary embolus 2 months after admission. Biopsy confirmed a diagnosis of fulminant hepatic failure and, in the absence of other causes, it was concluded that the fulminant hepatic failure was due to lamotrigine.

Renal failure has also been reported to the CSM in a 28-year-old man who initially stopped lamotrigine therapy because of drowsiness and aggressive behaviour but was restarted on the drug 6 months later. Shortly after lamotrigine was recommenced he had 2 secondary generalised seizures and developed severe hypertension and acute renal failure. Both hypertension and renal failure resolved with cessation of lamotrigine therapy and treatment with atenolol.[81]

Haematological Disturbances

Leucopenia has been reported with lamotrigine treatment in a 35-year-old woman who developed a rash and septicaemia soon after starting therapy. The white blood cell count started to rise 3 days after withdrawal, suggesting a causal relationship.[83] Anaemia has also been reported rarely.[84,85]

Lymphadenopathy

Lymphadenopathy is a recognised ADR to lamotrigine,[47] and is usually associated with other symptoms such as rash. Pseudolymphoma without concurrent rash or other systemic disturbances 14 weeks after starting lamotrigine, which resolved after drug discontinuation, has also been reported.[86]

There is little doubt that hypersensitivity reactions are major adverse reactions to lamotrigine. However, most of the hypersensitivity reactions are simple rashes. Moreover, the extensive usage of this drug worldwide and the relative paucity of reports of fatal outcomes suggests that these should

not unduly deter the prescription of this drug. It remains one of the most popular new anticonvulsants.

3.2.4 Interactions

In early clinical trials, lamotrigine was found to interact with carbamazepine. Patients had typical carbamazepine-induced dose-dependent cerebellar toxicity in the form of diplopia, nystagmus, dizziness and unsteadiness. The cerebellar symptoms abated with reduction of carbamazepine.[87,88] Because of these observations of dose-dependent toxicity, it was proposed that it might be due to pharmacokinetic interactions between lamotrigine and carbamazepine. A study of the pharmacokinetic interaction between lamotrigine and carbamazepine and its primary metabolite carbamazepine 10,11-epoxide in 9 consecutive patients (5 male, 4 female, aged 19 to 31 years) showed that after the introduction of lamotrigine (median dosage of 200 mg/day, range 100 to 300 mg/day), the mean serum carbamazepine epoxide concentration increased by 45% ($p < 0.01$) and the carbamazepine epoxide/carbamazepine ratio increased by 19% ($p < 0.02$). These changes were associated with clinical toxicity (dizziness, nausea and diplopia) in 4 patients.[89]

However, other researchers failed to find changes in plasma carbamazepine or carbamazepine epoxide in lamotrigine-treated patients.[90-95] They all suggested that the interaction between carbamazepine and lamotrigine was pharmacodynamic, and present evidence[95] would confirm this. This interaction can be easily controlled by dosage reduction of either carbamazepine or lamotrigine.

Three cases of unusual disabling tremor caused by concurrent use of lamotrigine with valproic acid have been reported. A severe, disabling, postural action tremor predominantly affecting the upper limbs was associated with ataxia and dysarthria. All patients recovered after dosage reduction of either lamotrigine or valproic acid.[96]

One of these cases highlights the significance of the pharmacokinetic interactions of lamotrigine with valproic acid and phenytoin.[96] The patient was receiving well tolerated daily dosages of phenytoin, valproic acid and lamotrigine. Withdrawal of phenytoin resulted in the development of disabling tremor and ataxia, and symptoms resolved when the lamotrigine dosage was lowered. The reaction was caused by phenytoin withdrawal unmasking the effect of valproic acid on lamotrigine metabolism. Most prescribing reference books, such as the Data Sheet Compendium, British National Formulary (BNF), Monthly Index of Medical Specialties (MIMS) and Physician's Desk Reference, although mentioning the need for awareness of the fact that valproic acid users should receive a lower dosage of lamotrigine, do not mention the possible consequences of the withdrawal of concomitant hepatic enzyme inducers such as phenytoin.

3.3 Safety in Pregnancy

Interim results of the lamotrigine pregnancy registry contains 149 prospective reports. The advisory committee to the registry reviewed the results and found no safety signal to date (January 1999). However, the sample size was insufficient to make definitive conclusions about the safety of lamotrigine use in pregnancy.[97]

4. Oxcarbazepine

Oxcarbazepine, the 10-keto analogue of carbamazepine, appears to have fewer adverse events and drug interactions than carbamazepine while retaining similar efficacy.[98,99] It has an adverse event profile similar to carbamazepine, although it is important to note 2 significant differences that are important in clinical practice.

The incidence of skin rash is less with oxcarbazepine than with carbamazepine, making oxcarbazepine a viable alternative for patients who experience skin reactions with carbamazepine. In a retrospective multicentre study of 947 patients, rash was reported in 6% of patients, 50% of whom had suffered a previous allergic reaction to carbamazepine.[100] Cross-reactivity is seen in about 25% of patients who have had skin problems with carbamazepine,[101] although it has been suggested that this figure may be higher.[102] In a double-blind clinical trial of monotherapy, 9 of 91 participants discontinued oxcarbazepine due to rash, compared with 16 of 95 in the carbamazepine group.[103]

Given the similarity in efficacy between the 2 drugs, oxcarbazepine may be a useful alternative in patients who derive significant benefit from carbamazepine but are unable to tolerate the drug because of skin rashes.

Hyponatraemia appears to be a common problem with oxcarbazepine,[104,105] and in rare situations may lead to serious complications,[106] necessitating vigilance to prevent acute water intoxication. However, this should not detract from its role as an effective anticonvulsant drug in many seizure types.

5. Tiagabine

Tiagabine is a specific GABA reuptake inhibitor drug that has recently been released in several countries as adjunctive therapy in partial seizures. It is moderately efficacious and appears to lack serious idiosyncratic ADRs. Data are available both from add-on, double-blind, placebo-controlled trials as well as preliminary data from long term non-blind clinical trials.[107-109]

5.1 Adverse Events in Clinical Trials

Most adverse effects are CNS-related and appear in the first 6 months of therapy, mostly resolving within a month.[110] Frequency of administration may be an important factor, as in a large study fewer patients on 8mg 4 times daily discontinued therapy due to adverse events than did patients on 16mg twice daily.[111] However, other studies have not found a significant correlation between regimen and adverse events.[107] In short term, placebo-controlled studies, 91% of patients experienced treatment-emergent events as compared with 79% in the placebo group.[107] Dizziness was experienced by 30% of patients (placebo 13%) and other common events were asthenia in 24% (placebo 12%), nervousness in 12% (placebo 3%), tremor in 9% (placebo 3%), depression in 5% (placebo 1%) and emotional lability in 4% (placebo 1%). Other CNS-related adverse events reported were somnolence, headache, abnormal thinking, ataxia and confusion, which occurred in similar numbers in the placebo group.

Diarrhoea (7%) was more commonly noted in the treatment group, although other events such as pharyngitis and abdominal pain were no more frequent than in the placebo group. Analysis of some placebo-controlled trials has shown that tiagabine appears not to impair cognitive function,[112-114] a definite advantage over most other anticonvulsants. In monotherapy studies, paraesthesiae have also been noted as occurring significantly more commonly (20%) than in placebo patients.[115]

5.2 Adverse Events from Clinical Observations

In longer term trials, similar ADRs were noted with similar frequencies.[104] These were dizziness (34%), somnolence (25%), asthenia (24%), headache (23%) and tremor (20%). The most worrying ADR to tiagabine is nonconvulsive status epilepticus (NCSE), which 9 patients have been reported to develop.[116-120] All patients recovered after tiagabine withdrawal, which suggests that tiagabine was the likely cause of NCSE.

There is a published report of tiagabine overdose where an individual consumed 30 to 40 tablets of 8mg each and was admitted in a coma that resolved in 24 hours.[121]

6. Topiramate

Topiramate is licensed for use as adjunctive therapy in partial seizures with or without secondary generalisation. It has several postulated mechanisms of action, including state dependent sodium channel blockade[122] and enhancement of GABA-mediated chloride influx into neurons.[123] It also inhibits kainate activity on the kainate/ a-amino-3-hydroxy-5-methyl-4-propionic acid (AMPA) subtype of glutamate receptors[124] and weakly inhibits the CA II and CA IV isoenzymes of carbonic anhydrase.[125]

6.1 Adverse Events in Clinical Trials

Though efficacious and with a high neuroprotective index in animals,[126] adverse events are frequently encountered and these are often responsi-

ble for discontinuation of therapy. Adverse synergism with other concomitant therapy is possible, and a recent report suggests that when used as monotherapy in low or moderate dosages, topiramate is considerably better tolerated.[127] Six placebo-controlled trials in Europe and North America have so far been conducted.[118-132] Adverse events occur early after initiation of therapy and appear to be directly related to the rapidity and magnitude of dosage titration.[133] A randomised, double-blind multicentre study showed that 38% of patients started on topiramate 100 mg/day and titrated rapidly to 400 mg/day over a 3-week period had adverse events, compared with 25% in a group titrated more slowly from 50 to 400 mg/day over 8 weeks.[134] The effect of these differing titration regimens on seizure control was similar in both groups, suggesting that slow titration starting with dosages as low as 25mg every alternate day and initially small increments of 25mg at appropriate 2-weekly intervals are preferable.

6.1.1 CNS Adverse Events

A wide range of ADRs have been reported, although dosage titration to large amounts was rapid in many studies. Central and peripheral nervous system problems are the most frequently observed adverse events of topiramate therapy and, in clinical trials where dosages ranged from 200 to 1000 mg/day, these occurred in 77% of patients (placebo 52.3%).[132] Dizziness in 31% (placebo 15%), headaches in 27% (placebo 28%), paraesthesiae in 18% (placebo 5%) and ataxia in 16% (placebo 7%) were the most commonly reported events. Headaches were more common in the placebo group. Perioral and digital paraesthesiae, an ADR shared with acetazolamide, are probably due to the alkalosis caused by carbonic anhydrase inhibition. Speech disturbances in 13% (placebo 2%) and language problems in 10% (placebo 0.5%) of patients were also frequently reported and, in clinical practice, many such patients describe problems that range from mild word finding difficulties to frank motor dysphasia. Some patients (3%) were noted to develop an exacerbation of seizures, although this was more commonly reported in the placebo groups (5%). ADRs seen with other anticonvulsants such as tremor (9%; placebo 6%), nystagmus (12%; placebo 9%), incoordination (4%; placebo 2%) and gait abnormalities (2%; placebo 1.4%) have also been reported. A greater incidence of cognitive ADRs than with lamotrigine and gabapentin have been reported in healthy adult volunteers, although this study involved very few individuals, dosage titration was very rapid and seizure reduction was not taken into account.[135]

Neuropsychiatric adverse events were almost as frequently reported as nervous system problems in clinical trials and occurred in 74% of patients (placebo 34%). Somnolence in 28% (placebo 10%) was the most common event, followed by psychomotor slowing in 20% (placebo 2%), nervousness in 19% (placebo 7%), memory problems in 14% (placebo 3%), lack of concentration in 13% (placebo 1.4%), depression in 12% (placebo 6%) and confusion in 13% (placebo 4%). Insomnia and anxiety were less frequently reported and at similar levels to the placebo group. Behavioural disturbances (aggression, agitation, emotional lability and euphoria) and symptoms of psychosis (psychosis, paranoia, delusions and mania) were uncommon observations. Occasional problems with libido, and sleep disorders such as somnambulism, were also reported, although less frequently than in the placebo group. Psychosis in particular appeared to be a relatively rare event and of 27 psychotic episodes only 2 cases were considered to be directly related to topiramate, whereas 13 were possibly related.[132]

6.1.2 Bodyweight Loss

Bodyweight loss is a frequently observed and not always unwelcome effect of topiramate therapy.[132,136] Data from 1300 adult patients in clinical studies showed that 22% of patients reported a decrease in bodyweight.[132] Analysis suggests that dosage as well as baseline bodyweight are important predictive factors. Decreases in bodyweight ranged from about 2% in patients who received less than 200 mg/day to 7% in patients who received more than 1000 mg/day. Duration of treatment in the latter group may be a contributory factor, as patients receiving higher dosages also tend to be

those who have consumed the drug for longer periods of time. However, it has also been observed that bodyweight loss peaked at around 12 to 18 months of treatment, with bodyweight gain towards pretreatment levels on continued topiramate therapy.[132] Bodyweight loss was greatest (8%) in patients who had baseline bodyweights of more than 100kg and least (3%) in those who weighed less than 60kg. Lack of appetite, at least in routine clinical practice, appears to be a significant factor and this was a common complaint in clinical trials (12%; placebo 4%).

6.1.3 Renal Calculi

Renal calculi are a well known, although uncommon, ADR of topiramate. They occurred in less than 2% of the study population.[132] Males were more commonly affected than female patients, although the effects of age, dosage and duration of treatment were all shown to be insignificant factors. However, a family history of nephrolithiasis, hypercalciuria and a prior history of renal stone formation are probably important. Although these are not necessarily contraindications to treatment, it is important to ensure adequate hydration. The exact mechanisms of stone formation are not clearly known. Out of 7 cases of topiramate-associated nephrolithiasis reported in clinical trials that were studied, 5 had calcium phosphate stones.[137] These can be associated with carbonic anhydrase inhibition where the urine is alkalinised and citrate excretion reduced.[138]

6.2 Adverse Events from Clinical Observations

Other ADRs have been reported in the literature, including transient myopia[139] and fulminant hepatic failure,[140] although the latter is a solitary occurrence in well over 100 000 patient-years of treatment.

6.3 Safety in Pregnancy

Topiramate has been found to be teratogenic in animal studies, although its effects on the human foetus are as yet unknown.[132] Careful risk-benefit assessments are therefore essential, as is expert supervision.

In summary, topiramate is an effective drug in the treatment of the epilepsies, and although therapy can be complicated by the occurrence of adverse events, measures such as gradual titration and small initial dosages are helpful in limiting these.

7. Vigabatrin

Vigabatrin is licensed for the treatment of epilepsy not satisfactorily controlled by other anticonvulsants and also as monotherapy for West's syndrome.[141] A minority of patients with Lennox-Gastaut syndrome have also demonstrated a good response.[142,143] The main anticonvulsant effect of vigabatrin is due to GABA aminotransferase inhibition. However, inhibition of glutamate and aspartate synthesis[144-146] and GABA uptake inhibition[147] may also contribute to the anticonvulsant effect.

7.1 Adverse Events in Clinical Trials

As with lamotrigine, the most common adverse events reported during the clinical trial were CNS-related. Table V summarises the 10 most frequently reported adverse events in 6 double-blind, placebo-controlled, cross-over, add-on trials.[148] Table VI shows the adverse events reported in a vigabatrin monotherapy study and, similarly to the add-on studies, most of the adverse events are CNS-related;

Table V. Incidence of 10 most frequently reported adverse events in double-blind studies of vigabatrin (reproduced from Reynolds,[148] with permission)

Adverse event	Incidence (%)	
	vigabatrin	placebo
Somnolence	27.2	13.0
Fatigue	7.5	6.1
Irritability	5.4	6.1
Dizziness	5.4	1.4
Headache	4.1	4.1
Depression	4.1	2.7
Confusion	3.4	0.7
Poor concentration	2.7	1.4
Abdominal pain	2.7	0.7
Anorexia	2.7	0.7

no life-threatening adverse events have been reported.[149]

7.2 Adverse Events from Clinical Observations

7.2.1 CNS Adverse Events

Psychotic and Behavioural Reactions

From the pre-1990 placebo-controlled clinical trials,[150-155] there was no indication that vigabatrin could cause serious psychiatric adverse drug reactions, such as psychosis, although 5 of 141 patients (3.6%) experienced confusion while taking vigabatrin, but not placebo. However, in 1990, Sander and Hart[156] reported that 7 of 145 patients developed psychotic symptoms after starting vigabatrin. In 6 patients, the symptoms only resolved on withdrawal of treatment, while in the seventh patient they resolved on halving the daily dose from 4000 to 2000mg. In 4 of the patients, seizures had been completely controlled at the time of onset of psychotic symptoms. Two of the 7 had a previous history of psychosis. Sander and Hart[156] suggested that the psychosis may result from 'forced normalisation' rather than the direct effect of vigabatrin. Thomas et al.[157] also suggested the suppression of seizures, or becoming seizure-free, was an important factor associated with vigabatrin-related psychosis.

However, when further cases of vigabatrin-associated psychiatric and behavioural disturbances were reported, it became clear that forced normalisation was unlikely to be the sole cause. Wong et al.[3] reviewed 16 studies and case reports and identified 91 cases of psychotic or behavioural disturbances; less than half of these cases were reported to have a complete or major improvement in seizure control.

There is also strong evidence to suggest that vigabatrin-related psychiatric and behavioural disturbances may have a pharmacological basis (i.e. a type A reaction), possibly mediated through its GABA-mimetic properties. First, vigabatrin overdose has been reported to cause psychosis.[158] Secondly, data from the manufacturer quoted in Schmidt and Kramer[159] showed a clear trend that increasing dosage of vigabatrin led to an increase in abnormal behaviour necessitating vigabatrin withdrawal, and also the higher the initial dosage of vigabatrin, the higher the incidence of behavioural adverse events at first visit. Thirdly, GABA agonists and other GABA-mimetic drugs such as benzodiazepines and phenobarbital (phenobarbitone) have also been reported to induce psychiatric symptoms.[160-162]

To complicate the situation further, sudden cessation of vigabatrin has also been reported to induce

Table VI. Adverse events observed in patients randomised to initial monotherapy with vigabatrin or carbamazepine, with noncompliant patients excluded (reproduced from Kalviainen et al.,[149] with permission)

Adverse event	Number of patients experiencing event	
	vigabatrin (n = 43)	carbamazepine (n = 45)
Intolerable events		
Generalised rash	0	7*
Hepatic toxic effects	0	3
Elevation of blood glucose level	0	1
Confusion and personality change	0	1
Tolerable events		
Drowsiness	19	28
Dizziness	3	9
Visual disturbances	7	0*
Myoclonic jerks	6	1*
Gastrointestinal symptoms	3	4
Cognitive disturbance	2	3
Eczema	1	4
Increased appetite	2	0
Loss of appetite	0	2
Drug interactions	1	2
Headache	1	1
Depressive mood	1	0
Insomnia	1	0
Loss of hair	1	0
Gynaecomastia	0	1
Arthralgia	1	0
Feeling of thirst	1	0
All events		
Some	31	39
None	12	6

***** indicates statistical significance ($p < 0.05$).

psychosis.[163,164] EEG evidence shows that the vigabatrin withdrawal psychosis was not associated with a sudden increase in epileptic discharges, and therefore these episodes were unlikely to be nonconvulsive status or post-ictal psychosis.[163,164] Abrupt withdrawal of other CNS depressants such as benzodiazepines, alcohol and barbiturates have also been known to cause psychiatric disturbances.[165] Sudden removal of CNS inhibition may be a possible cause of vigabatrin-withdrawal psychosis.

Finally, we consider the frequency of vigabatrin-related psychotic reactions. Data from the manufacturer, based on the Global Safety Data submitted to the FDA, suggests an incidence of psychosis of 1.1%,[166] but a prescription event monitoring study conducted by the Drug Safety Research Unit in the UK (an independent pharmacovigilance charity) suggests that the incidence of psychosis is only 0.64%.[166] However, data from an American placebo-controlled clinical trial in patients with resistant partial seizures suggests the incidence of psychosis, in this selected group, is 2.9%[166] and in tertiary referral centres the rate may be as high as 6%.[158]

Affective Disorder

In 1993, 10 patients were reported to develop a major depressive episode in association with vigabatrin treatment for intractable epilepsy.[167] No obvious psychosocial precipitants were present in these 10 patients and all patients recovered after vigabatrin withdrawal. The authors suggested the depression may be related either to the potency of vigabatrin in controlling seizures (i.e. forced normalisation) or its effect on GABA, or both.[167] However, other studies used the Beck Depression Inventory and Middlesex Hospital Questionnaire and Mood Adjective Checklist to rate the mood of the patients, and concluded that vigabatrin had no effects on mood.[168-172]

A case of bipolar affective psychosis after vigabatrin treatment was also reported.[173] After slow withdrawal of vigabatrin and addition of thioridazine, the mood of the patient stabilised. The author suggested that alteration of the GABA-ergic system can induce depression, and may also trigger bipolar affective disorder with rapid cycling.[173]

Another 37-year-old man was reported to develop a manic episode 2 weeks after adding vigabatrin 2 g/day to his usual anticonvulsant treatment and clomipramine 35 mg/day (clomipramine was started about 1 month prior to the development of the manic episode). The patient recovered after clomipramine was discontinued and antipsychotic treatment started. His seizures were well controlled by vigabatrin and therefore it was not stopped. The authors suggested there was an interaction between clomipramine and vigabatrin,[174] although they did not propose a mechanism.

Review of 6 placebo-controlled, clinical trials[150-155] gives an overall incidence of depression of 2.4%, which is comparable with the rate of 2.5% in 2081 patients with epilepsy, derived from data from the manufacturer.[175] However, Aldenkamp et al.[176] reported that 12% of patients stopped vigabatrin mainly due to mood problems, and another 8% stopped vigabatrin due to mood problems and lack of efficacy. Additionally, Wong[177] suggested a 7% discontinuation rate due to mood change.

Acute Encephalopathy

Two cases of acute encephalopathy have been reported in patients starting vigabatrin as add-on therapy to carbamazepine.[178] These were characterised by stupor, dysphoria, irritability and EEG slowing. One of the patients developed a novel type of seizure and the other had myoclonic status epilepticus, both of which recovered after vigabatrin was stopped. Three further cases of acute encephalopathy have been reported.[179] Pre-existing cerebral abnormalities were thought to be a possible risk factor, although at that stage most patients prescribed the drug had severe epilepsy and a confounding influence is likely.[3] Another report showed that 3 patients who developed encephalopathy had mild renal failure, and all patients recovered after dosage reduction or discontinuation of vigabatrin. The authors suggested that the renal impairment could have increased the vigabatrin plasma concentration, causing a dose dependent-toxicity.[180]

Seizure Worsening

Myoclonic status during vigabatrin therapy in patients with generalised epilepsy has also been reported.[178,181] Three other patients developed myoclonic jerks soon after they started taking a full dosage of vigabatrin, and all patients recovered after vigabatrin withdrawal.[182] A large retrospective study of 194 children showed seizure increases in 10% of the children, whereas 14% developed new seizure types, mostly myoclonic, which often resulted in a worsening of the overall condition.[183] Vigabatrin monotherapy has been reported to exacerbate myoclonic jerks in newly diagnosed epileptic patients.[149] Partial status epilepticus following vigabatrin treatment has also been reported,[184] although in some cases the causal relation has not been clear.[185] There is evidence to suggest that vigabatrin can sometimes cause myoclonus and should therefore be avoided in patients with myoclonic epilepsy.

Aphasia

Worsening of pre-existing aphasia has been reported in a patient who returned to his usual state 3 days after vigabatrin withdrawal.[186] The temporal relationship of exposure and dechallenge suggested a causal relationship. On the other hand, the patient had experienced a tonic-clonic seizure just prior to the aggravation of aphasia and it was difficult to eliminate the possibility of a temporary post-ictal neurological deficit.

Visual Field Constriction

Visual field defects in humans are now thought to be causally related to long term therapy with vigabatrin. This was first reported in the literature in 1993,[187] and then confirmed in 1997 by several centres using this drug to treat epilepsy.[188-191] Since then, many more cases have been reported.[192-196] The drug is known to cause prominent microvacuolation of myelin sheaths of visual pathway neurons, particularly the optic tract, in rodents and dogs, although similar changes have not been noted in primates and humans.[197-199] It acts by inhibiting GABA transaminase and, in addition to increasing GABA levels in the brain, probably increases levels in the inner retina as well.[200] Prolonged increase of GABA levels could lead to a toxic effect on these highly GABA-ergic amacrine retinal cells and thus produce visual field defects. The clinical picture is usually one of bilateral concentric reduction of visual fields with a relative sparing of visual acuity. Patients may complain of frequent bumping into objects or tunnel vision, although it is important to emphasise that they may be completely asymptomatic. Confrontational testing may reveal visual field constriction, although this method is a crude screening test and by no means establishes the absence of field defects with certainty. Fundal examination is normal, although some examiners have noted pale discs.[190] Perimetry best reveals the presence or absence of field defects and Humphrey fields analyses should be utilised to establish these. Visual evoked potentials[200] and electroretinograms[188] may be normal, and in any case are unlikely to be effective or efficient means of detecting and defining problems.

Many questions regarding the nature of this serious ADR remain unanswered, as no randomised, prospective, controlled clinical trials examining the phenomenon have yet been published. The cases so far analysed have mainly been adult patients who, in most cases, have been on multiple drug therapy for varying lengths of time.[188-191] Most affected patients had been taking vigabatrin for several years, suggesting the importance of chronicity in the pathogenesis of the field defects. Dosages have not always been recorded, and it may be possible that this is a crucial factor.[120] The CSM[192] has just issued the following guideline: 'Vigabatrin therapy should only be initiated by an epilepsy specialist. Vigabatrin is now indicated only when all other appropriate anti-epileptic drug combinations have proved ineffective or poorly tolerated and should not be initiated as monotherapy. The exception is that vigabatrin remains a first line therapy for infantile spasms (West's syndrome) where monotherapy may be appropriate. The maximum recommended daily dose of vigabatrin has been reduced to 3g. If seizure control is not significantly improved after an adequate trial, vigabatrin therapy should be gradually withdrawn under close

medical supervision. Vigabatrin is not recommended for patients with pre-existing visual field defects. Ophthalmological consultation and visual field assessment should be undertaken prior to initiation of vigabatrin and visual field screening should be repeated at 6-monthly intervals during therapy. Conventional perimetry is seldom possible in patients with a developmental age of less than 9 years. For such patients, alternative methods for testing visual fields should be used.'

Motor Disturbances

Two patients with unusual disturbances of motor behaviour associated with the introduction of vigabatrin as add-on therapy have been reported.[201] One of the patients was a 15-year-old girl with tuberous sclerosis and refractory epilepsy who had been on valproic acid and carbamazepine. Dosage increase was associated with increased seizure frequency and stereotyped involuntary movements. The abnormal movement pattern disappeared with dosage reduction. The second patient was a 2-year-old boy with severe symptomatic generalised epilepsy who had been on carbamazepine and valproic acid. Severe hyperkinesia with bouts of laughing developed following the gradual introduction of vigabatrin up to 1000 mg/day. EEG at this time showed a deterioration of background activity but the epileptiform discharges were unchanged. Withdrawal of vigabatrin resulted in disappearance of the abnormal motor behaviour, and EEG findings normalised. The motor disturbances were unlikely to have been caused by epileptic activity, as the EEG did not show epileptiform activity.[201] However, the cause of the motor disturbance is still unknown. Hyperkinesia has also been reported in 17 of 70 children who were being treated with vigabatrin.[202]

7.2.2 Overdose

Overdoses, most commonly at doses between 7.5 and 30g but up to 65g, have been reported. Approximately half of these cases involved multiple drug ingestion, none resulting in death.[141]

7.2.3 Hypersensitivity Reactions

Allergic vasculitis has been described in a patient 6 months after commencement of vigabatrin therapy. The patient had unilateral anterior ischaemic optic neuropathy with impairment of vision and concentric loss of visual fields. The patient recovered after vigabatrin withdrawal and corticosteroid therapy. No other cause of the vasculitis was found and the lymphocyte transformation test was positive to vigabatrin but not other anticonvulsants, suggesting a causal relationship.[203]

A case of erythema multiforme has been reported in a 38-year-old male alcoholic patient with epilepsy who also had a history of porphyria cutanea tarda. An autoimmune bullous skin disease or a relapse of porphyria cutanea tarda was thought to be unlikely, and it was concluded that vigabatrin was the cause of the erythema multiforme.[204] However, it must be noted that one-third of erythema multiforme cases are idiopathic and coincidence is a possibility.[205]

It is difficult to explain the above reactions in immunological terms as the structure of vigabatrin is similar to naturally occurring GABA and, because of its molecular simplicity, low antigenicity would be expected. Perhaps accordingly, vigabatrin has been used widely in European countries for many years and only 2 hypersensitivity cases have been reported,suggesting the rarity of such events.

8. Zonisamide

Zonisamide is a 1,2-benzisoxazole derivative which has been licensed for use as an anticonvulsant in Japan since 1989 for a variety of seizure disorders. European and American clinical trials were halted due to a high incidence of nephrolithiasis, presumably because of carbonic anhydrase inhibiting properties.[206] Although the incidence of renal stones in the US study was high (4%),[206] there were only 2 cases in 1008 patients in phase II and III studies in Japan.[207] Whether genetic and dietary factors explain this difference remains unknown.

In the Japanese clinical trials, the major adverse events were drowsiness (24%), ataxia (13%), loss of appetite (11%), gastrointestinal problems (7%) and slowing of mental activity (5%).[207] Less common adverse events such as gynaecomastia[208] (possibly

due to its effects on the dopaminergic system)[209] and drug rash have also been reported.[210]

A study of teratogenicity in 26 offspring of mothers receiving zonisamide found that 4 mothers on zonisamide monotherapy had normal offspring, whereas 2 infants whose mothers were receiving polytherapy had anencephaly and atrial septal defect, respectively.[211] In itself, the study does not conclusively prove or disprove teratogenicity although, as with most new anticonvulsant drugs, caution is advisable in its use in pregnancy. Behavioural disorders have also been reported in 2 children: a girl aged 13 months and a boy aged 35 months. Their behavioural disorders resolved after zonisamide withdrawal, which suggests a casual relationship.[212] A case of zonisamide-induced IgA and IgG2 deficiency has also been reported.[213] However, as this is an isolated case it is difficult to draw any conclusion.

9. Prevention of Adverse Drug Reactions to Anticonvulsants

The general guidelines for prevention of ADRs to anticonvulsants published by Schmidt and Kramer[159] still apply. These are:

- select the most appropriate drug for the individual patient based on consideration of the primary strength and weakness of the individual compound;
- transfer to single therapy in patients with refractory epilepsy where possible;
- avoid acute and chronic toxicity by dosage reduction;
- establish the lowest effective dosage, for that individual, by slow escalation, starting with a low dosage;
- avoid multiple drug therapy, if possible;
- increase awareness of toxicity by effective patient information.

10. Conclusions

Although a large number of case reports on adverse reactions to new anticonvulsants have been identified, few systematic studies have been conducted. There is therefore a paucity of information on the incidence of rare and serious adverse reactions.

Nevertheless, gabapentin appears to have low toxicity and so far no life-threatening ADR has been reported. Were it not for its relative lack of efficacy in seizure control, it would serve as a logical first choice adjunctive therapy for refractory partial seizures. Oxcarbazepine has a similar safety profile as carbamazepine but, as it is less likely to cause rash, it would be a useful alternative for patients who cannot tolerate carbamazepine. Although lamotrigine has been reported to cause life-threatening reactions, these have low incidences. The newly recommended lamotrigine administration schedule reduces the incidence of rash. In many situations, lamotrigine should serve as the adjunctive anticonvulsant of choice. Topiramate, tiagabine and zonisamide are relatively new anticonvulsants and should be reserved for patients who do not respond to gabapentin and lamotrigine.

Visual field constriction and psychiatric adverse reactions to vigabatrin have substantially limited the use of this drug. The possible ADRs should always be explained to patients prior to treatment. Baseline perimetry and close monitoring are essential.

Aplastic anaemia and hepatic toxicity restrict the use of felbamate. It is currently available only on a 'named patient' basis in the UK and is recommended in the US only for patients with intractable epilepsy. This drug too should only be used where absolutely necessary.

References

1. Lennox WG. Brain injury, drugs and environment as causes of mental decay in epilepsy. Am J Psychiatry 1942; 99; 174-80
2. Trimble MR, Reynolds EH. Anticonvulsant drugs and mental symptoms: a review. Psychol Med 1976; 6: 169-78
3. Wong ICK, Tavernor S, Tavernor R. Psychiatric adverse effects of anticonvulsant drugs: incidence and therapeutic implications. CNS Drugs 1997; 8 (6): 492-509
4. Parke-Davis. Neurontin [data sheet]. Eastleighs: Parke-Davis, 1998
5. Wamil AW, McLean MJ. Limitation by gabapentin of high frequency action potential firing by mouse central neurons in cell culture. Epilepsy Res 1994; 17 (1): 1-11
6. Gotz E, Feuerstein TJ, Lais A, et al. Effects of gabapentin on release of gamma-aminobutyric acid from slices of rat neostriatum. Arzneimittelforschung 1993; 43 (6): 636-8

7. Hill DR, Suman-Chauhan N, Woodruff GN. Localization of [3H]gabapentin to a novel site in rat brain: autoradiographic studies. Eur J Pharmacol 1993; 244 (3): 303-9
8. Gee NS, Brown JP, Dissanayake VU, et al. The novel anticonvulsant drug, gabapentin (Neurontin), binds to the alpha2delta subunit of a calcium channel. J Biol Chem 1996; 271 (10): 5768-76
9. Anhut H, Ashman P, Feuerstein TJ, et al. Gabapentin (Neurontin) as add-on therapy in patients with partial seizures: a double-blind, placebo-controlled study. Epilepsia 1994; 35 (40): 795-801
10. Sivenius J, Kalviainen R, Ylinen A, et al. Double-blind study of gabapentin in the treatment of partial seizures. Epilepsia 1991; 32: 539-42
11. US Gabapentin Study Group. Gabapentin as add-on therapy in refractory partial epilepsy: a double-blind, placebo-controlled, parallel-group study. Neurology 1993; 43: 2292-8
12. UK Gabapentin Study Group. Gabapentin in partial epilepsy. Lancet 1990; 335: 1114-7
13. Parke-Davis. Neurontin [product monograph]. Eastleigh: Parke-Davis, 1994
14. Chadwick DW, Anhut H, Greiner MJ, et al. A double-blind trial of gabapentin monotherapy for newly diagnosed partial seizures. International Gabapentin Monotherapy Study Group 945-77. Neurology 1998; 51 (5): 1282-8
15. Short C, Cook L. Hypomania induced by gabapentin. Br J Psychiatry 1995; 166: 679-80
16. Doherty KP, Gates JR, Penovich PE, et al. Gabapentin in a medically refractory epilepsy population: seizure response and unusual side-effects [abstract]. Epilepsia 1995; 36 Suppl. 4: 71
17. Litzinger MJ, Wiscombe N, Hanny A, et al. Increased seizures and aggression seen in persons with mental retardation and epilepsy treated with Neurontin [abstract]. Epilepsia 1995; 36 Suppl. 4: 71
18. Childers MK, Holland D. Psychomotor agitation following gabapentin use in brain injury. Brain Inj 1997; 11 (7): 537-40
19. Tallian KB, Nahata MC, Lo W, et al. Gabapentin associated with aggressive behavior in pediatric patients with seizures. Epilepsia 1996; 37 (5): 501-2
20. Lee DO, Steingard RJ, Cesena M, et al. Behavioral side effects of gabapentin in children. Epilepsia 1996; 37 (1): 87-90
21. Wolf SM, Shinnar S, Kang H, et al. Gabapentin toxicity in children manifesting as behavioral changes. Epilepsia 1995; 36 (12): 1203-5
22. Langan Y, Duncan JS, Sander JW. An audit of the perceived efficacy and tolerability of gabapentin therapy in a cohort outpatient with chronic epilepsy. Eur Neurol 1999; 41 (2): 111-3
23. Vossler DG. Exacerbation of seizures in Lennox-Gastaut syndrome by gabapentin [letter]. Neurology 1996; 46 (3): 852-3
24. Elger CE, Bauer J, Scherrmann J, et al. Aggravation of focal epileptic seizures by antiepileptic drugs. Epilepsia 1998; 39 Suppl. 3: S15-8
25. Asconape J, Diedrich A, Bellabadia J. Gabapentin associated myoclonus [abstract]. Epilepsia 1995; 45 Suppl. 4: A249-50
26. Scheyer RD, Assaf BA, Spencer SS, et al. Gabapentin related myoclonus [abstract]. Epilepsia 1996; 37 Suppl. 5: 203
27. Reeves AL, So EL, Sharbrough FW, et al. Movement disorders associated with the use of gabapentin. Epilepsia 1996; 37: 988-90
28. Perucca E, Gram L, Avanzini G, et al. Antiepileptic drugs as a cause of worsening seizures. Epilepsia 1998; 39 (1): 5-17
29. Berkovic SF. Aggravation of generalized epilepsies. Epilepsia 1998; 39 Suppl. 3: S11-4
30. Guerrini R, Belmonte A, Genton P. Antiepileptic drug-induced worsening of seizures in children. Epilepsia 1998; 39 Suppl. 3: S2-10
31. Buetefisch CM, Gutierrez A, Gutmann L. Choreoathetotic movements: a possible side effect of gabapentin. Neurology 1996; 46 (3): 851-2
32. Chudnow RS, Dewey Jr RB, Lawson CR. Choreoathetosis as a side effect of gabapentin therapy in severely neurologically impaired patients. Arch Neurol 1997; 54 (7): 910-2
33. Gould HJ. Gabapentin induced polyneuropathy. Pain 1998; 74 (2-3): 341-3
34. Wong ICK, Chadwick DW, Fenwick PBC, et al. The long-term use of gabapentin, lamotrigine and vigabatrin in patients with chronic epilepsy. Epilepsia 1999; 40 (10): 1439-45
35. Fischer JH, Barr AN, Rogers SL, et al. Lack of serious toxicity following gabapentin overdose. Neurology 1994; 44 (5): 982-3
36. Stewart BH, Kugler AR, Thompson PR, et al. A saturable transport mechanism in the intestinal absorption of gabapentin is the underlying cause of the lack of proportionality between increasing dose and drug levels in plasma. Pharm Res 1993; 10 (2): 276-81
37. Garofalo E, Koto E, Feuerstein T, et al. Experience with gabapentin overdose: five case studies [abstract]. Epilepsia 1993; 34 Suppl. 2: 157
38. White HS, Wolf HH, Swinyard ED, et al. A neuropharmacological evaluation of felbamate as a novel anticonvulsant. Epilepsia 1992; 33: 564-72
39. Leppik IE, Graves NM. Potential anti-epileptic drugs: felbamate. In: Levy R, Mattson R, Meldrum B, et al., editors. Antiepileptic drugs. New York (NY): Raven Press, 1989: 983-90
40. Pellock JM, Watermberg N. New antiepileptic drugs in children: present and future. Semin Pediatr Neurol 1997; 4: 9-18
41. Ahmad SR. Felbamate and aplastic anaemia. Lancet 1994; 344: 463
42. Schering-Plough. Taloxa [product monograph]. Kenilworth (NJ): Schering-Plough, 1995
43. Kaufman DW, Kelly JP, Anderson T, et al. Evaluation of cases reports of aplastic anaemia among patients treated with felbamate. Epilepsia 1997; 38: 1265-9
44. Pellock JM. The place of felbamate in epilepsy therapy: evaluating the risks. Drug Saf 1999; 21 (3): 225-39
45. Pellock JM. Felbamate. Epilepsia 1999; 40 Suppl. 5: S57-62
46. Brodie MJ, Pellock JM. Taming the brain storms: felbamate updated. Lancet 1995; 346: 918-9
47. Glaxo-Wellcome. Lamictal [data sheet]. Middlesex: Glaxo-Wellcome, 1998
48. Manonmani V, Wallace SJ. Epilepsy with myoclonic absences. Arch Dis Child 1994; 70 (4): 288-90
49. Ferrie CD, Robinson RO, Knott C, et al. Lamotrigine as an add-on drug in typical absence seizures. Acta Neurol Scand 1995; 91 (3): 200-2
50. Timmings PL, Richens A. Efficacy of lamotrigine as monotherapy for juvenile myoclonic epilepsy: pilot study results [abstract]. Epilepsia 1993; 34 Suppl. 2: 160
51. Leach MJ, Marden CM, Miller AA. Pharmacological studies on lamotrigine, a novel potential antiepileptic drug: II. Neurochemical studies on the mechanism of action. Epilepsia 1986; 27: 490-7
52. Cheung H, Kamp D, Harris. An in vitro investigation of the action on neuronal voltage-activated sodium channels. Epilepsy Res 1992; 13: 107-12
53. Richens A. Safety of lamotrigine. Epilepsia 1994; 35 Suppl. 5: S37-40

54. Brodie MJ, Richens A, Yuen AWC. UK Lamotrigine/Carbamazepine Monotherapy Trial Group. Double-blind comparison of lamotrigine and carbamazepine in newly diagnosed epilepsy. Lancet 1995; 345: 476-9
55. Committee on Safety of Medicines. Reminder: lamotrigine (Lamictal) and serious skin reactions. Curr Probl Pharmacovigilance 1996; 22: 12
56. Messenheimer J, Mullens EL, Giorgi L, et al. Safety review of adult clinical trial experience with lamotrigine. Drug Saf 1998; 18 (4): 281-96
57. Beran RG, Gibson RJ. Aggressive behaviour in intellectually challenged patients with epilepsy treated with lamotrigine. Epilepsia 1998; 39 (3): 280-2
58. Martin M, Munoz-Blanco JL, Lopez-Ariztegui N. Acute psychosis induced by lamotrigine [abstract]. Epilepsia 1995; 36 Suppl. 3: S118
59. Hennessy MJ, Wiles CM. Lamotrigine encephalopathy [letter]. Lancet 1995; 347: 974-5
60. Guerrini R, Dravet C, Genton P, et al. Lamotrigine and seizure aggravation in severe myoclonic epilepsy. Epilepsia 1998; 39 (5): 508-12
61. Genton P, Dravet C, Bureau M, et al. Aggravation of severe myoclonic epilepsy by lamotrigine [abstract]. Epilepsia 1997; 38 Suppl. 3: 32
62. Buckley NA, Whyte IM, Dawson AH. Self-poisoning with lamotrigine. Lancet 1993; 342: 1552-3
63. Goa KL, Ross SR, Chrisp P. Lamotrigine: a review of its pharmacological properties and clinical efficacy in epilepsy. Drugs 1993; 46 (1): 152-76
64. Messenheimer J, Ramsay RE, Willmore LJ, et al. Lamotrigine therapy for partial seizures: a multicenter, placebo-controlled, double-blind, cross-over trial. Epilepsia 1994; 35 (1): 113-21
65. Matsuo F, Bergen D, Faught E, et al. Placebo-controlled study of the efficacy and safety of lamotrigine in patients with partial seizures. Neurology 1993; 43: 2284-91
66. Yuen A. Safety issues. In: Richens A, editor. International clinical practice series. Clinical update on lamotrigine: a novel anti-epileptic agent. Kent: Wells Medical, 1992: 69-76
67. Chaffin JJ, Davis SM. Suspected lamotrigine-induced toxic epidermal necrolysis. Ann Pharmacother 1997; 31 (6): 720-3
68. Fogh K, Mai J. Toxic epidermal necrolysis after treatment with lamotrigine (Lamictal). Seizure 1997; 6 (1): 63-5
69. Page II RL, O'Neil MG, Yarbrough III DR, et al. Fatal toxic epidermal necrolysis related to lamotrigine administration. Pharmacotherapy 1998; 18 (2): 392-8
70. Sachs B, Ronnau AC, Ruzicka T, et al. Lamotrigine and toxic epidermal necrolysis [letter]. Lancet 1996; 348 (9041): 1597
71. Sullivan JR, Watson A. Lamotrigine-induced toxic epidermal necrolysis treated with intravenous cyclosporin: a discussion of pathogenesis and immunosuppressive management. Australas J Dermatol 1996; 37 (4): 208-12
72. Vukelic D, Bozinovic D, Tesovic G, et al. Lamotrigine and toxic epidermal necrolysis [letter]. Dermatology 1997; 195 (3): 307
73. Wadelius M, Karlsson T, Wadelius C, et al. Lamotrigine and toxic epidermal necrolysis [letter]. Lancet 1996; 348 (9033): 1041
74. Li LM, Russo M, O'Donoghue M, et al. Allergic skin rash associated with treatment with lamotrigine and concomitant sodium valproate: evidence for an increased risk. Arq Neuropsiquiat 1996; 54: 46-9
75. Wong ICK, Mawer GE, Sander JWAS. Factors influencing the incidence of lamotrigine-related skin rash: results of a case record survey. Ann Pharmacother 1999; 33 (10): 1037-42
76. Brodie MJ. Lamotrigine. Lancet 1992; 339: 1397-400
77. Yuen AWC, Bihari DJ. Multiorgan failure and disseminated intravascular coagulation in severe convulsive seizure [letter]. Lancet 1992; 340: 618
78. Wong ICK. Evaluation of the recently marketed anti-epileptic drugs (efficacy and adverse events) [thesis]. Manchester: University of Manchester, 1995
79. Schaub JEM, Williamson PJ, Barnes EW, et al. Multisystem adverse reaction to lamotrigine [letter]. Lancet 1994; 344: 481
80. Chattergoon DS, McGuigan MA, Koren G, et al. Multiorgan dysfunction and disseminated intravascular coagulation in children receiving lamotrigine and valproic acid. Neurology 1997; 49 (5): 1442-4
81. Wong ICK, Mawer GE, Sander JWAS. The post-marketing surveillance of gabapentin, lamotrigine and vigabatrin in patients with chronic epilepsy [abstract]. Seizure 1988; 7: 423
82. Makin AJ, Fitt S, Williams R, et al. Fulminant hepatic failure induced by lamotrigine. BMJ 1995; 311 (7000): 292
83. Nicholson R, Kelly KP, Grant IS. Leucopenia associated with lamotrigine. BMJ 1995; 310: 504
84. Haedicke C, Angrick B, Hauswaldt C. Lamotrigine versus carbamazepine in epilepsy [letter]. Lancet 1995; 345 (8960): 1302
85. Esfahani FE, Dasheiff RM. Anemia associated with lamotrigine. Neurology 1997; 49 (1): 306-7
86. Pathak P, McLachlan RS. Drug-induced pseudolymphoma secondary to lamotrigine. Neurology 1998; 50 (5): 1509-10
87. Mikati MA, Schachter SC, Schomer DL, et al. Long-term tolerability, pharmacokinetic and preliminary efficacy study of lamotrigine in patients with resistant partial seizures. Clin Neuropharmacol 1989; 12: 312-21
88. Mawer G, Richardson T, Lau C, et al. Carbamazepine toxicity provoked by concurrent treatment with lamotrigine [abstract]. Epilepsia 1993; 34 Suppl. 2: 90
89. Warner T, Patsalos PN, Prevett M, et al. Lamotrigine-induced carbamazepine toxicity: an interaction with carbamazepine 10,11-epoxide. Epilepsy Res 1992; 11: 147-50
90. Wolf P. Lamotrigine preliminary clinical observations on pharmacokinetics and interactions with traditional anti-epileptic drugs. J Epilepsy 1992; 5: 73-9
91. Besag FM, Subel B, Pool F, et al. Carbamazepine toxicity with lamotrigine: a pharmacokinetic or pharmacodynamic interaction [abstract]. Epilepsia 1994; 35 Suppl. 7: 73
92. Graves NM, Ritter FJ, Wagner ML, et al. Effect of lamotrigine on carbamazepine epoxide concentrations [abstract]. Epilepsia 1991; 32 Suppl. 3: 13
93. Pisani F, Fazio A, Arteri G, et al. Effect of lamotrigine on the pharmacokinetics of carbamazepine-10,11-epoxide [abstract]. Epilepsia 1993; 34 Suppl. 2: 159
94. Schapel GJ, Dollman W, Beran RG, et al. No effect of lamotrigine on carbamazepine and carbamazepine-epoxide concentrations [abstract]. Epilepsia 1991; 32; Suppl. 1: 58
95. Besag FM, Berry DJ, Pool F, et al. Carbamazepine toxicity with lamotrigine: pharmacokinetic or pharmacodynamic interaction? Epilepsia 1998; 39 (2): 183-7
96. Reutens DC, Duncan JS, Patsalos PN. Disabling tremor after lamotrigine with sodium valproate. Lancet 1993; 342: 185-6
97. Nulman I, Lsolo D, Koren G. Treatment of epilepsy in pregnancy. Drugs 1999; 57 (4): 535-44
98. Houtkooper MA, Lammertsma A, Meyer JW, et al. Oxcarbazepine (GP 47.680): a possible alternative to carbamazepine. Epilepsia 1987; 28: 693-8
99. Ciba-Geigy. Tolerability. In: Trileptal: a first-line antiepileptic. Basel: Ciba-Geigy, 1996: 21

100. Friis ML, Kristensen O, Boas J, et al. Therapeutic experiences with 947 epileptic out-patients on oxcarbazepine treatment. Acta Neurol Scand 1993; 87: 224-7
101. Dam M. Practical aspects of oxcarbazepine treatment. Epilepsia 1994; 35 Suppl. 3: S23-5
102. Beran RG. Cross-reactive skin eruption with both carbamazepine and oxcarbazepine. Epilepsia 1993; 34: 163-5
103. Dam M, Ekberg R, Loyning Y, et al. A double-blind study comparing oxcarbazepine and carbamazepine in patients with newly diagnosed, previously untreated epilepsy. Epilepsy Res 1989; 3: 70-6
104. Pendlebury SC, Moses DK, Eadie MJ. Hyponatremia during oxcarbazepine therapy. Hum Toxicol 1989; 8: 337-44
105. Nielsen OA, Johannessen AC, Bardrum B. Oxcarbazepine induced hyponatremia, a cross sectional study. Epilepsy Res 1988; 2: 269-71
106. Steinhoff BJ, Stoll KD, Stodieck SR, et al. Hyponatremic coma under oxcarbazepine therapy. Epilepsy Res 1992; 11: 67-70
107. Leppik IE. Tiagabine: the safety landscape. Epilepsia 1995; 36 Suppl. 6: S10-3
108. Adkins JC, Noble S. Tiagabine. Drugs 1998; 55: 437-60
109. Damgaard B, Friis S, Groes L. Long term safety of tiagabine (gabitril) [abstract]. Epilepsia 1998; 39: 5
110. Sommerville KW, Hearell M, Deaton R, et al. Adverse events with long term tiagabine therapy [abstract]. Epilepsia 1997; 38 Suppl. 8: 106
111. Sachdeo RC, Leroy RF, Krauss GL, et al. Tiagabine therapy for complex partial seizures: a dose frequency study. Arch Neurol 1997; 54: 595-601
112. Dodrill CB, Arnett JL, Sommerville KW, et al. Cognitive and quality of life effects of differing doses of tiagabine in epilepsy. Neurology 1997; 48: 1025-31
113. Sveinbjornsdottir S, Sander JWAS, Patsalos PN, et al. Neuropsychological effects of tiagabine, a potential new antiepileptic drug. Seizure 1994; 3: 29-35
114. Kalviainen R, Aikia M, Mervaala E, et al. Long term cognitive and EEG effects of tiagabine in drug resistant partial epilepsy. Epilepsy Res 1996; 25: 291-7
115. Schachter SC. Tiagabine monotherapy in the treatment of partial epilepsy. Epilepsia 1995; 36 Suppl. 6: S2-6
116. Schapel G, Chadwick D. Tiagabine and non-convulsive status epilepticus. Seizure 1996; 5: 153-6
117. Knake S, Hamer HM, Schomburg U, et al. Tiagabine-induced absence status in idiopathic generalized epilepsy. Seizure 1999 Aug; 8 (5): 314-7
118. Ettinger AB, Bernal OG, Andriola MR, et al. Two cases of non-convulsive status epilepticus in association with tiagabine therapy. Epilepsia 1999; 40 (8): 1159-62
119. Trinka E, Moroder T, Nagler M, et al. Clinical and EEG findings in complex partial status epilepticus with tiagabine. Seizure 1999 Feb; 8 (1): 41-4
120. Eckardt KM, Steinhoff BJ. Nonconvulsive status epilepticus in two patients receiving tiagabine treatment. Epilepsia 1998 Jun; 39 (6): 671-4
121. Leach JP, Stolarek I, Brodie MJ. Deliberate overdose with the novel anticonvulsant tiagabine. Seizure 1995; 4: 155-7
122. Rogawski MA, Porter RJ. Antiepileptic drugs: pharmacological mechanisms and clinical efficacy with consideration of promising developmental stage compounds. Pharmacol Rev 1990; 42: 223-86
123. Brown SD, Wolf HH, Swinyard ED, et al. The novel anticonvulsant topiramate enhances GABA-mediated chloride flux. Epilepsia 1993; 34 Suppl. 2: 122-3
124. Coulter DA, Sombati S, DeLorenzo RJ. Selective effects of topiramate on sustained repetitive firing and spontaneous bursting in cultured hippocampal neurons [abstract]. Epilepsia 1993; 34 Suppl. 2: 123
125. Reife RA. Topiramate. In: Shorvon SD, Dreifuss F, Fish DR, et al., editors. The treatment of epilepsy. Oxford: Blackwell Science, 1996: 471-81
126. Shank RP, Gardocki JF, Vaught JL. Topiramate: preclinical evaluation of a structurally novel anticonvulsant. Epilepsia 1994; 35: 450-60
127. Gilliam FG, Veloso F. Tolerability of topiramate as monotherapy in patients with recently diagnosed partial epilepsy [abstract]. Epilepsia 1998; 39 Suppl. 6: 56
128. Sharief M, Viteri C, Ben-Menachem E, et al. Double blind, placebo controlled study of topiramate in patients with refractory epilepsy. Epilepsy Res 1996; 25: 217-24
129. Ben-Menachem E, Henriksen O, Dam M, et al. Double blind, placebo controlled trial of topiramate as add-on therapy in patients with refractory partial seizures. Epilepsia 1996; 37: 539-43
130. Faught E, Wilder BJ, Ramsay RE, et al. Topiramate placebo-controlled dose-ranging trial in refractory partial epilepsy using 200, 400 and 600 mg daily doses. Neurology 1996; 46: 1684-90
131. Privitera M, Fincham R, Penry J, et al. Topiramate placebo-controlled dose-ranging trial in refractory partial epilepsy using 600, 800 and 1000mg daily dosages. Neurology 1996; 46: 1678-83
132. Janssen Cilag Ltd. Topiramate [monograph]. Cheshire: Gardiner Caldwell Communications Ltd, 1998
133. Shorvon SD. Safety of topiramate: adverse events and relationships to dosing. Epilepsia 1996; 37 Suppl. 2: S18-22
134. Edwards KR, Kamin M. The beneficial effect of slowing the initial titration rate of topiramate [abstract]. Neurology 1997; 48: A39
135. Martin R, Kuzniecky R, Ho S, et al. Cognitive effects of topiramate, gabapentin and lamotrigine in healthy young adults. Neurology 1999; 52: 321-7
136. Rosenfeld WE, Schaefer PA, Pace K. Weight loss patterns with topiramate therapy [abstract]. Epilepsia 1997; 38 Suppl. 3: 58
137. Wasserstein AG, Rak I, Reife RA. Nephrolithiasis during treatment with topiramate [abstract]. Epilepsia 1995; 36 Suppl. 3: S153
138. Wasserstein AG, Rak I, Reife RA. Investigation of the mechanistic basis for topiramate associated nephrolithiasis: examination of urinary and serum constituents [abstract]. Epilepsia 1995; 36 Suppl. 3: S153
139. Gubbay SS. The occurrence of drug induced myopia as a transient side effect of topiramate [letter]. Epilepsia 1998; 39: 451
140. Bjoro K, Gjerstad L, Bentdal O, et al. Topiramate and fulminant hepatic failure [letter]. Lancet 1998; 352: 1119
141. Hoechst Marion Roussel. Sabril [data sheet]. Middlesex: Hoechst Marion Roussel, 1996
142. Livingston JH, Beaumont D, Arzimanoglou A, et al. Vigabatrin in the treatment of epilepsy in children. Br J Clin Pharmacol 1989; 27 Suppl. 1: 109-12S
143. Dulac O, Chiron C, Luna D, et al. Vigabatrin in childhood epilepsy. J Child Neurol 1991; 6 Suppl. 2: S30-7
144. Loscher W, Horstermann D. Differential effects of vigabatrin, gamma-acetylenic GABA, aminooxyacetic acid, and valproate on levels of various amino acids in rat brain regions and plasma. Naunyn Schmiedebergs Arch Pharmacol 1994; 349 (3): 270-8

145. Waniewski RA, Martin DL. Repeated administration of gamma-Vinyl-GABA reduces rat brain glutamine synthetase activity. J Neurochem 1995; 65 (1): 355-62
146. Bernasconi R, Klein M, Martin P, et al. Gamma-vinyl GABA: comparison of neurochemical and anticonvulsant effects in mice. J Neural Transm 1988; 72 (3): 213-33
147. Jolkkonen J, Mazurkiewicz M, Lahtinen H, et al. Acute effects of gamma-vinyl GABA on the GABAergic system in rats as studied by microdialysis. Eur J Pharmacol 1992; 229 (2-3): 269-72
148. Reynolds EH. Gamma-vinyl-GABA: clinical experience in adult and adolescent patients with intractable epilepsy. Epilepsia 1992; 33 Suppl. 5: S30-5
149. Kalviainen R, Aikia M, Saukkonen AM, et al. Vigabatrin vs carbamazepine monotherapy in patients with newly diagnosed epilepsy: a randomized, controlled study. Arch Neurol 1995; 52 (10): 989-96
150. Gram L, Klosterskov P, Dam M. Gamma-vinyl-GABA: a double-blind placebo-controlled trials in partial epilepsy. Ann Neurol 1985; 17: 262-6
151. Loiseau P, Hardenberg JP, Pestre M, et al. Double-blind placebo-controlled study of vigabatrin (gamma-vinyl GABA) in drug-resistant epilepsy. Epilepsia 1986; 27: 115-20
152. Remy C, Favel P, Tell G, et al. Etude en double aveugle contre placebo en permutations croisees du vigabatrin dans I'epilepsie de I'adulte resistant a la therapeutique. Boll Lega Ital Epil 1986; 54 55: 241-3
153. Rimmer EM, Richens A. A double-blind study of gamma-vinyl-GABA in patients with refractory epilepsy. Lancet 1984; I: 189-90
154. Tartara A, Manni R, Galimberti CA, et al. Vigabatrin in the treatment of epilepsy: a double-blind placebo-controlled study. Epilepsia 1986; 27: 717-23
155. Tassinari CA, Michelucci R, Ambrosetto G, et al. Double-blind study of vigabatrin in the treatment of drug-resistant epilepsy. Arch Neurol 1987; 44: 907-10
156. Sander JWAS, Hart Y. Vigabatrin and behaviour disturbances [letter]. Lancet 1990; 335: 57
157. Thomas L, Trimble M, Bettina Schmitz, et al. Vigabatrin and behavioural disorders: a retrospective survey. Epilepsy Res 1996; 25: 21-7
158. Sander JWAS, Hart YM, Trimbles MR, et al. Vigabatrin and psychosis. J Neurol Neurosurg Psychiatry 1991; 54: 235-9
159. Schmidt D, Kramer G. The new anti-convulsant drugs: Implications for avoidance of adverse effects. Drug Saf 1994; 11: 422-31
160. Mayhew LA, Hanzel TE, Kalachnik JE, et al. Phenobarbital exacerbation of self-injurious behavior. J Nerv Ment Dis 1992; 180: 732-3
161. Kugoh T, Watanabe M, Obayashi K, et al. Two cases with epilepsy who manifested manic-depressive symptoms under barbiturates treatment. Jpn J Psychiatry Neurol 1991; 45 (2): 437-8
162. Ashton H. Guidelines for the rational use of benzodiazepines: when and what to use. Drugs 1994: 48 (1): 25-40
163. Ring HA, Reynolds EH. Vigabatrin and behaviour disturbances [letter]. Lancet 1990; 335: 970
164. Staples CI, King MA, Boyle RS. Acute psychosis after withdrawal of vigabatrin [letter]. Med J Aust 1992; 156: 291
165. Lloyd G. Psychiatry. In: Edwards CRW, Couchier RW, editors. Davidson's principles and practice of medicine. Edinburgh: Churchill Livingstone, 1991: 929-66
166. Levinson DF, Mumford JP, Devinsky O. Vigabatrin and psychosis [abstract]. Epilepsia 1995; 36 (Suppl.4): 32
167. Ring HA, Crellin R, Kirker S, et al. Vigabatrin and depression. J Neurol Neurosurg Psychiatry 1993; 56: 925-8
168. Dijkstra JB, McGuire AM, Trimble MR. The effect of vigabatrin on cognitive function mood. Hum Psychopharmacol 1992; 7 (5): 319-23
169. McGuire AM, Duncan JS, Trimble MR. Effects of vigabatrin on cognitive function and mood when used as add-on therapy in patients with intractable epilepsy. Epilepsia 1992; 33 (1): 128-34
170. Piazzini A, Vignoli A, Sgro V, et al. Effects of vigabatrin on cognitive functions [abstract]. Epilepsia 1994; 35 (Suppl.7): 67
171. Thomas L, Trimble M. Effects of vigabatrin on cognitive function and mood in healthy volunteers [abstract]. Epilepsia 1994; 35 (Suppl.7): 67
172. Grunewald RA, Jackson GD, Thompson PJ, et al. Effects of vigabatrin on cognitive function [abstract]. Epilepsia 1993; 34 (Suppl. 6): 78
173. Naumann M, Supprian T, Kornhuber J, et al. Bipolar affective psychosis after vigabatrin [letter]. Lancet 1994; 343: 606-7
174. Sastre-Garau P, Thomas P, Beaussart M, et al. Acces maniaque consecutif a une association vigabatrin-clomipramine [letter]. Encephale 1994; 20 (3): 363
175. Grant SM, Heel RC. Vigabatrin: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic potential in epilepsy and disorders of motor control. Drugs 1991; 41: 889-926
176. Aldenkamp AP, Vermeulen OG, Mulder JO, et al. Gamma-Vinyl GABA (VGB) and mood disturbances. Epilepsia 1994; 35: 999-1004
177. Wong ICK. Retrospective study of vigabatrin and psychiatric/behavioural disturbances. Epilepsy Res 1995; 21 (3): 227-30
178. Salke-Kellermann A, Baier H, Rambeck B, et al. Acute encephalopathy with vigabatrin [letter]. Lancet 1993; 342: 185
179. Sharif MK, Sander JWAS, Shorvon SD. Acute encephalopathy with vigabatrin [letter]. Lancet 1993; 342: 619
180. Ifergane G, Masalha R, Zigulinski R, et al. Acute encephalopathy associated with vigabatrin monotherapy in patients with mild renal failure. Neurology 1998; 51 (1): 314-5
181. Buti D, Rota M, Marvulli I, et al. Stato di male mioclonico in corso di trattamento con vigabatrin in un soggetto con spasmi infantili sintomatici. Boll Lega Ital Epil 1992; 79-80: 277-9
182. Marciani MG, Maschio M, Spanedda F, et al. Development of myoclonus in patients with partial epilepsy during treatment with vigabatrin: an electroencephalographic study. Acta Neurol Scand 1995; 91: 1-5
183. Lortie A, Chiron C, Mumford J, et al. The potential for increasing seizure frequency, relapse, and appearance of new seizure types with vigabatrin. Neurology 1993; 43 Suppl. 5: S24-7
184. Rogers D, Bird J, Eames P. Complex partial status after starting vigabatrin. Seizure 1993; 2: 155-6
185. Arzimanoglou A. Vigabatrin and complex partial status [letter]. Seizure 1994; 3: 79
186. Gil R, Neau JP. Rapid aggravation of aphasia by vigabatrin [letter]. J Neurol 1995; 242 (4): 251-2
187. Faedda MT, Giallonardo AT, Marchetti A, et al. Terapia con vigabatrin nelle epilessie parziali resistenti. G Neuropsicfarmacol 1993; 15: 105-8
188. Eke T, Talbot JF, Lawden MC. Severe persistent visual field constriction associated with vigabatrin. BMJ 199; 314: 180-1
189. Wilson EA, Brodie MJ. Severe persistent visual field constriction associated with vigabatrin: chronic refractory epilepsy may have role in causing these unusual lesions [letter]. BMJ 1997; 314: 1693

190. Wong ICK, Mawer GE, Sander JWAS. Reaction might be dose dependent [letter]. BMJ 1997; 314: 1693-1
191. Mackenzie R, Klistorner A. Asymptomatic as well as symptomatic defects occur with vigabatrin [letter]. BMJ 1997; 316: 232
192. Committee on Safety of Medicines. Vigabatrin (Sabril): visual field defects. Curr Probl Pharmacovig 1999; 25: 13
193. Wilton LV, Stephens MD, Mann RD. Visual field defect associated with vigabatrin: observational cohort study. BMJ 1999; 319 (7218): 1165-6
194. Versino M, Veggiotti P. Reversibility of vigabatrin-induced visual-field defect [letter]. Lancet 1999; 354 (9177): 486
195. Kalviainen R, Nousiainen I, Mantyjarvi M, et al. Vigabatrin, a gabaergic antiepileptic drug, causes concentric visual field defects. Neurology 1999; 53 (5): 922-6
196. Daneshvar H, Racette L, Coupland SG, et al Symptomatic and asymptomatic visual loss in patients taking vigabatrin. Ophthalmology 1999; 106 (9): 1792-8
197. Fisher RS, Kerrigan JF. Vigabatrin: toxicity. In: Levy RH, Mattson RH, Meldrum BS, editors. Antiepileptic drugs. New York (NY): Raven Press, 1995: 931-9
198. Gibson JP, Yarrington J, Loudy DE, et al. Chronic toxicity studies with vigabatrin, a GABA transaminase inhibitor. Toxicol Pathol 1990; 18: 225-38
199. Butler WH. The neuropathology of vigabatrin. Epilepsia 1989; 30 Suppl. 3: S15-7
200. Krauss GL, Johnson MA, Miller NR. Vigabatrin associated retinal cone system dysfunction: electroretinogram and ophthalmologic findings. Neurology 1998; 50: 614-8
201. Jongsma MJ, Laan LA, van Emde Boas W, et al. Reversible motor disturbances induced by vigabatrin [letter]. Lancet 1991; 338: 879
202. Chiron C, Dulac O, Beaumont D, et al. Therapeutic trial of vigabatrin in refractory infantile spasms. J Child Neurol 1991; 6 Suppl. 2: S52-9
203. Dieterle L, Becker EW, Berg PA, et al. Allergic vasculitis due to gamma-vinyl GABA treatment. Nervenarzt 1994; 65 (2): 122-4
204. Hommel L, Ruffieus PH, Masouye I, et al. Acute bullous skin eruption after treatment with Sabril [abstract]. Epilepsia 1995; 36 Suppl. 3: S109
205. Roujeau JC. Cutaneous reactions. In: Benichou C, editor. Adverse drug reactions: a practical guide to diagnosis and management. Chichester: Wiley, 1994: 31-56
206. Leppik IE, Willmore LJ, Homan RW, et al. Efficacy and safety of zonisamide: results of a multi-centre study. Epilepsy Res 1993; 14: 165-73
207. Yagi K, Seino M. Methodological requirements for clinical trials in refractory epilepsies: our experience with zonisamide. Prog Neuropsychopharmacol Biol Psychiatry 1992; 16: 79-85
208. Ikeda A, Hattori A, Odani A, et al. Gynaecomastia in association with phenytoin and zonisamide in a patient having a CYP2C subfamily mutation. J Neurol Neurosurg Psychiatry 1998; 65: 803-4
209. Okada M, Kaneko S, Hirano T, et al. Effects of zonisamide on dopaminergic system. Epilepsy Res 1995; 22: 193-205
210. Oommen KJ, Mathews S. Zonisamide: a new antiepileptic drug. Clin Neuropharmacol 1999; 22: 192-200
211. Kondo T, Kaneko S, Amano Y, et al. Preliminary report on teratogenic effects of zonisamide in the offspring of treated women with epilepsy. Epilepsia 1996; 37: 1242-4
212. Kimura S. Zonisamide-induced behavior disorder in two children. Epilepsia 1994; 35 (2): 403-5
213. Maeoka Y, Hara T, Dejima S, et al. IgA and IgG2 deficiency associated with zonisamide therapy: a case report. Epilepsia 1997; 38: 611-3

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