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Behavioural Effects of the New Anticonvulsants

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Contents

Abstract

Of the 9 new anticonvulsants that have been marketed recently in the UK or US, a number appear to have either adverse or beneficial effects on behaviour. There is now a considerable database of information, in terms of the number of patients treated and/or the number of published reports, on vigabatrin, lamotrigine, gabapentin and topiramate. Oxcarbazepine has been available in some centres for several years and there is extensive experience with the drug in Scandinavia. It appears that the profile of adverse and beneficial effects is similar to that of carbamazepine.

Behavioural effects have probably been greatest with vigabatrin, with psychosis, depression and other behavioural problems recorded, but the use of this drug has been limited because of the concern about visual field constriction. The cognitive and behavioural effects of topiramate have caused concern, but these may be much less of a problem if lower starting dosages and escalation rates are used. Psychosis and depression have been associated with topiramate, as they have with another carbonic anhydrase inhibiting drug, zonisamide. Although zonisamide has been used for many years in Japan and Korea, experience elsewhere with this drug is currently very limited. Gabapentin seems to be less associated with adverse behavioural effects than some of the other new anticonvulsant drugs. The

reports of behavioural disturbance with gabapentin in children may be related to dose escalation. Behavioural disturbance as a direct result of lamotrigine seems to be uncommon, although indirect effects on behaviour, through the so-called 'release phenomenon' from improved seizure control and consequent ability to misbehave, can occur.

Positive behavioural effects have been described with several of the new anticonvulsants, particularly gabapentin, lamotrigine and oxcarbazepine; all of these drugs may have mood-levelling effects that could be of value in treating affective disorders. The information on tiagabine and levetiracetam is too limited to allow any firm conclusions to be drawn with regard to positive or negative behavioural effects.

When interpreting reports of behavioural changes with anticonvulsants, it is important to avoid attributing the effect to the drug when one or more of the other multiple causes of behavioural disturbance in people with epilepsy may be responsible or when an indirect effect such as 'forced normalisation' may be the cause. Many of the published studies are retrospective and unblinded rather than double-blind, placebo-controlled, prospective trials, implying that much of the data must be interpreted with caution at this stage.

Anticonvulsant medication is the mainstay of treatment for people with epilepsy. Because the medication generally needs to be taken for long periods, there are understandable concerns about possible behavioural effects. Some of the older anticonvulsant drugs, such as phenobarbital (phenobarbitone) and primidone, were sedative in adults and caused significant behavioural problems in children. However, even with regard to phenobarbital, a drug that is notorious for causing behavioural disturbance in children, there is disagreement in the literature. For example, in the study carried out by de Silva et al.,[1] phenobarbital had to be withdrawn from the trial in children because of complaints of adverse behavioural effects. In contrast, Pal et al.[2] found no adverse behavioural effects of phenobarbital or phenytoin in a study on children in rural India.

What is the situation with the new anticonvulsant drugs? Is there unequivocal evidence indicating that they are different from the older anticonvulsant drugs? Are there differences between the new anticonvulsant drugs with regard to effects on behaviour? What strategies should be adopted to minimise any possible behavioural effects? Are there differences in tolerability if the drugs are prescribed in monotherapy rather than as add-on therapy? What are the specific problems relating to behavioural disturbance that arise when these drugs are prescribed to people with learning disability or children? The aim of this review is to examine the available evidence in order to enable recommendations to be made with regard to the prescription of the new anticonvulsant drugs, so as to allow patients the full benefit of these drugs while avoiding adverse behavioural effects.

The drugs will be discussed in turn, in the order in which they received product licences in the UK. Three drugs that do not yet have a product licence in the UK but have US Food and Drug Administration (FDA) approval will also be discussed: felbamate, zonisamide and levetiracetam.[1]

1. General Considerations Regarding Behavioural Effects of Anticonvulsant Drugs

1.1 Types of Behavioural Change

The term 'behavioural change' covers a wide range of situations. Many of the published papers do not specify the type of behavioural change. In

1 Levetiracetam was granted a product licence in the UK shortly after this paper was submitted.

this review, a systematic framework of headings has been used when discussing each of the new anticonvulsant drugs: psychosis, depression and mania, other adverse behavioural changes, beneficial behavioural changes and mechanism of action.

1.2 Measures of Behavioural Effects

It is surprising that so few studies have used validated questionnaires or other standardised measures of behaviour when assessing the effects of new anticonvulsant drugs. Although there is an increasing interest in assessing quality of life in both children and adults with epilepsy, again there are very few studies of the effects of anticonvulsant drugs that use validated quality-of-life measures.

The proper assessment of both the beneficial and adverse effects of anticonvulsant medication requires double-blind comparative trials using either placebo or another active drug as the comparator. Most of the published literature on behavioural disturbance with new anticonvulsant drugs consists of unblinded studies or individual anecdotal case reports. Even double-blind comparative trials have been criticised on the basis that only small numbers from highly selected patient groups are generally included. Extensive, long term, systematic postmarketing surveillance of the type carried out by Mackay et al.[3] would overcome some of these problems.

1.3 Causes of Behavioural Change

1.3.1 Multiple Causes of Behavioural Change in People with Epilepsy

When examining behavioural disturbance in people with epilepsy, a systematic approach must be adopted if some of the pitfalls are to be avoided.[4] There are many possible causes of behavioural disturbance in people with epilepsy, of which anticonvulsant medication is only one. It is important to exclude other causes so as avoid discontinuing anticonvulsant medication unnecessarily. McClelland[5] has classified various types of psychiatric adverse drug reactions and Wong et al.[6] have developed an algorithm for the assessment of psychiatric disturbances in people with epilepsy which places considerable emphasis on the role of adverse drug reactions.

1.3.2 Adverse Drug Interactions

It is necessary to understand not only the adverse effects of individual anticonvulsants but also the adverse effects of interactions between the drugs. These issues are of even greater importance in people with learning disability who may not have adequate expressive language (see section 1.4).[7]

1.3.3 Relationships between Behaviour and Seizures

The relationships of behaviour to the seizures and electroencephalogram (EEG) also need to be appreciated so as to avoid the trap of attributing behavioural change to a direct effect of a particular anticonvulsant drug when it may be through an effect on the seizures that could occur with other drugs. There are 2 specific mechanisms that are relevant in this context: alternative or reciprocal psychosis and post-ictal psychosis/mood change.

The concept of alternative or reciprocal psychosis has been discussed in detail by Trimble.[8] This is the clinical counterpart of 'forced normalisation'. The term 'forced normalisation' refers to the fact that the EEG may be more normal during periods of psychosis and less normal when the patient is not psychotic. Trimble, in his review, pointed out that it was in the early decades of the twentieth century that several authors noted a low frequency of seizures in people with psychosis, which led to the speculation that there might be some kind of antagonism between epilepsy and schizophrenia. This was the basis for the introduction of convulsive therapy by von Meduna. The relevance for this review is that if a drug suddenly achieves seizure control this may, in some people, precipitate a psychosis. The psychosis may incorrectly be attributed to the specific drug when it would have occurred with any drug that achieved a similar level of control.

The second issue regarding the relationship between seizures and behaviour is the concept of post-ictal psychosis. This subject has been reviewed in detail by Logsdail and Toone.[9] A schizophreniform or manic psychosis may occur after a seizure

or typically after a cluster of seizures. If a new drug worsens seizure control then a post-ictal psychosis may emerge. Again, this may be incorrectly attributed to the drug itself rather than to the seizure exacerbation. Furthermore, some of the reported studies involve discontinuing previous anticonvulsant drugs shortly before introducing the new drug. In those circumstances the seizure exacerbation and consequent post-ictal psychosis may be related entirely to the withdrawal of the previous medication and have nothing whatever to do with the introduction of the new drug.

Subtle seizure activity may also affect behaviour in a major way.[10] Transitory cognitive impairment may cause frustration and irritability. Nonconvulsive status epilepticus is liable to be misinterpreted as a psychiatric state of withdrawn, depressed or autistic behaviour rather than the direct result of the ongoing seizure activity. Some anticonvulsant drugs can precipitate nonconvulsive status epilepticus and the accompanying behavioural change. This has particularly been noted with tiagabine.[11-15] Emergence from bouts of nonconvulsive status epilepticus can, understandably, sometimes be accompanied by very difficult behaviour. This situation is similar to, although not necessarily identical to, the 'release phenomenon' described in section 1.4.

1.4 Special Situations: Children and People with Learning Disability

Assessing the cause of behavioural disturbance in people with learning disability requires additional care and skill.[4,7] The use of lamotrigine in treating epilepsy in people who have learning disability provides a good example. Besag[16] emphasised the importance of recognising classical adverse drug interactions. Diplopia or dizziness may occur when lamotrigine is added to carbamazepine.[17] In a person who is unable to express in words the fact that he or she is experiencing anxiety-provoking adverse effects, the consequence may be aggressive or disturbed behaviour. This behavioural disturbance is not a direct behavioural effect of the drug but is the result of the person attempting to communicate their distress from other adverse effects. The reaction of the physician may be to reason that because the behavioural disturbance occurred when the lamotrigine was added, the lamotrigine must be causing the problem and must be stopped. However, if the physician recognises the likelihood of such adverse effects occurring when lamotrigine is added to carbamazepine, the situation can easily be overcome simply by reducing the carbamazepine dosage slightly. The diplopia and/or dizziness resolve, removing the anxiety, and the secondary behavioural disturbance ceases.

Another situation that can occur in people who have had significant learning disability from ongoing epilepsy is the so-called 'release phenomenon'. If a sudden improvement in seizure control occurs, these patients may have an accompanying increase in ability, without the social skills to use this new-found ability to good advantage. The solution is not to stop the anticonvulsant drug that has caused the improvement in seizure control but to assist the patient to develop the necessary social skills to make good use of their new-found ability. This requires appropriate input from a skilled professional team rather than a change in the anticonvulsant medication.

Children may respond to medication in a very different way from adults. For example, as already stated, phenobarbital can cause sedation in adults but can cause overactive, excitable behaviour in children. Specific studies on the adverse effects of new anticonvulsant drugs in children are required but have seldom been performed in a well controlled, systematic, manner.

2. Vigabatrin

2.1 Psychosis

One of the earliest reports of behavioural disturbances in association with vigabatrin is that of Sander and Hart,[18] who treated 145 patients and found that the most common adverse effects were behavioural disturbances, ranging from irritability and confusion to psychosis. Seven of these patients had an episode of psychosis, which resolved in ev-

ery case. In 6 patients the psychosis resolved on withdrawal of treatment and in the seventh it resolved on halving the dosage from 4 to 2 g/day. Two of the 7 had a previous history of psychosis. Four of the 7 patients had complete control of the seizures at the time of the psychosis. The authors raised the possibility of 'forced normalisation' as a possible mechanism in these patients. They suggested that vigabatrin should be used cautiously, with close monitoring, particularly in patients with a past history of psychiatric disorder.

Sander et al.[19] subsequently reported 14 cases of psychosis in patients with severe epilepsy treated with vigabatrin. Nine of these patients had no previous history of psychosis. In 8 of the 14 patients, the psychosis occurred after a change in the pattern of seizure activity; in 4 it developed after a period of seizure freedom followed by a cluster of seizures and in the other 4 it occurred in a period of freedom from seizures as a possible 'alternative psychosis'. In the other 5 patients there was no clear relationship to seizure pattern. They also commented on a patient who developed a self-limiting psychosis after having taken an overdose of between 8 and 12g of vigabatrin. They did not include a further 3 patients who developed a psychosis after vigabatrin withdrawal. The mean dosage at onset of psychosis was 2580 mg/day. The period from initiation of therapy to the onset of psychosis was 5 days to 32 weeks. In all cases the psychosis resolved when the vigabatrin was withdrawn.

Betts and Thomas[20] provided one of the earlier reports of psychosis with vigabatrin. They described 2 patients with frank psychotic symptoms. They recommended that the dosage escalation rate should not be rapid, that dosages should be no higher than necessary and that patients, especially those with severe learning disability, should be monitored closely in the early stages of treatment.

In the first 117 patients treated by Dam,[21] 2 had frank psychotic symptoms. Thomas et al.[22] carried out a retrospective survey on vigabatrin and behaviour disorders. They identified 136 cases from clinical trials but satisfactory information was available on only 81 of these. There were 28 cases of psychosis. They compared this group with patients in their hospital who had epilepsy and psychosis but had never taken vigabatrin and with another group who had taken vigabatrin without behavioural problems. They concluded that psychosis was seen in patients with more severe epilepsy and was related to a right-sided EEG focus. 64% of these patients became seizure free. It should be noted that reviews of this type are liable to report on some cases that already appear in the literature.

Levinson and Devinsky[23] reviewed data from double-blind, placebo-control trials of vigabatrin and found those treated with the drug had a higher incidence of psychosis (2.5 *vs* 0.3%, $p = 0.028$). Psychosis was usually observed during the first 3 months of treatment. However, they commented that most studies were brief in duration, lasting only 12 to 18 weeks, implying that definite conclusions could not be reached about the timing of the psychiatric disturbance. As had been reported in other studies, psychosis was generally transient and responded to reduction or discontinuation of the vigabatrin. Treatment with antipsychotic medication was required in some cases. They concluded that vigabatrin treatment was associated with an increased occurrence of psychosis and that this responded to a reduction in vigabatrin or to the prescription of antipsychotic medication. Cockerell et al.[24] used a different approach. They collected data from the British Neurological Surveillance Unit over a period of 1 year. Their cases were defined as patients with epilepsy who developed an acute psychological disorder, whatever the cause, such as psychosis or depression. 64 cases were identified. In 12 patients the acute psychological disorder was attributed to vigabatrin. However, they pointed out that this was not a true incidence study.

Robinson et al.[25] noted psychotic type behavioural disturbances in 9 of 119 patients treated with vigabatrin for refractory epilepsy. The seizures were fully controlled in only 1 of these 9 patients. Aggression was a prominent symptom in this group and was exhibited by 6 males and 2 females. Seven of the 8 patients in this group had a history of ag-

gression and varying degrees of brain damage, but the authors emphasised that the aggressive behaviour that appeared with vigabatrin was both atypical and unexpected. They recommended that vigabatrin be used with caution in patients with aggressive traits, particularly those with organic brain damage.

In contrast, Ring and Reynolds[26] reported psychosis in only 1 of 60 patients treated with vigabatrin and in this case the symptoms only arose when the drug was inadvertently abruptly withdrawn. Brodie and McKee[27] also reported a single case of psychosis in a 38-year-old woman 48 hours after vigabatrin was discontinued.

Veggiotti et al.[28] examined the possible relationship between behavioural disturbance and a past history of learning disability or psychosis by selecting 10 patients with such a history from a total of 90 patients treated with vigabatrin. None of the 10 patients in this small study had episodes that could be interpreted as psychotic reactions. This is contrary to the impression gained by others that psychosis might be more likely to occur when people with learning disability are treated with vigabatrin.

With regard to children, Caviedes et al.[29] studied 97 children aged 6 months to 16 years with resistant epilepsy who were treated with vigabatrin or lamotrigine. In only 1 child treated with vigabatrin was treatment discontinued because of a psychotic reaction. Canovas et al.[30] reported a case of a 7-year-old boy who developed acute psychosis 3 days after starting vigabatrin. The symptoms resolved within 48 hours after stopping the drug. It was of interest to note that when vigabatrin was re-introduced 2 months later using a slower escalation rate it was well tolerated and could be continued.

2.2 Depression and Mania

In the retrospective study carried out by Thomas et al.,[22] 22 cases of depression were identified. Depression was associated with a past history of depressive illness and occurred in patients who had little or no change in seizure frequency, in contrast to the patients who developed psychosis (section 2.1), a large proportion of whom had markedly improved seizure control.

The review by Levinson and Devinsky[23] of data from double-blind, placebo-controlled trials revealed that patients treated with vigabatrin had a higher incidence of depression (12.1 *vs* 3.5% on placebo, $p < 0.001$). As was the case for psychosis, depression was usually observed during the first 3 months of treatment but, as previously stated, since most of these studies only lasted 12 to 18 weeks, no definite conclusions could be drawn with regard to the timing of the psychiatric disturbance. The depression was usually mild; serious depression, defined as the need to withdraw from vigabatrin, hospitalisation, suicide attempt or psychotic depression, occurred in only 9 cases. As for psychosis, they concluded that vigabatrin treatment was associated with an increased occurrence of depression and that this tended to respond to a reduction in vigabatrin.

Ring et al.[31] reported 10 patients who developed a major depressive episode in association with vigabatrin. The depression usually occurred early in the course of treatment or after a recent increase in dosage. The dosages varied from 1.5 to 4 g/day. As had been reported earlier in this section,[22] in contrast to psychosis, which often occurred in association with control of seizures, the depression was not necessarily associated with a decrease in seizure frequency. Most patients in this series had a history of affective disturbance, sometimes in association with other drugs that were thought to have a mechanism of action involving the γ-amino butyric acid (GABA) system.

2.3 Other Behavioural Disturbances

Dam,[21] in his review of the first 117 patients he treated, noted that 8 had behavioural disturbances other than psychosis. The behavioural changes included irritability, confusion and aggression. He commented that these behavioural disturbances were usually seen in patients with mental retardation and severe brain lesions. In

most of these cases it was not necessary to withdraw the vigabatrin.

Betts and Thomas,[20] in addition to the cases of psychosis associated with vigabatrin (section 2.1), reported that other behavioural disturbances such as irritability, confusion and aggression were noted in 8 of their patients, usually those with learning disability with severe brain lesions. The behavioural disturbances resolved when the dosage was reduced or when the drug was stopped.

Levinson and Devinsky[23] found no significant differences between the vigabatrin and placebo-treated groups for aggression reaction, manic symptoms, agitation, emotional lability, anxiety or suicide attempt in their review of data from double-blind, placebo-controlled, trials of vigabatrin.

Ferrie et al.[32] reviewed the literature on behavioural disturbance in both adults and children treated with vigabatrin. They found that the incidence was 3.4% in adults and 6% in children. Sheth et al.[33] carried out a study on 31 children and adolescents treated with vigabatrin, of whom 3 developed severe aggressive agitation. They concluded that the use of vigabatrin might be limited by unacceptable behavioural adverse effects in some patients. There appears to be strong anecdotal evidence of gross behavioural disturbance occurring in some children when vigabatrin is prescribed.[34-36] It has been suggested that this might be more likely to occur in children who have learning disability. However, there is a lack of systematic studies.

Most of the other published papers on vigabatrin and behavioural disturbance are general reviews or include only small numbers of disturbed patients.[37-46]

2.4 Beneficial Behavioural Effects of Vigabatrin

In the study by Veggiotti et al.[28] on 10 patients with learning disability and a history of psychosis there was an improvement in cognitive function in two-thirds of the patients. They were of the opinion that their data did not confirm the suggestion that vigabatrin should be avoided in patients with a history of psychiatric disturbance. Ylinen[47] found that 3 of 36 patients with learning disability and epilepsy could be discharged from institutional care during follow-up because of a positive response to vigabatrin. Provinciali et al.[48] evaluated 40 patients, equally divided between vigabatrin and placebo. They found no relevant adverse effects on cognition or behaviour in the group treated with vigabatrin. In contrast, there was a slight improvement in cognitive performance of the patients in the vigabatrin treatment group and a positive change in their overall psychological status. They concluded that their results might help to reject the hypothesis that vigabatrin may adversely affect cognitive performance and behaviour.

2.5 Mechanism

Thomas et al.[22] suggested that the emergence of psychosis with vigabatrin could be related to good control of seizures and a right-sided focus. However, these are more general issues related to epilepsy and psychosis and are not specific to the use of vigabatrin. Ring et al.[49] used a specific dopamine D_2 ligand and single photon emission tomography. They found that vigabatrin treatment for 1 month was associated with a decrease in specific binding of this ligand to D_2 receptors in the left hemisphere basal ganglia. This is consistent with the hypothesis that vigabatrin releases dopamine. They suggested that this change might provide an explanation for the development of psychosis in vulnerable patients.

2.6 Comment

Concerns about behavioural disturbance, psychosis and depression have been overtaken by the major issue of visual field constriction with vigabatrin.[50-52] Although there is some suggestion that both psychosis in teenagers/adults and behavioural disturbance in children might be more common in those who have learning disability, there is a lack of data on large numbers of patients. Current practice is to recommend vigabatrin only for the treatment of infantile spasms.[53] Although some babies with this condition may exhibit irritability, this would generally be considered as being a rea-

sonable price to pay for the control of such a devastating epilepsy syndrome. Furthermore, the drug will probably only be required for a relatively short time in these infant patients. Children and adults treated with vigabatrin should be monitored closely for behavioural disturbance. If a decision is made to use vigabatrin to treat partial seizures then it would seem wise to follow the recommendation that the dosage should be escalated slowly,[22] although there is disagreement about whether this is an important factor.[38]

3. Lamotrigine

3.1 Psychosis

There are very few published reports of psychosis attributed to lamotrigine treatment. Data on 3501 patients treated with lamotrigine in trials revealed 8 (0.2%) patients who were reported to have had psychosis, 1 of whom stopped taking lamotrigine because of this adverse event.[54] In the audit carried out by Crawford[55] in a general neurology clinic the incidence of psychotic symptoms in 270 patients taking lamotrigine was 0.7%. Martin et al.[56] reported acute psychosis induced by lamotrigine in a 44-year-old woman who was also taking carbamazepine. The psychosis resolved 16 weeks after the lamotrigine was discontinued, at which stage she had been treated with antipsychotic medication for 1 month. Polselli et al.[57] described a case of psychosis in a 34-year-old man with temporal lobe epilepsy 10 days after lamotrigine was added to carbamazepine and phenobarbitone. It should be noted, however, that lamotrigine replaced vigabatrin in this patient and psychosis resulting from vigabatrin withdrawal has been reported. Coppola and Pascotto[58] treated 37 children with epilepsy and mental delay with lamotrigine as add-on therapy in a nonblind trial. One child developed psychotic-like symptoms with extreme aggressiveness and delirium, which resolved when the lamotrigine dosage was decreased. Caviedes et al.[29] treated 97 children aged 6 months to 16 years with vigabatrin or lamotrigine. One child in each group had to discontinue treatment because of a psychotic reaction.

3.2 Depression and Mania

There appear to be no published reports of depression or mania precipitated by lamotrigine. In contrast, this drug has been used to treat depression, mania and bipolar disorder (section 3.4).

3.3 Other Behavioural Disturbances

There are relatively few reports of other types of behavioural disturbance with lamotrigine. Again, on the whole, published papers refer to improvement rather than deterioration. Ettinger et al.[59] reported on both positive and negative psychotropic effects of lamotrigine in patients with epilepsy and learning disability. Adverse behavioural effects were seen in 3 patients: a 43-year-old man with comedication consisting of phenytoin, phenobarbital, lorazepam, sertraline and thioridazine, in whom lamotrigine produced irritability, hyperactivity and poor cooperation; a 29-year-old woman whose comedication was valproic acid (sodium valproate), in whom frequent screaming, temper tantrums, increased rocking movements and hyperactivity occurred with lamotrigine; and a 29-year-old man whose comedication was valproic acid and phenytoin in whom a severe exacerbation of baseline behaviours, including self-injurious activity, temper tantrums and failure to obey simple instructions, occurred. Coppola and Pascotto[58] noted that 2 of the 37 children in their study had insomnia and/or hyperexcitation.

The largest published study suggesting that lamotrigine might have a negative effect on behaviour is that of Beran and Gibson.[60] They reported aggressive behaviour in patients with learning difficulty and epilepsy treated with lamotrigine. 19 patients, 16 men and 3 women, aged 17 to 54 years were reported in this study. Five patients discontinued lamotrigine because of 'unprovoked aggressive behaviour'. However, because of deterioration in seizure control when lamotrigine was stopped it was recommenced in 2 patients. One of the patients who became aggressive was treated with a reduced

lamotrigine dosage and in 1 other case the aggression responded to psychiatric intervention. Another patient had aggression that was said to be unrelated to lamotrigine. Four patients had behavioural problems other than aggression. Four were unchanged in behaviour and in 1 the behaviour improved. The authors concluded that the potential for behavioural disturbance justifies close observation of patients with epilepsy and learning disability treated with lamotrigine; lamotrigine should be used if necessary. This article is somewhat atypical in stating that lamotrigine was associated with a high rate of behavioural disturbance. The comments made in section 1 about indirect adverse effects, especially those relating to the release phenomenon and distress from drug interactions in people with learning disability, might, in part, account for their findings.

3.4 Beneficial Behavioural Effects

There are many reports on the beneficial effect of lamotrigine in reducing behavioural disturbance and in treating psychiatric disorder. In particular, there are several published papers reporting a positive effect on bipolar mood disorder, depression and mania.[61-66] There are also some reports suggesting that lamotrigine may be of benefit in treating schizoaffective disorder[67] and self-injurious behaviour.[68] Several papers referred to overall improvement in behaviour. In a properly controlled double-blind study, Smith et al.[69] found significant improvements in scales of mastery and happiness with lamotrigine treatment compared with placebo. Gillham et al.[70] used a standardised self-report questionnaire (SEALS). They showed that there was a significantly greater improvement in scores for patients taking lamotrigine compared with those taking carbamazepine. De Leon and Furmaga[71] suggested that lamotrigine might have a role in treating epileptic psychosis. Uvebrant and Bauziene[72] stated that the parents of 24 out 50 children with epilepsy who were treated with lamotrigine observed an improvement in mental state, including better contact, longer attention span, improved alertness and less irritability. In addition, 8 of 13 children with autistic features had a decrease of these features and 2 of 3 children with severe attention deficit hyperactivity disorder improved markedly.

In the international multicentre trial of lamotrigine in children,[73] 69% were said to have improved on global assessment, and 19% showed marked improvement. A long term follow-up study on 155 of these children and adolescents aged 2 to 19 years recorded subjective improvement for 19 patients in behaviour, alertness, seizure severity, quality of life and mobility.[74] Coppola and Pascotto,[58] in their study of the effects of add-on lamotrigine in 37 children and adolescents with epilepsy, noted improved attentiveness and mood in 2 patients. Fowler et al.[75] used Rutter behavioural scales to assess 47 children who were treated with lamotrigine. Assessments by residential care workers indicated that 13 of these children passed from the disturbed to the nondisturbed range and only 2 from the nondisturbed range to the disturbed range. Buchanan[76] reported particularly good behavioural outcomes in his nonblind trial of adjunctive lamotrigine in 34 patients, mean age 14.4 years, range 3 to 26 years, with refractory epilepsy and brain damage. 80% of the children aged 14 years or younger had an improvement of quality of life, primarily characterised by increased alertness and functional independence.

Mullens et al.,[77] in a randomised, double-blind, placebo-controlled trial of add-on lamotrigine used to treat 169 patients with Lennox-Gastaut syndrome, found significant improvements in behaviour: 30% in the lamotrigine group improved, compared with 14% in the placebo group. Jacoby et al.[78] noted significant improvements in mood and sociability in the reports from parents/carers of 130 patients with Lennox-Gastaut syndrome treated with lamotrigine. In a series of 7 patients with epilepsy and learning disability who were treated with lamotrigine, Ettinger et al.[59] found improvements in behaviour in 4. Two had less irritability and hyperactivity, 1 had less hyperactivity, less lethargy and more appropriate speech, and 1 had less lethargy and enhanced social interaction.

3.5 Mechanism

It has been suggested that the positive effect of lamotrigine on psychiatric disturbance and behaviour may occur through the reduction of abnormal glutaminergic activity. For example, Anand et al.[79] reported on the attenuation of neuropsychiatric effects of ketamine by lamotrigine in a group of 16 healthy individuals. They concluded that glutamate release-inhibiting drugs might reduce the hyperglutamatergic consequences of *N*-methyl-D-aspartate (NMDA) receptor dysfunction implicated in the pathophysiological processes of neuropsychiatric illnesses such as schizophrenia. They recommended further studies to investigate this possibility. The prediction is that such drugs would have a generally calming effect that might be beneficial in mania and schizophrenia. However, further basic scientific studies are required to determine whether this mechanism is relevant.

3.6 Comment

Although the prescription of lamotrigine may be associated with deterioration in behaviour in some patients, this might be explained through the 'release phenomenon' or through the frustration of being unable to express the distress caused by adverse drug interactions. This would account for a higher degree of behavioural disturbance seen in people with learning disability, contrasting with the reports of increases in happiness, mastery and overall well-being in people who do not have learning disability. The majority of published papers suggest that lamotrigine has a beneficial effect on behaviour rather than an adverse effect.

4. Gabapentin

4.1 Psychosis

In the audit of the use of anticonvulsants in a general neurology clinic carried out by Crawford,[55] 0.5% of 191 patients receiving gabapentin, that is 1 patient, was said to have had psychotic symptoms.

4.2 Depression and Mania

Short and Cooke[80] reported a case of hypomania associated with gabapentin treatment. Hauck and Bhaumik[81] suggested that 'alternative psychosis' might be an explanation for this episode. Leweke et al.[82] reported another case: a 35-year-old woman with epilepsy who developed a manic episode with gabapentin treatment. They stated that the seizure frequency and EEG remained unchanged, excluding the possibility of alternative psychosis as an explanation. Most of the reports of gabapentin in mood disorder have indicated that this drug may be of value in treating the disturbance rather than causing it (see section 4.4).

4.3 Other Behavioural Disturbances

Doherty et al.[83] performed a chart review of 119 adult patients taking gabapentin as adjunctive therapy for epilepsy. 15 (13%) had aggressive and/or irritable behaviour and gabapentin was stopped in 7 (6%). Of the 15 patients, 7 had a previous history of behavioural problems, 9 had an IQ below 70 and 6 had an IQ in the range 79 to 103. Morris[84] reviewed the use of gabapentin and stated that there were reports of behavioural changes in children, including hyperactivity, irritability and agitation. Holmes[85] reviewed the use of gabapentin in children and drew similar conclusions, namely that those with pre-existing behavioural disturbance were more likely to have adverse behavioural effects, such as hyperactivity or other behavioural disturbance.

Mikati et al.[86] compared 26 children with intellectual disability and 6 children without such impairment, all of whom were treated with gabapentin for refractory partial seizures in a nonblind study. The dosage range was 10 to 50 mg/kg/day, mean 26.7 mg/kg/day, as add-on medication. They found that adverse behavioural effects were more likely to occur in the children with intellectual disability and in those who were younger than 10 years of age. The adverse effects they recorded were generally mild and appeared in children who had pre-existing attention deficit disorder or

behavioural problems. It was necessary to discontinue the gabapentin in only 3 of the patients. The severity of intellectual disability did not affect the extent of the response or the occurrence of adverse effects. They concluded that children with intellectual disability who are less than 10 years of age with baseline attention deficit appeared to be at higher risk of behavioural adverse effects with gabapentin.

Khurana et al.[87] reported on 32 children with refractory partial epilepsy treated with gabapentin added to the existing medication in a nonblind study. The dosage ranged from 10 to 50 mg/kg/day. The major reported adverse effects were behavioural. These were hyperactivity, irritability and agitation, occurring in children who had baseline learning disability and attention deficit. Tallian et al.[88] found that gabapentin treatment could be associated with aggressive behaviour in children with seizures. Two children developed intolerable aggressive behaviour requiring dosage reduction or discontinuation. Lee et al.[89] reported 7 children who were taking gabapentin in addition to other anticonvulsant medication and developed behavioural adverse effects. Again, these authors emphasised that all the children had baseline attention deficit hyperactivity disorder and developmental delay. However, the adverse behavioural effects included both intensification of baseline behaviours and new behavioural problems. The most troublesome were tantrums, aggression directed towards others, hyperactivity and defiance. All the behavioural changes were reversible and were managed by dosage reduction or discontinuation.

Wolf et al.[90] reported gabapentin toxicity in children manifesting as behavioural changes in 3 children with learning disability, 1 of whom was aged 7 and the other 2 of whom were 10 years of age. These children developed severe behavioural problems while receiving modest doses of gabapentin. They became hyperactive with explosive outbursts consisting of aggression and oppositional behaviour. The adverse behavioural problems were considered to be sufficiently severe to require discontinuation of gabapentin, despite the fact that seizure control had been moderately improved. It should be noted that these reports on the behavioural effects of gabapentin in children reflected initial 'off label' prescribing which was probably in children with severe refractory epilepsy and other pre-existing problems.

Besag[91] studied 23 children and teenagers treated with gabapentin for resistant epilepsy. Most of these patients had learning disability. Results of Rutter behavioural scales were available for 14 of these patients. On the parent scores, 2 patients moved from the 'nondisturbed' to the 'disturbed' range and 1 moved from the 'disturbed' to the 'nondisturbed' range. On the teacher scales, none of the patients moved from the 'nondisturbed' to the 'disturbed' range or vice versa. A further behavioural study of these patients compared 16 patients treated with gabapentin with control participants who were matched for gender and as closely as possible for other parameters. Examination of the changes in Rutter scale scores revealed no significant differences between the gabapentin and control groups. These findings are in contrast to those already discussed, suggesting that a much closer examination of the risk factors for behavioural disturbance is necessary. Perhaps the group treated by Besag had less prominent pre-existing behavioural problems.

4.4 Beneficial Behavioural Effects

There are many reports of the use of gabapentin as a mood stabiliser or as a treatment for affective disorder.[61,92-97] These studies include patients with hypomania, mania, depression and bipolar disorder. Most of the studies are nonblind and include the use of gabapentin both as an add-on drug and as monotherapy. In addition, Maurer et al.[98] have reported on a single case of remission of pain beginning as lower abdominal pain and progressing to the whole body in a 48-year-old woman with a history of major depressive illness. Gabapentin prescribed at a dosage of 1.8 g/day resulted in a remission of both the pain and the depressive mood. Hardoy et al.[99] reported on improvement of movement disorders induced by antipsychotic medica-

tion in 14 of 16 patients. The movement disorders included blepharospasm and involuntary oromandibular movements. They suggested that gabapentin might have a use in treating tardive dyskinesia in patients who have this as an adverse effect of antipsychotic treatment. Brown and Hong[100] reported the successful treatment with gabapentin of a man with bipolar mood disorder who presented with anxiety and bruxism when treated with venlafaxine for depression. The gabapentin resolved both the anxiety and the bruxism. It is of interest to note that the majority of these studies did not involve people with epilepsy, but the paper by Harden et al.[101] reports a beneficial effect on mood in patients with partial epilepsy who were treated with gabapentin. They compared 20 patients who were treated with gabapentin and 20 who were in a control group. Their conclusion was that gabapentin treatment was associated with an improvement in mood which could not be attributed to improvement in seizure control.

The majority of the studies of gabapentin in the treatment of mood disorder are relatively small nonblind studies. There is clearly a need for properly conducted, double-blind, placebo-controlled trials. However, the results of a large number of preliminary nonblind trials of the use of gabapentin in mood disorders appear promising.

4.5 Mechanism

Because the mechanism of action of gabapentin as an anticonvulsant drug remains uncertain, it is difficult to comment on specific mechanisms of action with regard to the behavioural effects of this drug.

4.6 Comment

In contrast to vigabatrin and topiramate, for which the rates of dosage escalation and target dosages were initially too high, the starting dosages of gabapentin represent a small fraction of the target dosages that are now prescribed by some practitioners. Would more adverse behavioural effects be seen if the starting dosage was one-sixth to one-quarter of an adult target dosage of 4.8 to 6 g/day? It is interesting to note that there are reports of adverse behavioural effects in children in whom the dosage escalation rate in mg/kg/day may have been relatively high. There are no available data to answer this question and it might be argued that the potential benefits of achieving seizure control sooner rather than later would not justify using such high initial dosages. Whether the relative lack of adverse behavioural effects with gabapentin represents a better tolerated mechanism of action or whether it is a consequence of gentler dosage escalation regimens is a matter that remains open to debate.

5. Topiramate

5.1 Psychosis

Trimble et al.,[102] in their review paper on psychiatric symptoms with anticonvulsant medication, reported 18 cases of psychosis with topiramate. Although there was relatively little detail on individual cases it was interesting to note that, of the 18 patients, 2 were seizure free, 3 had an improvement in seizure control, 5 had no change in seizure frequency, 3 had more seizures and 5 had a seizure-free period followed by a cluster of seizures, suggesting that these patients had a post-ictal psychosis. Kellett et al.[103] reviewed their first year's postlicensing experience with topiramate. They carried out a retrospective case note study on 174 of the 178 patients who were prescribed topiramate over a 12-month period. The classification system they used for adverse events did not allow detailed analysis of the types of psychiatric disturbance. However, they stated that 4 patients required admission to hospital and 1 of these developed depression with psychotic features (see section 5.2). They reported no cases of psychosis without affective symptoms.

Betts et al.[104] described 12 patients who developed a formal psychiatric illness, of whom 5 had a paranoid psychosis. Little detail of the individual patients is provided but all symptoms resolved rapidly after the topiramate was stopped. Khan et al.[105] reported that the incidence of psychosis dur-

ing clinical trials of topiramate was 0.8%, which was not significantly different from the rate for placebo. They added that it was also not significantly different from reported rates of psychosis in patients with refractory epilepsy in general. They carried out a chart review of the first 80 patients who were treated with topiramate and identified 5 who developed definite psychotic symptoms 2 to 46 days after starting treatment. The dosage at symptom onset was 50 to 400 mg/day. Paranoid delusions were reported in 4 and auditory hallucinations in 3. The symptoms resolved quickly when the topiramate was stopped in 3 patients, when the dosage was reduced from 300 to 200mg a day in 1 and when the remaining patient was treated with antipsychotic medication in hospital. Three of the patients had no significant past psychiatric history, 1 had a history of auditory hallucinations and 1 had previously had aggressive and suicidal thoughts.

Crawford[55] carried out an audit of topiramate used in a general neurology clinic. She identified 94 patients who had been treated with topiramate, 48 of whom had taken part in clinical trials. The incidence of psychotic symptoms was 12%. This was significantly higher than in those who were treated with gabapentin or lamotrigine. Bittermann and Steinhoff[106] identified 2 patients with psychotic episodes in a series of 23 patients who were treated with topiramate in a nonblind prospective study. Tartara et al.[107] assessed 15 patients in a nonblind, add-on, prospective study for periods of 14 to 21 months. One patient developed psychotic symptoms.

One of the current author's teenage patients with partial epilepsy, a left temporal lobe lesion and features of Asperger syndrome developed a psychosis with topiramate. The symptoms resolved when the topiramate was stopped.

5.2 Depression and Mania

No reports of mania have been identified in the literature. Kellett et al.[103] described a patient with psychotic depression whose symptoms resolved within 2 to 3 weeks of stopping topiramate. When topiramate was re-introduced, with cautious dosage escalation to 50mg twice daily, he again had good control of the seizures but profound depression returned and the topiramate had to be stopped. As stated earlier, the classification of adverse events in this paper was rather broad and does not allow more detailed analysis of the types of behavioural disturbance that occurred in almost half the patients treated. In the series reported by Betts et al.,[104] 4 patients developed unipolar depression and 1 had a depressive illness with marked paranoid ideation while taking topiramate. They commented on the fact that the 12 patients who developed a formal psychiatric disorder accounted for 15% of those that they had treated with this drug.

5.3 Other Behavioural Disturbances

One of the patients described by Kellett et al.[103] required hospital admission because of marked cognitive/behavioural adverse effects. 85 of the 174 patients whose case notes were examined had 'cognitive/behavioural' adverse effects but the detail of these is lacking. Bittermann and Steinhoff[106] stated that aggression was an adverse effect that did not appear to be related to dosage in their study of 23 patients with partial seizures who were treated with topiramate. Fowler et al.[108] reported on 16 adolescents with epilepsy and learning disability who were assessed with Rutter Behavioural Scales before and during treatment with topiramate. There was a significant ($p < 0.05$) increase in negative reported behaviour on both the parents and teachers scales.

5.4 Beneficial Behavioural Effects

Marcotte[109] evaluated 58 consecutive patients with mood disorders refractory to previous therapies, including other new anticonvulsants. 36 (62%) showed marked or moderate improvement with topiramate, usually within days or weeks. 23 of 44 patients (52%) with bipolar affective disorders showed marked or moderate improvement. Minimal improvement or none was reported in 16. Six were rated as worse. They concluded that topiramate may be useful in the treatment of mood disorders unresponsive to other medication.

Normann et al.[110] have also commented on the benefit of topiramate in treating acute mania.

5.5 Mechanism

In view of the fact that topiramate is a highly effective anticonvulsant drug, the reports of psychosis may represent the phenomenon of alternative psychosis discussed in section 1.3.3.

Topiramate may have multiple modes of action, suggesting that it might have beneficial effects in some patients and detrimental effects in others. This is consistent with clinical experience.

5.6 Comment

The initial recommendations for topiramate treatment involved starting dosages that were too high and target dosages that were also unnecessarily high for most patients. There is currently insufficient evidence to conclude whether lower starting dosages and final target dosages would reduce the incidence of psychiatric symptoms, although there is strong evidence to suggest that cognitive slowing might be less.

6. Tiagabine

6.1 Psychosis

Leach and Brodie[111] reviewed nonblind studies in 2185 patients treated with tiagabine. They commented that the percentage of patients with symptoms suggesting psychosis in those taking tiagabine (2%) was not statistically different from that on placebo (1%). Leppik[112] and Adkins and Noble[113] also reviewed the use of tiagabine and concluded that psychosis occurred with similar frequency among patients treated with tiagabine and those treated with placebo. In the review by Trimble et al.[102] of 89 patients who developed psychiatric symptoms during treatment with topiramate, vigabatrin or tiagabine, only 3 psychoses were listed for tiagabine. There is a lack of detailed information on these patients. Because experience with this drug is still relatively limited it is too early to say whether an excess of patients with psychosis will emerge, but there appears to be little evidence for this at present.

6.2 Depression and Mania

Depressed mood is mentioned in the reviews of the use of tiagabine but the number of reported patients appears to be small. Using the Coding Symbol and Thesaurus for Adverse Event Terminology (COSTART) codes, Leppik,[112] in his review of 5 add-on, placebo-controlled trials in which 675 patients received tiagabine, found that 5% of those taking tiagabine were reported as having depression as a treatment-emergent event compared with 1% on placebo. Leach and Brodie[111] quote depressed mood as occurring in 1%. Mention is also made of depressed mood in the reviews by Kalviainen[114] and Pita-Calandre.[115] Uthman et al.,[116] in a randomised, double-blind, placebo-controlled study with a parallel-group, add-on design involving 297 patients, reported an increased incidence of depressed mood in the patients treated with tiagabine taking 16mg and 56mg daily. In contrast, Dodrill et al.[117] used quality-of-life and cognitive measures in a study with similar design in 162 patients and found no clinically important changes with tiagabine on the test batteries used. In the study of 89 patients with psychiatric symptoms treated with topiramate, vigabatrin or tiagabine, Trimble et al.[102] reported 2 patients treated with tiagabine who were said to have developed signs of affective disorders. This number was much smaller than those reported for vigabatrin and topiramate, namely 22 and 16 patients respectively but the experience with tiagabine is much shorter. It would appear that depressed mood might be precipitated by tiagabine in a small number of patients, but more extensive data are required before firm conclusions can be drawn.

6.3 Other Behavioural Disturbances

There is a lack of reports of disturbed behaviour with tiagabine. Sveinbjornsdottir et al.[118] initially carried out a nonblind trial in 22 adult patients and then followed this with a double-blind, placebo-controlled, crossover trial in 12 patients treated

with tiagabine. 11 patients completed the double-blind phase. They reported that adverse effects were transient, most commonly aggression/irritability, lethargy, headache and drowsiness. This paper suggests that transient behavioural disturbance may occur in some patients. In section 1.3.3 it was pointed out that nonconvulsive status epilepticus can lead to a variety of behavioural disturbances. There are several reports of tiagabine precipitating nonconvulsive status epilepticus,[11-15] and it is likely that this would present with adverse behavioural effects in some cases.

6.4 Beneficial Behavioural Effects

Kaufman[119] reported treatment of 3 patients with psychiatric symptoms: 2 with bipolar disorder and 1 with schizoaffective disorder of a bipolar type. All 3 patients were said to have improved during add-on treatment with low dosages of tiagabine. No untoward adverse effects were recorded. They concluded that controlled trials were indicated. This is in contrast with the findings of Grunze et al.,[120] who treated 8 patients with acute mania with tiagabine, 2 of whom were treated with monotherapy and 6 with add-on therapy to mood-stabilising drugs that had previously been inadequate in controlling the symptoms. This study was of short duration, only 14 days. Two of the patients had pronounced adverse effects: nausea and vomiting in 1 and generalised tonic-clonic seizures in the other. They concluded that tiagabine appeared to have no pronounced antimanic effect compared with standard treatment such as valproic acid, lithium or antipsychotic medication, but that rapid dosage increase for antimanic treatment could cause potentially severe adverse effects. On theoretical grounds[121] tiagabine might be expected to have antimanic effects because it potentiates GABA. Until adequate placebo-controlled trials have been performed it will not be possible to state whether this potentially beneficial effect will be evident in clinical practice.

6.5 Mechanism

There are currently insufficient data to enable any firm conclusions to be drawn about possible mechanisms of adverse behavioural effects. On theoretical grounds, the comments made earlier about the behavioural effects of drugs that may potentiate GABA would apply to tiagabine. In addition, the point made about tiagabine precipitating nonconvulsive status epilepticus will occasionally be relevant to behavioural changes with this drug.

6.6 Comment

Because the overall clinical experience with tiagabine is still limited, it would be unwise to conclude that behavioural disturbances are no more common with this drug than with placebo, although early studies suggest that this may be the case. There is some evidence for an increase in depressed mood in patients treated with tiagabine. It should also be noted that dizziness is a relatively prominent adverse effect and that this may cause great distress in people with learning disability who are unable to express themselves adequately verbally. Whether such adverse effects presenting as behavioural disturbance accounted for some of the cases of irritability and aggression remains to be determined. It is interesting to note the number of reports of nonconvulsive status epilepticus precipitated by this drug. However, it is too early too say whether this will be a significant problem in practice.

7. Oxcarbazepine

7.1 Psychosis

No cases of psychosis precipitated by oxcarbazepine were found in the literature.

7.2 Depression and Mania

Hagenah et al.[122] described a 15-year-old girl with tuberous sclerosis who developed a rapid cycling bipolar disorder with oxcarbazepine. She had tonic-clonic seizures and valproic acid was added but failed to prevent relapses of the bipolar disorder. Mood stabilisation was achieved with the addition of lithium. Tuberous sclerosis might represent a special case. Because there are anecdotal reports of young people with this condition whose

behaviour was said to have deteriorated markedly when other anticonvulsant medication was prescribed in an attempt to control seizures, no conclusions can be drawn from this single case report. More data are clearly needed.

7.3 Other Behavioural Disturbances

Behavioural disturbance does not usually appear in the list of adverse effects reported in the reviews of this drug.

7.4 Beneficial Behavioural Effects

Emrich[123] reviewed the results of double-blind multicentre trials comparing oxcarbazepine with haloperidol. The oxcarbazepine was titrated to a mean dosage of 2400 mg/day and the haloperidol 42 mg/day. Although the effect of the oxcarbazepine was said to be somewhat slower in onset, by the second week it was comparable to that of haloperidol. Haloperidol was associated with a much higher incidence of adverse effects than oxcarbazepine. In a second trial, oxcarbazepine titrated to a mean dosage of 1400 mg/day was compared with lithium titrated to a mean of 1100 mg/day. Again, the oxcarbazepine was similar in effect but the lithium tended to be better tolerated.

Emrich et al.[124] had previously used oxcarbazepine in dosages of 1800 to 2100 mg/day in 6 patients with acute mania in a double-blind placebo-controlled trial. They concluded that the effect was similar to that of valproic acid or lithium. Wildgrube[125] reported results of a 3-year randomised study of oxcarbazepine compared with lithium as prophylactic treatment in 18 patients with affective disorders in a single centre. The affective disorders included bipolar mood disorder, unipolar mania or schizoaffective psychosis. Eight patients treated with oxcarbazepine and 7 treated with lithium were evaluated. The results for the oxcarbazepine group were less favourable, both in terms of relapses and with regard to withdrawals. Grant and Faulds[126] pointed out the limitations in this study. There were a greater number of older patients and patients with a longer history of illness in the oxcarbazepine group, which showed no clear beneficial effect at an average dosage of 1000 to 1550 mg/day. In an earlier study, Müller[127] showed similar results comparing oxcarbazepine with haloperidol.

7.5 Mechanism

The mechanism of action of oxcarbazepine is almost certainly similar to that of the closely related drug carbamazepine. In the circumstances, it is not surprising that oxcarbazepine appears to have mood-levelling properties. Hyponatraemia is said to be more common with oxcarbazepine than with carbamazepine. Although the hyponatraemia is asymptomatic in most cases, it is quite clear that it can cause lethargy with resultant irritability in some cases.

7.6 Comment

Physicians who are now prescribing oxcarbazepine do so with a moderate degree of confidence, not only because of years of favourable experience in Scandinavia, but also because it is so similar to one of the most well established anticonvulsant drugs, namely carbamazepine. It seems unlikely that greater experience with this drug will reveal more potential for adverse behavioural effects, but it is unwise to be dogmatic about such predictions.

8. Felbamate

8.1 Psychosis

A few isolated reports of psychosis appear in the literature. Knable and Rickler[128] were among the first to report this as a possible adverse effect. Theodore et al.[129] carried out a double-blind, placebo-controlled parallel monotherapy trial on 40 patients; 8 of the 19 placebo-treated patients and 13 of the 21 patients treated with felbamate completed this brief study. Two of the patients receiving felbamate withdrew because of seizures and 6 because of other adverse effects, including psychosis, anxiety, sleeping difficulty, abdominal discomfort and orobuccal dyskinesias. It should be noted, however, that the titration over 4 days was rapid and that all the baseline anticonvulsant drugs had been

stopped leaving the patients free of drugs for only 5.3 ± 2.4 days before randomisation to felbamate or placebo. In these circumstances it could be argued that the adverse effects might have occurred as a result of the withdrawal of previous anticonvulsant medication rather than because of the introduction of felbamate.

McConnell et al.[130] reported 7 patients with neuropsychiatric symptoms which they attributed to felbamate. One patient receiving felbamate monotherapy had a new-onset psychosis. The other neuropsychiatric symptoms among these 7 patients included anergia, apathy, bradyphrenia and increased irritability.

8.2 Depression and Mania

Hill et al.[131] reported secondary mania associated with the use of felbamate. No other reports were identified

8.3 Other Behavioural Disturbances

Li et al.[132] carried out a nonblind, add-on study of the tolerability and efficacy of felbamate in 111 adult patients with refractory epilepsy. The mean follow-up period was 4 months (range 1 to 8 months). 23 patients (21%) discontinued felbamate because of adverse events. Behavioural disturbance occurred in 14 patients and was reported as being the most likely adverse event necessitating discontinuation. Ketter et al.[133] assessed the psychiatric effects of felbamate on 30 inpatients undergoing intensive presurgical monitoring. During early treatment, insomnia, anorexia and anxiety appeared. Longer term treatment with felbamate resulted in stimulant-like effects, with half the patients displaying psychiatric deterioration and the other half showing modest improvement compared with baseline. They suggested that baseline insomnia and anxiety might be markers for poorer psychiatric response to treatment with felbamate.

8.4 Beneficial Behavioural Effects

Gay et al.[134] examined the behavioural effects of felbamate in 20 patients aged 2 to 19 years who were taking part in a protocol for treatment of Lennox-Gastaut syndrome. Questionnaires to determine behavioural change were completed by parents when the medication had reached a constant regimen. They reported that significant improvements appeared to occur in social functioning, intellectual functioning, motor functioning, attention and concentration, alertness, initiative, variability in performance and memory. They added that there was a tendency for these effects to be reversed when felbamate was discontinued. It appears very likely that these positive effects were related to better seizure control as much as to any direct effect to the felbamate itself on mood or behaviour.

8.5 Mechanism

McConnell et al.[130] suggested that the action of felbamate through NMDA receptor antagonism and GABA potentiation might be the cause of the neuropsychiatric adverse events they reported in 7 patients. This suggested mechanism of action is consistent with that offered in other papers discussing the more general effects of anticonvulsant medication on behaviour.[121,135]

8.6 Comment

The potentially fatal adverse effects of aplastic anaemia and hepatotoxicity have overshadowed concerns about possible behavioural adverse effects of felbamate. However, the current author is among those who continue to use the drug. There is a reasonable argument for continuing to consider using felbamate for those patients who have severe disabling epilepsy and for whom other options have been exhausted.

9. Zonisamide

9.1 Psychosis

Miyamoto et al.[136] identified 14 patients with psychotic episodes among a total of 74 patients with a history of zonisamide treatment over a 10-year period. They commented that the incidence of psychotic episodes during zonisamide treatment

was several times higher than the previously reported prevalence of epilepsy-associated psychosis. They also noted that the risk of psychotic episodes appeared to be higher in young patients. In 13 of the 14 patients the psychotic episodes occurred 'within a few years' of the commencement of zonisamide. It was conceded that there was no definite proof that the zonisamide caused the psychotic episodes, but they recommended that this drug should be terminated as soon as such an episode is suspected and that it should not be restarted even if the seizure control deteriorated. They also commented that in children, obsessive-compulsive symptoms appeared to be related to psychotic episodes. The broad time scale of this study must cast some suspicion over the relationship between the psychotic episodes and the prescription of zonisamide, notwithstanding their comment that psychosis appeared to be much more common in this population than is generally observed in people with epilepsy.

Murai et al.[137] described an unusual form of psychosis in a male patient that appeared to be precipitated by zonisamide. He consistently mistook people who were new to him, such as the staff of the hospital, for people he had met a long time ago.

Matsuura and Trimble[138] reviewed 5 studies of psychosis with zonisamide: Ono et al.[139] 10 of 538 patients (1.9%), Kawasaki et al.[140] 7 cases, Matsuura et al.[141] 8 cases, Hara et al.[142] 5 cases and Mayahara et al.[143] 3 of 128 patients (2.3%). They commented that the overall frequency of psychosis, about 2%, was similar to that reported for other anticonvulsant drugs and that many of the cases may have been examples of alternative psychosis.

9.2 Depression and Mania

Charles et al.[144] provided a single report of zonisamide-induced mania. Data from 1598 patients in clinical trials,[145] not all of which were placebo-controlled, indicated that 6% in the group treated with zonisamide had depression as an adverse event, compared with 3% receiving placebo.

9.3 Other Behavioural Disturbances

Pooled trial data from the manufacturer[145] indicate that agitation/irritability was reported as an adverse event in 9% compared with 4% for placebo and nervousness in 2% compared with 1% for placebo. Kimura[146] described behavioural disorders in 2 children treated with zonisamide: a 1-year-old girl and a 3-year-old boy, neither of whom had previous developmental or psychiatric problems. They remarked that the serum zonisamide concentrations were within the reference range. Ozawa et al.[147] described a single case of behaviour disorder with gait and sleep disturbances induced by zonisamide.

9.4 Beneficial Behavioural Effects

Kanba et al.[148] examined 24 patients with psychiatric diagnoses: 15 with bipolar affective illness in the manic state, 6 with schizoaffective manic states and 3 with schizophrenic excitement. 25% of the 24 patients and 33% of patients with bipolar mania were said to have shown a remarkable global improvement with the addition of zonisamide. 71% of the total number of patients and 80% of the bipolar group had at least moderate global improvement associated with the zonisamide treatment.

9.5 Mechanism

The apparently broad anticonvulsant spectrum of zonisamide suggests that, like other carbonic anhydrase inhibitors that are used as anticonvulsant drugs, it probably has multiple modes of action.

9.6 Comment

Zonisamide has been used for many years in Japan and Korea but the experience in other countries is very limited. As with other carbonic anhydrase inhibitors, initial concern was expressed about the possibility of renal stones but this may be less of a problem than anticipated, particularly if attention is paid to adequate hydration. Because this drug appears to have a broad spectrum of action and is said to be of particular advantage in at

least some forms of myoclonic epilepsy, it is likely to be used to an increasing degree. It remains to be seen whether this additional experience will yield further evidence of both adverse and beneficial behavioural effects.

10. Levetiracetam

10.1 Psychosis

Trimble examined the records of 59 cases of psychiatric problems identified as serious treatment-emergent events from 1422 patients in clinical trials on levetiracetam (personal communication). For 10 of these cases the patients were either not on the drug at the time or insufficient data were available. Ten of the remaining 49 patients had a psychotic disorder. However, 4 of these had a previous history of psychosis. The incidence of psychosis was estimated as being 0.7%, which was favourable compared with other anticonvulsants. Data from the manufacturer[149] indicate that, in controlled trials of patients with epilepsy, 5 patients (0.7%), developed psychosis compared with 1 patient (0.2%) receiving placebo.

10.2 Depression and Mania

In the analysis carried out by Trimble (section 10.1), 25 of the 49 patients had an affective disorder (depression, suicide attempts). Of these 25 patients, 14 had a previous history of affective disorder. The estimated incidence of affective disorder was 1.8%, which was again favourable compared with other anticonvulsants. Data from the manufacturer[149] using the COSTART terms indicate that, in controlled trials on patients with epilepsy, 4 out of 769 patients (0.5%) developed depression compared with a very similar rate of 2 out of 439 patients (0.5%) on placebo.

10.3 Other Behavioural Disturbances

The COSTART term data[149] indicate that, of the 769 patients in the placebo-controlled trials, the following additional behavioural events were noted: emotional lability 2 patients, hostility 2 and nervousness 4. The respective figures for the 439 participants given placebo were: emotional lability 0 patients, hostility 1 and nervousness 2.

There is very little further information available on the behavioural effects of levetiracetam, which is the most recent anticonvulsant drug to gain FDA approval.

10.4 Beneficial Behavioural Effects

Kastleijn-Nolst Trenite et al.[150] treated 12 patients with levetiracetam and noted some reported enhancement of mood. No serious adverse effects were seen.

10.5 Mechanism

The mechanism of action of levetiracetam appears to be unlike that of other drugs and it has an unusual profile of action in animal models. It will be interesting to see whether these factors influence the behavioural effects of the drug. As a result of this different mechanism, it might have a very different behavioural profile from other anticonvulsants.

10.6 Comment

Levetiracetam is the most recent anticonvulsant drug to be approved by the FDA. As with many other new drugs, the initial promise appears to be very good. It may be successful in treating seizures that are resistant to other medication. At present, it appears to be relatively free of adverse effects apart from somnolence, but much more clinical experience will be needed before a definitive statement on adverse effects can be made.

11. Conclusions

A number of questions were raised in the introduction to this review. Some but by no means all of the answers are available in the published literature. It seems that at least 1 or 2 of the new anticonvulsant drugs are better tolerated, in terms of behavioural adverse effects, than the older drugs. Gabapentin and lamotrigine, in particular, seem to be well tolerated, notwithstanding reports of behavioural disturbance in particular circumstan-

ces. With regard to strategies that might be adopted to reduce the chance of behavioural adverse effects, it would seem wise to use slow dosage escalation rates and to avoid dosages that are higher than necessary. Will topiramate become a very well tolerated drug if these guidelines are followed? We do not yet have that information. A good knowledge of drug adverse interactions, such as the pharmacodynamic interaction when lamotrigine is added to carbamazepine, can also minimise or avoid problems. Until well-conducted double-blind comparative trials of monotherapy with appropriately slow escalation rates and avoiding excessive dosages have been completed, using well-validated behavioural measures, it will be difficult to assess the situation with certainty. Even then, since there are so many confounding factors that can affect behaviour in people with epilepsy, the outcome of such trials will have to be interpreted with a degree of caution. The situation appears promising, however, particularly in view of the fact that a number of the new anticonvulsant drugs seem to have beneficial effects on mood and behaviour in at least some patients. It will be very interesting to see what evidence the additional and much needed controlled studies will provide.

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References

1. de Silva M, MacArdle B, McGowan M, et al. Randomised comparative monotherapy trial of phenobarbitone, phenytoin, carbamazepine, or sodium valproate for newly diagnosed childhood epilepsy. Lancet 1996; 347: 709-13
2. Pal DK, Das T, Chaudhury G, et al. Randomised controlled trial to assess acceptability of phenobarbital for childhood epilepsy in rural India. Lancet 1998; 351: 19-23
3. Mackay FJ, Wilton LV, Pearce GL, et al. Safety of long-term lamotrigine in epilepsy. Epilepsia 1997; 38: 881-6
4. Besag FMC. Epilepsy, learning, and behavior in childhood. Epilepsia 1995; 36 Suppl. 1: S58-S63
5. McClelland HA. Psychiatric disorders. In: Davies DM, editor. Textbook of adverse drug reactions. Oxford: Oxford University Press, 1991: 549-77
6. Wong ICK, Tavernor SJ, Tavernor RME. Psychiatric adverse effects of anticonvulsant drugs: incidence and therapeutic implications. CNS Drugs 1997; 8: 492-509
7. Alvarez N, Besag F, Iivanainen M. Use of antiepileptic drugs in the treatment of epilepsy in people with intellectual disability. J Intell Disabil Res 1998; 42 Suppl. 1: 1-15
8. Trimble MR. Anticonvulsant-induced psychiatric disorders. The role of forced normalisation. Drug Saf 1996; 15: 159-66
9. Logsdail SJ, Toone BK. Post-ictal psychoses: a clinical and phenomenological description. Br J Psychiatry 1988; 152: 246-52
10. Besag FM. The therapeutic dilemma: treating subtle seizures or indulging in electroencephalogram cosmetics? Semin Pediatr Neurol 1995; 2: 261-8
11. Holtkamp M, Pfeiffer M, Buchheim K, et al. Tiagabine and non-convulsive status epilepticus [in German]. Nervenarzt 1999; 70: 1104-6
12. Ettinger AB, Bernal OG, Andriola MR, et al. Two cases of nonconvulsive status epilepticus in association with tiagabine therapy. Epilepsia 1999; 40: 1159-62
13. Knake S, Hamer HM, Schomburg U, et al. Tiagabine-induced absence status in idiopathic generalized epilepsy. Seizure 1999; 8: 314-7
14. Eckardt KM, Steinhoff BJ. Nonconvulsive status epilepticus in two patients receiving tiagabine treatment. Epilepsia 1998; 39: 671-4
15. Schapel G, Chadwick D. Tiagabine and non-convulsive status epilepticus. Seizure 1996; 5: 153-6
16. Besag FM. Lamotrigine in the treatment of epilepsy in people with intellectual disability. J Intell Disabil Res 1998; 42 Suppl. 1: 50-6
17. Besag FM, Berry DJ, Pool F, et al. Carbamazepine toxicity with lamotrigine: pharmacokinetic or pharmacodynamic interaction? Epilepsia 1998; 39: 183-7
18. Sander JW, Hart YM. Vigabatrin and behaviour disturbances [letter]. Lancet 1990; 335: 57
19. Sander JW, Hart YM, Trimble MR, et al. Vigabatrin and psychosis. J Neurol Neurosurg Psychiatry 1991; 54: 435-9
20. Betts T, Thomas L. Vigabatrin and behaviour disturbances. Lancet 1990; 335: 605-6
21. Dam M. Vigabatrin and behaviour disturbances [letter]. Lancet 1990; 335: 605
22. Thomas L, Trimble M, Schmitz B, et al. Vigabatrin and behaviour disorders: a retrospective survey. Epilepsy Res 1996; 25: 21-7
23. Levinson DF, Devinsky O. Psychiatric adverse events during vigabatrin therapy. Neurology 1999; 53: 1503-11
24. Cockerell OC, Moriarty J, Trimble M, et al. Acute psychological disorders in patients with epilepsy: a nationwide study. Epilepsy Res 1996; 25 (2): 119-31
25. Robinson MK, Richens A, Oxley R. Vigabatrin and behaviour disturbances [letter]. Lancet 1990; 336: 504
26. Ring HA, Reynolds EH. Vigabatrin and behavioural disturbances [letter]. Lancet 1990; 335: 970
27. Brodie MJ, McKee PJW. Vigabatrin and psychosis [letter]. Lancet 1990; 335: 1279
28. Veggiotti P, De Agostini G, Muzio C, et al. Vigabatrin use in psychotic epileptic patients: report of a prospective pilot study. Acta Neurol Scand 1999; 99: 142-6
29. Caviedes BE, Herranz JL, Arteaga R, et al. In children with refractory epilepsy: vigabatrin or lamotrigine? [in Spanish]. Revista de Neurol 1999; 28: 444-8

30. Canovas MA, Ordovas Baines JP, Beltran MM, et al. Vigabatrin-associated reversible acute psychosis in a child. Ann Pharmacother 1995; 29: 1115-7
31. Ring HA, Crellin R, Kirker S, et al. Vigabatrin and depression. J Neurol Neurosurg Psychiatry 1993; 56: 925-8
32. Ferrie CD, Robinson RO, Panayiotopoulos CP. Psychotic and severe behavioural reactions with vigabatrin: a review. Acta Neurol Scand 1996; 93: 1-8
33. Sheth RD, Buckley D, Penney S, et al. Vigabatrin in childhood epilepsy: comparable efficacy for generalized and partial seizures. Clin Neuropharmacol 1996; 19: 297-304
34. Wallace SJ. A comparative review of the adverse effects of anticonvulsants in children with epilepsy. Drug Saf 1996; 15: 378-93
35. Dulac O, Chiron C, Luna D, et al. Vigabatrin in childhood epilepsy. J Child Neurol 1991; Suppl. 2: S30-S7
36. Appleton RE. The role of vigabatrin in the management of infantile epileptic syndromes. Neurology 1993; 43: S21-S3
37. Guberman A. Vigabatrin. Can J Neurol Sci 1996; 23: S13-S7
38. Wong IC. Retrospective study of vigabatrin and psychiatric behavioural disturbances. Epilepsy Res 1995; 21: 227-30
39. Schmidt D. Behavioural abnormalities and retention rates of anti-epilepsy drugs during long-term treatment of epilepsy: a clinical perspective. Acta Neurol Scand 1995; Suppl. 162: S7-S10
40. Jawad S, Clarke E, Richens A. Vigabatrin-induced psychosis--management problems. Seizure 1994; 3: 309-10
41. Chiaretti A, Castorina M, Tortorolo L, et al. Acute psychosis and vigabatrin in childhood [in Italian]. Pediatria Med Chirurgica 1994; 16: 489-90
42. van der Zwan Jr A, van der Zwan A. Vigabatrin: results with a new antiepileptic agents in 57 patients in a general neurological practice [in Dutch]. Ned Tijdschr Geneeskd 1994; 138: 1859-63
43. Naumann M, Supprian T, Kornhuber J, et al. Bipolar affective psychosis after vigabatrin [letter]. Lancet 1994; 343: 606-7
44. Tartara A, Manni R, Galimberti CA, et al. Six-year follow-up study on the efficacy and safety of vigabatrin in patients with epilepsy. Acta Neurol Scand 1992; 86: 247-51
45. Sabers A, Gram L. Pharmacology of vigabatrin. Pharmacol Toxicol 1992; 70: 237-43
46. Staples CI, King MA, Boyle RS. Acute psychosis after withdrawal of vigabatrin [letter]. Med J Aust 1992; 156: 291
47. Ylinen A. Antiepileptic efficacy of vigabatrin in people with severe epilepsy and intellectual disability. J Intell Disabil Res 1998; 42 Suppl. 1: 46-9
48. Provinciali L, Bartolini M, Mari F, et al. Influence of vigabatrin on cognitive performances and behaviour in patients with drug-resistant epilepsy. Acta Neurol Scand 1996; 94: 12-8
49. Ring HA, Trimble MR, Costa DC, et al. Effect of vigabatrin on striatal dopamine receptors: evidence in humans for interactions of GABA and dopamine systems. J Neurol Neurosurg Psychiatry 1992; 55: 758-61
50. Eke T, Talbot JF, Lawden MC. Severe persistent visual field constriction associated with vigabatrin. BMJ 1997; 314: 180-1
51. Harding GF. Severe persistent visual field constriction associated with vigabatrin. Benefit: risk ratio must be calculated for individual patients [letter]. BMJ 1998; 316: 232-3
52. Vanhatalo S, Paakkonen L, Nousiainen I. Visual field constriction in children treated with vigabatrin. [Published erratum appears in Neurology 2000 Jan 11; 54 (1): 277]. Neurology 1999; 52: 1713-4
53. Committee on Safety of Medicines. Vigabatrin (Sabril): visual field defects. Curr Probl Pharmacovigilance 1999; 25: 13
54. Data on file, Glaxo Wellcome, 2000
55. Crawford P. An audit of topiramate use in a general neurology clinic. Seizure 1998; 7: 207-11
56. Martin M, Munnoz-Blanco JL, Lopez-Ariztegui N, et al. Acute psychosis induced by lamotrigine [abstract]. Epilepsia 1995; 36 Suppl. 3: S118
57. Polselli GM, Pennisi EM, Talamanca F, et al. Psychotic disorder after lamotrigine. Ital J Neurol Sci 1998; 19: 124-5
58. Coppola G, Pascotto A. Lamotrigine as add-on drug in children and adolescents with refractory epilepsy and mental delay: an open trial. Brain Dev 1997; 19: 398-402
59. Ettinger AB, Weisbrot DM, Saracco J, et al. Positive and negative psychotropic effects of lamotrigine in patients with epilepsy and mental retardation. Epilepsia 1998; 39: 874-7
60. Beran RG, Gibson RJ. Aggressive behaviour in intellectually challenged patients with epilepsy treated with lamotrigine. Epilepsia 1998; 39: 280-2
61. Botts SR, Raskind J. Gabapentin and lamotrigine in bipolar disorder. Am J Health Syst Pharm 1999; 56: 1939-44
62. Suppes T, Brown ES, McElroy SL, et al. Lamotrigine for the treatment of bipolar disorder: a clinical case series. J Affect Disord 1999; 53: 95-8
63. Bowden CL, Calabrese JR, McElroy SL, et al. The efficacy of lamotrigine in rapid cycling and non-rapid cycling patients with bipolar disorder. Biol Psychiatry 1999; 45: 953-8
64. Calabrese JR, Bowden CL, Sachs GS, et al. A double-blind placebo-controlled study of lamotrigine monotherapy in outpatients with bipolar I depression. Lamictal 602 Study Group. J Clin Psychiatry 1999; 60: 79-88
65. Fatemi SH, Rapport DJ, Calabrese JR, et al. Lamotrigine in rapid-cycling bipolar disorder. J Clin Psychiatry 1997; 58: 522-7
66. Kusumakar V, Yatham LN. An open study of lamotrigine in refractory bipolar depression. Psychiatry Res 1997; 72: 145-8
67. Erfurth A, Walden J, Grunze H. Lamotrigine in the treatment of schizoaffective disorder. Neuropsychobiology 1998; 38: 204-5
68. Davanzo PA, King BH. Open trial lamotrigine in the treatment of self-injurious behavior in an adolescent with profound mental retardation. J Child Adolesc Psychopharmacol 1996; 6: 273-9
69. Smith D, Baker G, Davies G, et al. Outcomes of add-on treatment with lamotrigine in partial epilepsy. Epilepsia 1993; 34: 312-22
70. Gillham R, Baker G, Thompson P, et al. Standardisation of a self-report questionnaire for use in evaluating cognitive, affective and behavioural side-effects of anti-epileptic drug treatments. Epilepsy Res 1996; 24: 47-55
71. De Leon OA, Furmaga KM. Effect of lamotrigine treatment in epileptic psychosis [letter]. J Clin Psychopharmacol 1999; 19: 186-8
72. Uvebrant P, Bauziene R. Intractable epilepsy in children. The efficacy of lamotrigine treatment, including non-seizure-related benefits. Neuropediatrics 1994; 25: 284-9
73. Besag FM, Wallace SJ, Dulac O, et al. Lamotrigine for the treatment of epilepsy in childhood. J Pediatr 1995; 127: 991-7
74. Besag FM, Dulac O, Alving J, et al. Long-term safety and efficacy of lamotrigine (Lamictal) in paediatric patients with epilepsy. Seizure 1997; 6: 51-6
75. Fowler M, Besag F, Pool F. Effects of lamotrigine on behaviour in children [abstract]. Epilepsia 1994; 35 Suppl. 7: 69
76. Buchanan N. The efficacy of lamotrigine on seizure control in 34 children, adolescents and young adults with intellectual and physical disability. Seizure 1995; 4: 233-6

77. Mullens L, Gallagher J, Manasco P. Improved neurological function accompanies effective control of the Lennox-Gastaut syndrome with Lamictal: results of a multinational, placebo-controlled trial [abstract]. Epilepsia 1996; 37: 163
78. Jacoby A, Baker G, Bryant Comstock L, et al. Lamotrigine add-on therapy is associated with improvement in mood in patients with severe epilepsy [abstract]. Epilepsia 1996; 37 Suppl. 5: 42
79. Anand A, Charney DS, Oren DA, et al. Attenuation of the neuropsychiatric effects of ketamine with lamotrigine: support for hyperglutamatergic effects of N-methyl-D-aspartate receptor antagonists. Arch Gen Psychiatry 2000; 57: 270-6
80. Short C, Cooke L. Hypomania induced by gabapentin [letter]. Br J Psychiatry 1995; 166: 679-80
81. Hauck A, Bhaumik S. Hypomania induced by gabapentin [letter]. Br J Psychiatry 1995; 167: 549
82. Leweke FM, Bauer J, Elger CE. Manic episode due to gabapentin treatment [letter]. Br J Psychiatry 1999; 175: 291
83. Doherty KP, Gates JR, Panovich PE, et al. Gabapentin in a medically refractory epilepsy population: seizure response and unusual side effects [abstract]. Epilepsia 1995; 36 Suppl. 4: 71
84. Morris GL. Gabapentin. Epilepsia 1999; 40 Suppl. 5: S63-S70
85. Holmes GL. Gabapentin for treatment of epilepsy in children. Semin Pediatr Neurol 1997; 4: 244-50
86. Mikati MA, Choueri R, Khurana DS, et al. Gabapentin in the treatment of refractory partial epilepsy in children with intellectual disability. J Intell Disabil Res 1998; 42 Suppl. 1: 57-62
87. Khurana DS, Riviello J, Helmers S, et al. Efficacy of gabapentin therapy in children with refractory partial seizures. J Pediatr 1996; 128: 829-33
88. Tallian KB, Nahata MC, Lo W, et al. Gabapentin associated with aggressive behavior in pediatric patients with seizures. Epilepsia 1996; 37: 501-2
89. Lee DO, Steingard RJ, Cesena M, et al. Behavioral side effects of gabapentin in children. Epilepsia 1996; 37: 87-90
90. Wolf SM, Shinnar S, Kang H, et al. Gabapentin toxicity in children manifesting as behavioral changes. Epilepsia 1995; 36: 1203-5
91. Besag FMC. Gabapentin use with paediatric patients. Rev Contemp Pharmacother 1996; 7: 233-8
92. Sokolski KN, Green C, Maris DE, et al. Gabapentin as an adjunct to standard mood stabilizers in outpatients with mixed bipolar symptomatology. Ann Clin Psychiatry 1999; 11: 217-22
93. Perugi G, Toni C, Ruffolo G, et al. Clinical experience using adjunctive gabapentin in treatment-resistant bipolar mixed states. Pharmacopsychiatry 1999; 32: 136-41
94. Hatzimanolis J, Lykouras L, Oulis P, et al. Gabapentin as monotherapy in the treatment of acute mania. Eur Neuropsychopharmacol 1999; 9: 257-8
95. Cabras PL, Hardoy MJ, Hardoy MC, et al. Clinical experience with gabapentin in patients with bipolar or schizoaffective disorder: results of an open-label study. J Clin Psychiatry 1999; 60: 245-8
96. Young LT, Robb JC, Hasey GM, et al. Gabapentin as an adjunctive treatment in bipolar disorder. J Affect Disord 1999; 55: 73-7
97. Erfurth A, Kammerer C, Grunze H, et al. An open label study of gabapentin in the treatment of acute mania. J Psychiatr Res 1998; 32: 261-4
98. Maurer I, Volz HP, Sauer H. Gabapentin leads to remission of somatoform pain disorder with major depression. Pharmacopsychiatry 1999; 32: 255-7
99. Hardoy MC, Hardoy MJ, Carta MG, et al. Gabapentin as a promising treatment for antipsychotic-induced movement disorders in schizoaffective and bipolar patients. J Affect Disord 1999; 54: 315-7
100. Brown ES, Hong SC. Antidepressant-induced bruxism successfully treated with gabapentin. J Am Dent Assoc 1999; 130: 1467-9
101. Harden CL, Lazar LM, Pick LH, et al. A beneficial effect on mood in partial epilepsy patients treated with gabapentin. Epilepsia 1999; 40: 1129-34
102. Trimble MR, Rusch N, Betts T, et al. Psychiatric symptoms after therapy with new antiepileptic drugs: psychopathological and seizure related variables. Seizure 2000; 9: 249-54
103. Kellett MW, Smith DF, Stockton PA, et al. Topiramate in clinical practice: first year's postlicensing experience in a specialist epilepsy clinic. J Neurol Neurosurg Psychiatry 1999; 66: 759-63
104. Betts T, Smith K, Khan G. Severe psychiatric reactions to topiramate [abstract]. Epilepsia 1995; 38: 64
105. Khan A, Faught E, Gilliam F, et al. Acute psychotic symptoms induced by topiramate. Seizure 1999; 8: 235-7
106. Bittermann HJ, Steinhoff BJ. Topiramate: an effective new anticonvulsant. An open prospective study [in German]. Nervenarzt 1997; 68: 836-8
107. Tartara A, Sartori I, Manni R, et al. Efficacy and safety of topiramate in refractory epilepsy: a long-term prospective trial. Ital J Neurol Sci 1996; 17: 429-32
108. Fowler M, Besag FMC, Strange M, et al. Effects of topiramate on behaviour in adolescents with learning disability [abstract]. Epilepsia 1997; 38: 131
109. Marcotte D. Use of topiramate, a new anti-epileptic as a mood stabilizer. J Affect Disord 1998; 50: 245-51
110. Normann C, Langosch J, Schaerer LO, et al. Treatment of acute mania with topiramate [letter]. Am J Psychiatry 1999; 156: 2014
111. Leach JP, Brodie MJ. Tiagabine. Lancet 1998; 351: 203-7
112. Leppik IE. Tiagabine: the safety landscape. Epilepsia 1995; 36 Suppl. 6: S10-S3
113. Adkins JC, Noble S. Tiagabine: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic potential in the management of epilepsy. Drugs 1998; 55: 437-60
114. Kalviainen R. Tiagabine: a new therapeutic option for people with intellectual disability and partial epilepsy. J Intell Disabil Res 1998; 42 Suppl. 1: S63-S7
115. Pita-Calandre E. Clinical implications of pharmacology and pharmacokinetics of tiagabine [in Spanish]. Rev Neurol 1999; 28: 337-9
116. Uthman BM, Rowan AJ, Ahmann PA, et al. Tiagabine for complex partial seizures: a randomized, add-on, dose-response trial. Arch Neurol 1998; 55: 56-62
117. Dodrill CB, Arnett JL, Sommerville KW, et al. Cognitive and quality of life effects of differing dosages of tiagabine in epilepsy. Neurology 1997; 48: 1025-31
118. Sveinbjornsdottir S, Sander JW, Patsalos PN, et al. Neuropsychological effects of tiagabine, a potential new antiepileptic drug. Seizure 1994; 3: 29-35
119. Kaufman KR. Adjunctive tiagabine treatment of psychiatric disorders: three cases. Ann Clin Psychiatry 1998; 10: 181-4
120. Grunze H, Erfurth A, Marcuse A, et al. Tiagabine appears not to be efficacious in the treatment of acute mania. J Clin Psychiatry 1999; 60: 759-62
121. Ketter TA, Post RM, Theodore WH. Positive and negative psychiatric effects of antiepileptic drugs in patients with seizure disorders. Neurology 1999; 53: S53-S67

122. Hagenah U, Coners H, Kotlarek F, et al. Tuberous sclerosis and organic bipolar disorder in a 15-year-old adolescent [in German]. Z Kinder Jugendpsychiatr 1999; 27: 283-9
123. Emrich HM. Studies with oxcarbazepine (Trileptal) in acute mania. Int Clin Psychopharmacol 1990; 5: 83-8
124. Emrich HM, Altmann H, Dose M, et al. Therapeutic effects of GABA-ergic drugs in affective disorders. A preliminary report. Pharmacol Biochem Behav 1983; 19: 369-72
125. Wildgrube C. Case studies of prophylactic long-term effects of oxcarbazepine in recurrent affective disorders. Int Clin Psychopharmacol 1990; 5: 89-94
126. Grant SM, Faulds D. Oxcarbazepine: a review of its pharmacology and therapeutic potential in epilepsy, trigeminal neuralgia and affective disorders. Drugs 1992; 43: 873-88
127. Müller A. Oxcarbazepine in acute mania. In: Pichot P, Berner P, Wolf R, et al., editors. Proceedings of the VII World Congress of Psychiatry. Psychiatry: the state of the art. 3. Pharmacopsychiatry. Vol. 83. New York: Plenum Press, 1983: 495-500
128. Knable MB, Rickler K. Psychosis associated with felbamate treatment [letter]. J Clin Psychopharmacol 1995; 15: 292-3
129. Theodore WH, Albert P, Stertz B, et al. Felbamate monotherapy: implications for antiepileptic drug development. Epilepsia 1995; 36: 1105-10
130. McConnell H, Snyder PJ, Duffy JD, et al. Neuropsychiatric side effects related to treatment with felbamate. J Neuropsychiatr Clin Neurosci 1996; 8 : 341-6
131. Hill RR, Stagno SJ, Tesar GE. Secondary mania associated with the use of felbamate. Psychosomatics 1995; 36: 404-6
132. Li LM, Nashef L, Moriarty J, et al. Felbamate as add-on therapy. Eur Neurol 1996; 36: 146-8
133. Ketter TA, Malow BA, Flamini R, et al. Felbamate monotherapy has stimulant-like effects in patients with epilepsy. Epilepsy Res 1996; 23: 129-37
134. Gay PE, Mecham GF, Coskey JS, et al. Behavioral effects of felbamate in childhood epileptic encephalopathy (Lennox-Gastaut syndrome). Psychol Rep 1995; 77: 1208-10
135. Bauer J, Elger CE. Anticonvulsive drug therapy. Historical and current aspects [in German]. Nervenarzt 1995; 66: 403-11
136. Miyamoto T, Kohsaka M, Koyama T. Psychotic episodes during zonisamide treatment. Seizure 2000; 9: 65-70
137. Murai T, Kubota Y, Sengoku A. Unknown people believed to be known: the 'assoziierende Erinnerungs-falschungen' by Kraepelin. Psychopathology 2000; 33: 52-4
138. Matsuura M, Trimble MR. Zonisamide and psychosis. J Epilepsy 1997; 10: 52-4
139. Ono T, Yagi K, Seino M. Clinical efficacy and safety of new antiepileptics: zonisamide [in Japanese]. Seishin-Igaku 1988; 30: 482
140. Kawasaki J, Sengoku A, Kanemoto K, et al. The occurrence of acute paranoid-hallucinatory state in epilepsy – in association with antiepileptic drugs [in Japanese]. Seishin-Igaku 1991; 33: 595-600
141. Matsuura M, Senzaki A, Okubo Y, et al. Eight epileptic patients showing delusional-hallucinatory state during zonisamide administration [in Japanese]. Seishin-Igaku 1993; 35: 413-9
142. Hara S, Imasaka Y, Takei S, et al. Five cases of zonisamide-related psychosis: with particular reference to the drug interaction between zonisamide and phenytoin and to the risk factors for epileptic psychosis [in Japanese]. Jpn J Psychiatric Ther 1993; 1993: 59-64
143. Mayahara K, Kanemoto K, Kawasaki J, et al. Zonisamide and epileptic psychosis. J Jpn Epilepsy Soc 1995; 13: 177-83
144. Charles CL, Stoesz L, Tollefson G. Zonisamide-induced mania. Psychosomatics 1990; 31 : 214-7
145. Data on file, Elan Pharmaceuticals, 2000
146. Kimura S. Zonisamide-induced behavior disorder in two children. Epilepsia 1994; 35: 403-5
147. Ozawa H, Sasaki M, Sugai K, et al. A case of behavior disorder with gait and sleep disturbances induced by zonisamide [in Japanese]. Brain Dev 1995; 27: 496-8
148. Kanba S, Yagi G, Kamijima K, et al. The first open study of zonisamide, a novel anticonvulsant, shows efficacy in mania. Prog Neuro-Psychopharmacol Biol Psychiatry 1994; 18: 707-15
149. Levetiracetam. Data on file, UCB Pharma, 2000
150. Kasteleijn-Nolst Trenite DG, Marescaux C, Stodieck S, et al. Photosensitive epilepsy: a model to study the effects of antiepileptic drugs. Evaluation of the piracetam analogue, levetiracetam. Epilepsy Res 1996 Nov; 25 (3): 225-30

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