Vigabatrin and psychosis

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Abstract

We report a series of 14 cases of psychosis occurring in patients with severe intractable epilepsy, following the prescription of vigabatrin, a new anti-epileptic drug. Nine patients had no previous history of psychosis. In eight patients the psychosis occurred following a change in the habitual pattern of seizure activity; in four it developed after a period of seizure freedom followed by a cluster of seizures, and in the other four patients an alternating psychosis was observed. In five patients there was no clear relationship to seizure pattern. Another patient developed psychosis after taking an overdose of between eight and 12 g of vigabatrin. A further three patients, who developed psychosis following vigabatrin withdrawal, were not included in this series. The mean dose at onset of the psychosis (excluding the patient who took an overdose) was 2580 mg, and the period from initiation of therapy to the onset of psychosis varied from five days to 32 weeks (and occurred 24 hours after the overdose of vigabatrin). In all cases the psychosis resolved, but necessitated the withdrawal of vigabatrin, except in the single patient who took the overdose. The mechanism of this behaviour change is unclear, but in some instances may reflect vigabatrin's powerful anti-epileptic action. This is clearly not the case for all patients. Vigabatrin should be started with caution in patients with severe epilepsy, particularly in the presence of a previous history of psychosis, and such patients should be carefully monitored.

Vigabatrin, a new anti-epileptic drug, is an irreversible inhibitor of gamma-aminobutyric acid aminotransferase (GABA-T), the main catabolic enzyme of the cerebral inhibitory neurotransmitter GABA. It leads to a rise in GABA concentrations in cerebrospinal fluid and in the brain¹⁻⁴ which is believed to be the basis of its anti-epileptic action. The efficacy of vigabatrin as a new anti-epileptic drug has been established in controlled studies and it has been shown to reduce partial and generalised tonic-clonic seizures.⁵⁻¹⁰ Vigabatrin has recently been registered in the United Kingdom for use as an anti-epileptic drug in refractory epilepsy.

The side effect profile of vigabatrin is not dissimilar to other anticonvulsants, especially in the early phases of treatment, and to date no particular long term hazards have been identified. Reversible intra-myelinic oedema has been described in early toxicity studies in experimental animals. This was seen in rodents and beagles, but has not been seen in primates or humans.¹¹⁻¹³

Behavioural changes associated with the initiation of vigabatrin therapy have been reported. Behaviour has been variously documented as being improved¹⁴ or deteriorating.¹⁵ In investigations, however, using standardised and validated rating scales, evidence for a consistent effect on affective symptoms is lacking.¹⁶

More severe behavioural problems reported, sufficient in some cases to lead to withdrawal of the drug, include severe agitation^{17,18} and psychosis.^{19,20} We report here a series of 14 cases of psychosis which occurred following the prescription of vigabatrin, some of which were noted during a clinical trial of the drug reported elsewhere.^{21,22}

Patients and methods

During the past four years, we have treated approximately 210 patients with vigabatrin (GVG), either during the course of a clinical trial of vigabatrin, or during the prescription of the drug to patients (mostly on compassionate grounds) from the specialist clinics of the National Hospitals for Neurology and Neurosurgery, including the National Hospital-Chalfont Centre for Epilepsy. We identified 14 patients who became psychotic after the prescription of the drug. None of the patients was psychotic at the time of starting vigabatrin, although five had a history of previous psychosis. Here we have documented the relevant clinical details of their epilepsy and the psychoses, and other demographic and clinical information on sex, seizure type, classification and frequency, dose of vigabatrin, IQ, past psychiatric history and concomitant medications. Psychoses were regarded as paranoid or schizophrenia-like if the patients presented with an incongruent mood, hallucinations or delusions in the setting of clear consciousness, and many of these had Schneiderian first-rank symptoms. The term "organic psychosis" was used when there was clear evidence of alteration of consciousness in association with the psychotic phenomena. No statistical methods have been applied to the data.

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Table Clinical details of patients

No	Age	Sex	Aetiology	Age of onset	Seizure classification	Neurological examination	EEG
01	39	M	Cryptog	12 yrs	B C	Ataxia	Right front-temp focus
02	22	F	Cryptog	8 yrs	D G*	Normal	Diffuse
03	21	M	Cryptog	11 yrs	B C	Normal	Bi-temp foci
04	26	F	Symptom	9 yrs	A B C	Left sided focal	Right occip pariet. focus
05	20	M	Symptom	2 yrs	D C*	Normal	Diffuse with R emphasis
06	28	F	Symptom	2 yrs	B	Normal	Bi-temp foci
07	21	F	Cryptog	3 yrs	B C	Normal	Multifocal
08	29	M	Symptom	20 yrs	D G*	Right sided focal	Slow spike and waves
09	34	M	Symptom	15 yrs	B C	Normal	Multifocal
10	31	M	Cryptog	12 yrs	B C	Normal	Bi-temp foci
11	23	F	Symptom	5 yrs	B C	Normal	Multifocal, left temp seizure recorded
12	40	M	Cryptog	6 yrs	A B C	Normal	Bi-temp foci
13	25	F	Cryptog	11 yrs	G M*	Normal	General spike and waves, right sided onset
14	32	F	Cryptog	12 yrs	B C	Normal	Bi-temp foci

Key: Seizure classification: A = simple partial seizure; B = complex partial seizure; C = secondary generalised seizures; D = atonic seizures; G = gen. tonic clonic; M = myoclonic seizures; * = atypical absences.

Results

The data from the 14 cases are shown in the table. The mean age of the patients was 28, and half were female. All patients had severe refractory epilepsy, identifiable causes being present in six. With regard to the seizure type, nine had partial seizures with secondary generalisation, one had complex partial seizures only and the four remaining cases had a generalised seizure disorder. Eleven patients had a normal neurological examination and the CT scan was normal in 11 patients.

Eight patients were on anti-epileptic drug (AED) monotherapy at the initiation of GVG, five were taking two concomitant AEDs and the remaining patient was taking three concomitant AEDs. The commonest concomitant AED was carbamazepine ($n = 11$) followed by phenytoin ($n = 5$). EEG data revealed that five patients had bilateral temporal changes, one had a right fronto-temporal focus, and one had a right occipito-parietal focus. Three patients had multifocal abnormalities in their EEG, and in one of these seizures originating in the left temporal region were recorded on telemetry. The remaining four patients had generalised abnormalities; in one, however, seizure recording showed initial ictal electrographic activity widely over the right hemisphere.

Nine patients had no previous history of psychosis, although two of these patients had a long history of behavioural disorders and one had a previous diagnosis of anorexia nervosa. Two patients had had an earlier psychotic episode when clobazam was prescribed and the remaining three patients had an earlier history of interictal psychosis not associated with seizures or drugs.

The pattern of seizures in eight of these patients was of particular interest, with four patients falling into each of two readily identifiable patterns. In the first (pattern 1), patients (3, 8, 9, and 10) became seizure free fairly soon, or virtually so, following the introduction of vigabatrin, only to develop a cluster of seizures, following which the psychosis erupted (in all

within five days and in most within 48 hours of the cluster). The clinical diagnosis in three was of a schizophrenic psychosis with auditory and visual hallucinations and religious delusions. The fourth developed a twilight state with visual hallucinations and delusions. In this pattern, in all patients the period of seizure freedom was unusually long, and some patients' notes contained comments such as "this is the longest ever free of attacks", identifying the change of pattern. In one case EEG recordings were obtained after the seizure cluster when the patient was psychotic. The record had normalised in contrast to recordings taken in the pre-treatment, pre-psychotic state (fig 1). In patients 3 and 9, the psychosis resolved on halving the dose of vigabatrin, only to recur after a period of five weeks to four months without a seizure cluster, necessitating complete withdrawal of the drug.

In the other pattern (pattern 2), the patients became seizure free, and developed the psychosis some time after the onset of the seizure remission. The time elapsing varied from ten days to six weeks. This pattern was seen in four cases (patients 6, 7, 11 and 14). Three of these patients had a schizophrenic-like psychosis, and the fourth had an organic psychosis. EEG records in two patients with pattern 2 show some evidence of forced normalisation^{23,24} (one example is shown in fig 2). This is the change from a patient's usual abnormal interictal EEG, during the non-psychotic state, to a normal or near normal EEG during the psychosis.

It is worth noting that two of these patients had had an earlier psychotic episode when their seizures were treated and remitted in a similar way. Both (patients 6 and 11) were then prescribed clobazam, although at the time patient 11 also had phenytoin toxicity. Patient 14 had a previous history of interictal psychosis not clearly related to her seizure pattern. Patients 1, 2, 4, 5 and 13 developed psychiatric disturbances after initiation of vigabatrin with no clear relation to seizure pattern. Patient 1 had a

CT	Full IQ	Concom AEDs	Past Psychiatric history	Psychiatric diagnosis	Initial therapy to episode	Pattern	Dose of GVG
Normal	80	CBZ SVP CZP	Organic psychosis	Organic psychosis	2 weeks	n/a	2.0 g
Normal	82	CBZ	Behav disturbances	Schiz like psychosis	3 weeks	n/a	2.5 g
Right temp lesion	117	CBZ DPH	Nil	Schiz like psychosis	12 weeks	Type 1	4.0 g
Normal	87	CBZ	Nil	Schiz like psychosis	6 weeks	n/a	2.0 g
Normal	61	CBZ	Behav disturbances	Paranoid state	3 weeks	n/a	3.0 g
Normal	93	CBZ	Similar episode on COZ	Schiz like psychosis	4 weeks	Type 2	3.0 g
Normal	92	DPH	Anorexia nervosa	Organic psychosis	2 weeks	Type 2	2.0 g
Normal	96	CBZ	Nil	Schiz like psychosis	5 weeks	Type 1	3.0 g
		DPH					
Normal	118	DPH PRM	Nil	Schiz-manic	32 weeks	Type 1	4.0 g
Normal	122	CBZ DPH	Nil	Twilight state/Org psychosis	5 weeks	Type 1	4.0 g
Occip lesion	80	CBZ	Similar episode on COZ	Schiz like psychosis	4 weeks	Type 2	1.5 g
Normal	94	CBZ SVP	Nil	Organic psychosis	1 day after GVG overdose	n/a	?8–12 g
Normal	87	CBZ	Psychosis	Schiz like psychosis	5 days	n/a	0.5 g
Mild atrophy	88	PRM	Schiz like psychosis	Schiz like psychosis	6 weeks	Type 2	2.0 g

Anti-Epileptic Drugs (AEDs): CBZ = carbamazepine; COZ = clobazam; CZP = clonazepam; DPH = phenytoin; GVG = vigabatrin; PRM = primidone; SVP = sodium valproate.

previous history of recurrent psychosis, and developed a florid organic psychosis two weeks after the start of vigabatrin. Patient 2 developed an organic psychosis after starting vigabatrin. She had ceased to have generalised attacks, although atypical absences continued unabated at an increased rate. She had diffuse abnormality on EEG. Patient 4 developed psychotic symptoms after being seizure free for 17 days, six weeks after starting the drug, but had had previous episodes in which she had been seizure free for up to three months without psychiatric disorder. She had, however, been having almost daily seizures in the period immediately before starting vigabatrin. Patient 5 developed a paranoid state three weeks after starting vigabatrin. His seizure pattern was unchanged. Patient 13 became psychotic five days after starting vigabatrin, during which time she had continued to have atypical absences.

Patient 12 developed a psychotic episode lasting 36 hours after having taken an overdose of between eight and 12 g of vigabatrin during post-ictal confusion. The mean dose of vigabatrin at the onset of psychosis was 2500 mg (excluding patient 12) with a range of 500 mg to 4000 mg. All patients made a full recovery, and in all but one patient (patient 12) vigabatrin has now been stopped. Three patients (1, 6 and 14) required neuroleptic drugs.

We have also noted the development of psychosis within days of the withdrawal of vigabatrin in a further three of our patients not documented above; two of these patients were admitted to hospitals other than our own.

Discussion

It is well recognised that patients with chronic epilepsy may present with interictal psychosis or episodic psychosis related to drug therapy. Nevertheless, since the advent of GVG, we have noted an increased incidence of such cases, to an extent which is not associated with any of the major anti-epileptic drugs nor other drugs on clinical trial in our unit. We report

here 14 patients who developed a psychosis after starting vigabatrin. Although isolated cases of psychosis have been noted as a possible side effect of this drug in clinical trials^{19,20} to date there has been no attempt at documenting such cases from the clinical and EEG viewpoint.

Psychosis in these patients in association with GVG has followed a cluster of seizures (post-ictal psychosis—pattern 1), a period of seizure freedom (alternating psychosis—pattern 2), withdrawal of anti-epileptic drugs, drug overdose, or in some cases occurred independently of all these factors.

In pattern 1 (4 cases), patients had suppression of their seizures following drug initiation, and then suddenly had a burst or cluster of seizures (representing a change in pattern) which was followed by the psychosis. Psychotic episodes were short lasting, and resolved with reduction or withdrawal of the vigabatrin. In the two patients who had the dose reduced, however, there was a subsequent recurrence of the psychosis (without a seizure cluster), necessitating the complete withdrawal of the drug. In pattern 2 (4 cases), an alternating psychosis occurred with EEG evidence in two (patients 6 and 14) of forced normalisation (fig 2). The remaining six cases did not fit clearly into either of these two patterns. Two of these patients had had a previous history of psychosis, however, and a third developed psychosis after an overdose of vigabatrin. In addition to these 14 cases, three further patients were seen who developed psychosis on withdrawal of vigabatrin.

The literature on post-ictal psychosis is limited, and such states, while being common in practice, are not well documented. In the largest series, that of Levin,²⁵ clinical features similar to our cases in pattern 1 were noted, and it was reported that the onset could be up to seven days after the seizures. Two or more attacks usually preceded the psychosis. In the more recent series of Logsdale and Toone,²⁶ clusters were again a frequent herald to the psychosis, and there was often a lucid interval of several (up to six) days before the psychosis appeared.

Figure 1 showing EEG recordings of patient 9 (A, interictal, before vigabatrin, B, during the psychotic episode), demonstrating the marked improvement in the EEG during the psychotic phase.

The second pattern is also well recorded in the literature. Of interest in our series is that in two cases the EEG showed marked improvement during the psychotic phase compared with previous EEGs. Landolt^{23,24} coined the phrase "forced normalisation" when he reported a group of patients who developed psychosis with epilepsy, and noted that during these episodes, seizures abated and pathological EEGs normalised. He pointed out that

such attacks could last several weeks, and they could be provoked by anticonvulsant therapies. Further, the psychoses could be relieved by ECT, or a spontaneous seizure, and the EEG would revert to its previous abnormal state. Although the term forced normalisation may not have been well chosen, similar events have now been well documented.²⁷ In many settings, confirmation of the EEG changes is not possible, and Tellenbach²⁸ introduced the term alternating psychosis as a clinical expression of the alternation between seizures or psychosis as seen in these cases. In his earlier work Landolt tended to emphasise a relationship to temporal lobe epilepsy and partial seizures, although he later noted cases in association with generalised seizure disorders.

The possibility that anticonvulsant drugs played a role in the development of these states was earlier raised by Gibbs²⁹ in trials with phenacetylurea (phenurone), and in Landolt's studies, particular attention was drawn to the succinimides. Wolf^{27,30} has reinforced this suggestion, noting especially a link between generalised seizures, alternating psychoses and ethosuximide. In his studies valproic acid was not associated in the same way, although other authors have described cases of forced normalisation on this anticonvulsant.³¹ Wolf speculates that disturbed sleep is an early manifestation of the ethosuximide induced alternating psychosis, this drug sometimes provoking arousal.^{27,30} It is of interest that of the anticonvulsants tested using Critical Flicker Fusion (CFF), a measure of cortical arousal, all decrease values, with the exception of vigabatrin,³² and clobazam.³³ It is the more remarkable therefore that two of our cases had previous episodes of alternating psychosis while on clobazam with similar clinical features. Although the influence of ethosuximide on CFF is untested, these ideas are in keeping with the views of Wolf.

The relationship between GABA and psychosis is unclear. At first sight a GABA agonist may be expected to be antipsychotic. GABA levels in schizophrenic brain material and in CSF are probably normal,^{34,35} and theoretically a GABA agonist should antagonise dopamine release. Certainly the acute rise in CSF homovanillic acid (HVA) noted on treatment with vigabatrin is similar to that seen with typical neuroleptics.³ In contrast, the known GABA pathways from limbic forebrain areas such as the nucleus accumbens to ventral pallidum and the ventral tegmental area suggest possible associations between vigabatrin, GABA and anatomical pathways thought to be involved in the pathogenesis of the psychoses.³⁶ Further work in this area is urgently required.

Vigabatrin is a potent anti-epileptic drug, and in our experience^{21,22} and that of others,⁵⁻¹⁰ has been highly effective in controlling seizures in some patients. All our patients had severe epilepsy and had been prescribed vigabatrin only after conventional anti-epileptic treatment had failed. The role of vigabatrin in the development of psychosis in these patients may be due to a number of factors. In the cases exhibiting patterns 1 and 2, the psychosis may

Figure 2 showing EEG recordings of patient 6 (A, before vigabatrin, B, during the psychotic episode), shows features similar to that of figure 1.

result from an alteration in seizure activity. Furthermore, it is common clinical experience that epileptic psychosis is more frequent in patients with severe epilepsy; all patients in this series had a severe and intractable seizure disorder and over one third had a previous history of psychosis. Whatever the mechanism of the psychosis, and the relationship between this and the prescription of vigabatrin, we would urge caution when starting vigabatrin, particularly in patients with a previous history of psychosis or with severe chronic epilepsy. Other behaviour disturbances were also seen in some of our patients, including agitation, confusion, hyperactivity, stupor and depression and certainly in our series and others, behaviour changes were the most common important side effect of this anti-epileptic drug.

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in the book leading to unnecessary complexity which in my view interrupts the flow when reading. Overall Professor Al-Mefty has achieved his aim of embodying the progress which has occurred in the fifty years since Cushing and Eisenhardt published their monograph on meningiomas.

MDM SHAW

Essentials of Neuroimaging. By J R KIRKWOOD. (Pp 497; Illustrated. Price £65.00). Edinburgh, Churchill Livingstone, 1990. ISBN 0443-08479-3.

This book is an attempt to provide an overview of Neuroimaging and its role in clinical management for trainees in Neuroradiology, Neurology and Neurosurgery. There are twelve chapters devoted to intracranial pathology, including trauma, and two to the spine.

The first chapter, dealing with techniques and anatomy, is disappointing. Twenty-eight pages are devoted to a detailed description of arterial and venous anatomy, eight to Magnetic Resonance, and only half a page to Computed Tomography, which is dismissed erroneously as "based on the same principles as all radiography". Radionuclide scanning and Doppler Ultrasound appear briefly in a separate section on cerebrovascular disease. No mention is made of the merits of digital acquisition of data.

The clinical approach in succeeding chapters is better balanced, both in regard to clinical topics and radiological investigations. The role of each imaging method is discussed and emphasis placed on conditions of clinical importance. Revision lists are provided in strategically placed boxed inserts throughout. The method works well in the sections dealing with intracranial disorders, less well in the spine where insufficient stress is placed on the increasing importance of Magnetic Resonance. The illustrations, which are numerous, well chosen and generally of good quality, are the chief strength of this book and make it worthy of study.

Here is a brave effort to cover a very wide range of clinical activity. It inevitably lacks depth and unfortunately the imaging techniques themselves are disappointingly presented.

I ISHERWOOD

Tremor By RJ ELBLE AND WC KOLLER. (Pp 204; Price: \$39.50). Baltimore, The Johns Hopkins University Press. 1991. ISBN 0-8018-4024-4

Despite its high population prevalence, in publishing terms tremor has always been the poor relation to Parkinson's disease. Thus, other than the multi-author book edited by Findley and Capildeo in 1984, I am not aware of any other volumes devoted to the subject. Thus "duograph" by Elble and Koller admirably fills the gap. It is one of that select band of neurology books that is actually produced with the reader in mind. Thus, it is not too big, not too heavy and not too long, and divided into bite-sized chapters that can even be tackled in a standing position on the Northern Line. The book itself is well produced and printed and, miraculously for a first edition, I could detect only one typographical error in the text itself. The list of 786 references is at the end of the book, and each chapter ends with a summary. This latter feature is particularly useful for innumerate like myself who might balk at the sight of seemingly complex equations in the chapter on measurement of tremor.

The authors tell us clearly and concisely not only what we do know about tremor but also, just as importantly, expose considerable areas of uncertainty. Thus, after reading both sides of the arguments, we learn how many of the questions concerning the whereabouts of tremor generators, the significance of alternating versus co-contracting EMG patterns, and the capacity of peripheral perturbations to reset certain tremors, are still open and undecided. To take another example, where does enhanced physiological tremor end and benign essential tremor begin (not known), and can tremor recordings distinguish between them? (no).

It is difficult to find fault. However, the 1955 paper by Schwab and Chafetz concerned procyclidine, not amantadine. Perhaps dystonic tremor could have been given more space, the tremor of dysgammaglobulinaemic neuropathy a mention, and the usefulness of jaw tremor in distinguishing between parkinsonian and essential tremor might have been addressed, but these are only minor quibbles.

Overall this is an excellent book. It should be a part of all neurological libraries, and many neurologists will also wish to have a personal copy on their shelves.

NIAL QUINN

Neural Transplantation: From Molecular Basis to Clinical Applications. Progress in Brain Research Vol 82. Edited by SB DUNNETT AND S-J RICHARDS. (Pp 743 Illustrated; Price: Dfl 440). 1990. Amsterdam, Elsevier Science Publishers BV. ISBN 0-444-81137-0

This volume records some of the papers presented at the Symposium on Neural Transplantation in 1989. It is already two years out of date and is published only one year before the next Symposium on this subject is due to take place. However it brings within the covers of one volume a comprehensive review of knowledge and experience in this field to 1989.

There are few areas of basic and clinical research where there is a more pressing need for an understanding of biological mechanisms and their clinical application than in the field of neural transplantation. This volume has sections devoted to genetic manipulation of cells for neural grafts, immunological considerations in the brain, and extensive review of experience of glial and neuronal grafting in animals. Finally there are reports of clinical experience with adrenal and nigral grafts.

This is a useful book because it provides information on the experience of most of the centres with an active programme of research in 1989. Inevitably most of the papers pose more questions than they answer but progress has been so rapid that some of the answers are already available in subsequent publications.

This book is an essential reference work for the library of any institution where neural transplantation research is being done. It is also a valuable source of data and references for anyone seeking information in this rapidly advancing area of neuroscience.

R GODWIN-AUSTEN

Erratum

Vigabatrin and psychosis—JNNP 1991;54:435–9.

The authors omitted the following paragraph from the "Patients and methods" section:

The illustrated awake EEG recordings were carried out using the standard 10/20 system of electrode placement, an amplitude of 100 mV/cm and a paper speed of 30 mm per second (the time marker in seconds is shown at the top of each illustration), with a high frequency filter of 120 Hertz (fig 1b, 2a and 2b) or 60 Hertz (fig 1a) and a time constant of 0.3 second.