MIANSERIN AND CONVULSIVE SEIZURES

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- 1 Forty patients have been reported to the Committee on Safety of Medicines (CSM) because of convulsions occurring during treatment with mianserin, suggesting that this drug is more epileptogenic than tricyclic antidepressants.
- 2 Details concerning 83% of these cases were obtained in a questionnaire study carried out in collaboration with the CSM and compared with those of a control group.
- 3 Ratings of the relationship between drug and effect carried out by neurologists and J.G.E. showed considerable variations and confidence of a causal connection in only a minority of patients.
- 4 As the CSM data do not allow for a reliable assessment of the relative epileptogenic effects of antidepressants, a comparison has been made between unpublished work on seizures occurring during treatment with imipramine and amitriptyline and published research on mianserin. This suggests that mianserin is no more epileptogenic than tricyclic antidepressants.
- 5 Factors that might predispose to seizures include relevant family and past medical history, starting treatment, a change in dose, benzodiazepine withdrawal and concomitant treatment with other drugs that have epileptogenic properties.

Introduction

Convulsive seizures have been reported during treatment with therapeutic doses of many psychotropic drugs including antipsychotic agents (Logothetis, 1967; Remick & Fine, 1979), lithium (Baldessarini & Stephens, 1970; Demers *et al.*, 1970), tricyclic and newer tricyclic-like antidepressants (Betts *et al.*, 1968; Dallos & Heathfield, 1969; Edwards, 1977, 1979; Toone & Fenton, 1977; Shepherd & Kerr, 1978; Trimble, 1978). This paper will focus on convulsions occurring during treatment with mianserin.

At the time the study was carried out 40 cases had been reported to the CSM. This is a similar number to that for amitriptyline and a higher number than that for imipramine (see Table 1). As these drugs have been marketed for a much longer period and have a higher percentage share of prescriptions for antidepressants, the findings suggest that mianserin is more epileptogenic than conventional tricyclic antidepressants. More than that, in the case of only one other antidepressant, namely maprotiline, have there been more cases of convulsions reported to the CSM implying that mianserin is the second most epileptogenic antidepressant marketed in Britain (see Table 2).

In this study we investigate this possibility and assess factors in the patients' background history and aspects of treatment that might predispose to mianserin-induced seizures.

Method

A structured questionnaire was designed to elicit information concerning the nature of the seizure, any relevant family or past history, the findings on physical examination, the results of investigations, the dose and frequency of administration of the drug, any change in dose during the week prior to the attack, the duration of the treatment, concurrent drug treatment, recent drug withdrawal and follow-up data (see Appendix). Most questions had fixed-alternative response categories but some sought quantitative information or invited comments.

The questionnaire was sent with accompanying letters to all practitioners who had reported cases of convulsions occurring during treatment with antidepressants to the CSM (though only those occurring during treatment with mianserin will be dealt with in this paper). These letters stressed the importance and confidential nature of the enquiry. If the notifying doctor had changed his address or had died since reporting the convulsion, attempts were made wherever possible to obtain the relevant information from colleagues, partners or successors in the practice. In the case of patients who had changed their doctors or moved home, with permission of the notifying doctor, attempts were made to obtain the information from the patient's new practitioner. This often involved tracing the new practitioner with the help of the local Family Practitioner Committee.

Table 1 Cases of convulsions reported to the CSM

<i>Antidepressant</i>	<i>Year introduced into UK as anti- depressant</i>	<i>% Market share^a</i>	<i>No. cases convulsions (Dec. 1980)</i>	<i>%</i>
Amitriptyline	1961	44.9	37	11.3
Butriptyline	1975	—	0	0.0
Clomipramine	1972	5.9	25	7.6
Desipramine	1963	—	8	2.4
Dibenzepin	1970	—	3	0.9
Dothiepan	1969	31.6	12	3.7
Doxepin	1969	4.1	4	1.2
Flupenthixol	1973	—	10	3.0
Imipramine	1959	17.2	18	5.5
Iprindole	1967	—	2	0.6
Iproniazid	1960	—	0	0.0
Isocarboxazid	1960	—	0	0.0
Lithium	1965	2.2	7	2.1
L. tryptophan	1971	0.8	2	0.6
Maprotiline	1975	3.1	117	35.7
Mianserin	1976	8.8	40	12.2
Nomifensine	1977	2.4	0	0.0
Nortriptyline	1963	1.6	13	4.0
Oxipranol	1971	—	0	0.0
Phenelzine	1959	1.2	5	1.5
Protriptyline	1966	0.5	3	0.9
Tofenacin	1971	—	0	0.0
Tranlycypromine	1960	0.4	4	1.2
Trimipramine	1970	11.5	12	3.7
Viloxazine	1974	—	6	1.8
Total			328	100.0

^aOf the 7956000 prescriptions for antidepressants written in 1980. Source: Medical Data Index (1980). Harrow, Middlesex: Intercontinental Medical Statistics.

—These antidepressants have *in toto* less than 2% market share

Table 2 Antidepressants and convulsions

<i>Drug</i>	<i>No. of cases reported to CSM</i>
Maprotiline	117
Mianserin	40
Amitriptyline	37
Clomipramine	25
Imipramine	18
Nortriptyline	13
Dothiepin	12
Trimipramine	12
Desipramine	8
Lithium	7

A control group of patients was obtained from those referred to the Department of Psychiatry at the Royal South Hants Hospital, Southampton. They consisted of patients who had been prescribed mianserin either by their general practitioner or a hospital based colleague. They were randomly selected from the case records by one of the medical records staff. The same data were elicited from the patients' case records or from their general

practitioners as for the experimental (convulsions) group.

In the convulsions group the probability of a cause-and-effect relationship between mianserin and attacks was assessed and rated on an item taken from an unwanted effects questionnaire designed by one of us (Edwards *et al.*, 1980). This item is based on a 5-point scale ranging from 'almost certainly due to the drug' to 'almost certainly not due to the drug' (as seen in Tables 10 and 11). In making the ratings it was often thought that more clinical information was required, but scores were given on the basis of the data available, however much or little there might have been.

As an element of subjectivity necessarily enters into such assessments, the essential clinical findings in 29 of the cases were presented verbally at a meeting attended by four consultant neurologists, a consultant neurosurgeon, a consultant neurophysiologist, two senior registrars, one registrar and four senior house officers in neurological specialities and they were asked to

carry out independent ratings on the same scale. The name of the antidepressant was not revealed until they had completed their ratings.

Results

The results for all antidepressants will be reported in detail elsewhere; only those concerning convulsions occurring during treatment with mianserin will be presented here. Thirty-three of the 40 practitioners who had reported cases to the CSM provided information on their patients, giving a response rate of 83%.

Features of attack

With one possible exception, the case of a patient said to have had 'tonic spasms of voluntary muscles', the information given concerning the nature of the seizure left little or no doubt that the attacks were epileptic. Most patients had a single attack, although 11 (33%) had more than one attack. Four patients (12%) had two attacks, one patient (3%) had three attacks, two patients (6%) four attacks, and two patients (6%) had status epilepticus. Most attacks occurred on one day but three patients (9%) had attacks on separate days.

Sex

The sex distribution of the subjects in the convulsions and control groups is shown in Table 3. The female:male sex ratio in the former is more than 2:1 and in the latter just under 2:1.

Table 3 Sex of patients

Sex	Convulsions		Controls	
	No.	%	No.	%
Men	10	30	12	36
Women	23	70	21	64
Total	33	100	33	100

Age

The age distribution of both groups is shown in Table 4. Eighteen patients (60%) in the convulsions group and 22 patients (67%) in the control group were aged 50 years or younger.

Table 4 Age of patients

Age (years)	Convulsions		Controls	
	No.	%	No.	%
0-20	1	3	1	3
21-30	5	17	7	21
31-40	5	17	6	18
41-50	7	23	8	24
51-60	3	10	6	18
61-70	3	10	5	15
71-80	4	13	0	0
81-90	2	7	0	0
Total	30	100	33	100
50 or younger	18	60	22	67
Older than 50	12	40	11	33
Total	30	100	33	100

Family history

Three patients (9%) in the convulsions group were thought by their notifying practitioner to have a relevant family history; in two of these cases (6%) there was a family history of epilepsy. None of the control group had a family history of epilepsy.

Previous medical history

Seventeen patients (52%) in the convulsions group were thought by their reporting doctor to have a past history that might have been relevant to the convulsions: we regarded 15 (45%) of these as having a previous history of relevance. These histories included head injury, cerebrovascular accidents, psychosurgery, excessive drinking and epilepsy itself. Only four (12%) of the control group had a relevant past history, this difference being statistically significant ($\chi^2=7.4$, 1 d.f., $P<0.01$).

Physical examination

Some of the findings reported, for example dilated pupils or cyanosis, were related to the seizures but four patients (12%) had physical signs of pre-existing physical illness thought by the notifying practitioner to be relevant to the aetiology of the attack. We regard the signs in two (6%) of these cases as being relevant. Most of the patients in the control group had not been examined.

Investigations

Thirteen patients (39%) in the convulsions group had an electroencephalogram. Five (38%) of these were said to be within normal limits, while comments were made on six others. Of these the comments in three (23% of EEGs) were indicative of epilepsy; they were 'temporal lobe focus', 'spike activity—excess slow waves' and 'atypical spike and wave'.

The results of many haematological, biochemical, electrocardiographic and radiological investigations were reported but they threw no light on the cause of the attacks. Brain scans were carried out in three cases (9%) but they revealed no abnormalities.

Administration of mianserin

Dose. The total daily doses of mianserin that patients in both groups were receiving are shown in Table 5. The most frequently used dose in the group who had convulsions was 30 mg a day. In both groups there were more patients receiving 40 mg a day or less than doses exceeding 40 mg a day.

Table 5 Dose of mianserin

Dose (mg/day)	Convulsions		Controls	
	No.	%	No.	%
10	0	0	5	15
20	3	10	5	15
30	17	55	8	24
40	2	6	1	3
50	2	6	0	0
60	6	19	12	36
80	0	0	1	3
120	0	0	1	3
180	1	3	0	0
Total	31	100	33	100
40 mg or less	22	71	19	58
More than 40 mg	9	29	14	42
Total	31	100	33	100

Frequency of administration. The frequency of administration of mianserin in the convulsion and control groups are shown in Table 6. The majority of patients in the convulsions group were receiving the antidepressant three times a day, while the majority in the control group were taking it once daily, mostly at night. The difference between the two groups is statistically significant. (χ^2 8.7, 2 d.f., $P < 0.05$).

Table 6 Frequency of administration

Frequency	Convulsions		Controls	
	No.	%	No.	%
Once daily	11	35	20	63
Twice daily	3	10	6	19
Three times a day	17	55	6	19
Total	31	100	32	100

Table 7 Duration of treatment

Duration	Convulsions		Controls	
	No.	%	No.	%
1 dose only	3	10	0	0
1 day to 1 week	11	35	1	3
8 days to 2 weeks	6	19	4	13
>2 weeks to 3 months	8	26	16	52
>3 to 6 months	3	10	4	13
>6 months	0	0	6	19
Total	31	100	31	100
2 weeks or less	20	65	5	16
More than 2 weeks	11	35	26	84
Total	31	100	31	100

Duration of treatment. This is shown in Table 7. In three patients the convulsions occurred after only a single dose of mianserin while 20 patients (65%) had been receiving treatment for less than two weeks when the attacks occurred. Only five (15%) of the control group had been receiving treatment for less than two weeks, the difference being statistically significant (χ^2 13.1, 1 d.f., $P < 0.001$).

Change in dose. Seven patients (21%) had a change in dose during the week preceding the convulsions, while none of the patients in the control group had their doses of mianserin changed during the week before they were selected. This difference also is statistically significant (χ^2 5.8, 1 d.f., $P < 0.05$). The actual changes in dose are shown in Table 8.

Concomitant drug treatment. Twenty-two (67%) of the patients who had convulsions were receiving a

Table 8 Change in dose

Change	Convulsions		Controls	
	No.	%	No.	%
Increase	6	18	0	0
Decrease	1	3	0	0
Total	7	21	0	0

Actual changes

	Dose prior to seizure	Dose at time of seizure	% change
Increases	20	40	+33
	20	30	+50
	30	50	+67
	30	60	+200
	30	60	+200
	90	180	+200
Decrease	80	60	-25

total of 50 other drugs concurrently giving a mean for the total population of 1.5 other drugs per patient (2.5 drugs including mianserin). This is to be compared with 17 patients (52%) in the control group taking 28 other drugs giving a mean of 0.9 other drugs per patient (1.9 including mianserin), although the difference is not statistically significant. Some of the drugs have been documented as causes of convulsions though not necessarily in the low doses used, while some others have anticonvulsant properties. Many of the drugs had themselves been notified to the CSM as having been associated with, though not necessarily causing, convulsions. These included phenytoin, which was clearly not the cause of the convulsion.

Drug withdrawal. In two cases lorazepam was discontinued during the week prior to the convulsions and in three other patients treatment with tricyclic antidepressants, namely amitriptyline, clomipramine and protriptyline, was stopped. No drugs were discontinued during the week prior to selection in the control group.

Follow-up

The lengths of follow-up in the convulsions group are shown in Table 9. No attempt was made to obtain follow-up data for the control group. In most instances follow-up was carried out by the notifying practitioner but some patients were followed up for longer periods, for example when referred to a neurologist. Two patients continued to take mianserin and there were no further attacks

Table 9 Follow-up ($n=27$)

Length of follow-up	No. of patients	%
Less than 1 month	3	11
1-2 months	3	11
3-6 months	10	37
7-12 months	1	4
12 months and longer	10	37

during a four and more than three-year follow-up period.

Relationship between drug and convulsions

The consultants' and trainees', and J.G.E.'s ratings of the probability of a causal connection between mianserin and convulsions are shown in Tables 10 and 11 respectively. It will be noted that there is considerable inter-individual variation in both consultants' and trainees' ratings. In four patients there was a scatter of opinions from 'almost certainly caused by the antidepressant' to 'almost certainly not caused by the antidepressant', in 15 patients a scatter across four of the five probability ratings and in 10 patients a scatter across three of the ratings. Consultants tended to relate the convulsions to the drug to a greater extent than trainees. When J.G.E. repeated his ratings after an interval of more than a week, different results were obtained in six cases but these did not exceed one-point differences. Overall, there was confidence about the causal connection between drug and convulsions in only a minority of patients and in several cases the convulsions were rated as being unlikely to be due to the drug.

Discussion**Response to enquiry**

A response rate of 83% for a questionnaire study of this kind is most acceptable, although it was thought at the outset it would have been even higher because, if a practitioner is sufficiently motivated to notify a case to the CSM, he should be equally motivated to provide further information that might assist in identifying factors that predispose to antidepressant-induced convulsions. Possible reasons for the response rate not being higher include notifying doctors changing jobs, retiring or dying, inability to find colleagues who might provide the information required and lost records. But there is also another reason well illustrated by one respondent, a consultant

Table 10 Relationship between convulsions and mianserin: neurologists' ratings

<i>Relationship</i>	<i>C1</i>		<i>C2</i>		<i>C3</i>		<i>C4</i>		<i>C5</i>		<i>C6</i>	
	<i>No.</i>	<i>%</i>	<i>No.</i>	<i>%</i>	<i>No.</i>	<i>%</i>	<i>No.</i>	<i>%</i>	<i>No.</i>	<i>%</i>	<i>No.</i>	<i>%</i>
Convulsions almost certainly caused by mianserin	0	0	4	14	0	0	7	24	0	0	7	24
Convulsions probably caused by mianserin	0	0	10	34	16	55	12	41	1	3	7	24
Convulsions possibly caused by mianserin but equally likely due to other cause(s)	18	62	4	14	8	28	7	24	18	62	4	14
Convulsions probably not caused by mianserin	8	28	8	28	4	14	3	10	9	31	8	28
Convulsions almost certainly not caused by mianserin	3	10	3	10	1	3	0	0	1	3	3	10
Total	29	100	29	100	29	100	29	100	29	100	29	100

C consultant

Table 11 Cause-and-effect relationship: J.G.E.'s ratings

<i>Relationship</i>	<i>No.</i>	<i>%</i>
Convulsions almost certainly caused by mianserin	0	0
Convulsions probably caused by mianserin	9	27
Convulsions possibly caused by mianserin but equally likely due to other causes	16	48
Convulsions probably not caused by mianserin	7	21
Convulsions almost certainly not caused by mianserin	1	3
Total	33	100

neurologist, who indicated that he does not report antidepressant-induced convulsions to the CSM as they occur so frequently.

The response rate might well have been increased by a follow-up letter and another copy of the questionnaire being sent from the CSM, but as the Committee relies on voluntary reporting it is feared that too much pressure put on practitioners to provide additional information might discourage them from reporting new cases. For this reason follow-up letters were not sent, but there was a considerable amount of follow-up correspondence with those respondents who indicated they were willing to provide additional information. Although data are not available on all patients notified to the

CSM there are no grounds for believing that the sample reported is biased or unrepresentative of the total population.

Relationship between drug and convulsions

There was considerable variation between neurologists in their ratings of the probability of a cause-and-effect relationship between mianserin and convulsions. There are many possible reasons for this, including difficulty in carrying out assessments without first-hand knowledge of the patient, different criteria for relating effect to drug based on experience and knowledge of the epileptogenic properties of antidepressants and different interpretations of the criteria for scoring. Such problems are magnified in conditions of multifactorial aetiology such as epilepsy in which predisposing and precipitating factors are important.

Overall, there was confidence about the causal connection between drug and convulsions in only a minority of patients and J.G.E.'s ratings suggest that only 27% of cases are probably due to mianserin with 21% probably not due to mianserin. In just under a half of the cases convulsions were possibly due to mianserin but equally likely due to other causes. These results are to be contrasted with those of Inman & Price-Evans (1972) who showed that 78% of all adverse reactions reported to the CSM are probably due to the drug and 13% possibly due to the drug.

Relative epileptogenic properties of mianserin

Only about 10–15% of all drug reactions are notified to the CSM (Inman & Vessey, 1968; Dunlop, 1971) and reporting varies with the clinician, the drug and the type of reaction. For mianserin and convulsions there is also, as we have shown, considerable uncertainty as to the causal connection between drug and effect. The CSM data therefore do not allow for a reliable assessment of the relative epileptogenic effects of mianserin and one therefore has to turn to other sources for comparative purposes.

Earlier attempts at assessing the incidence of seizures during tricyclic antidepressant drug treatment do not provide sufficient information on the methodology of the search or literature reviewed, the reasons for including some studies and excluding others, and data on any predisposition to epilepsy that the subjects might have had. A.W. Peck, W. Stern and C. Watkinson, in work that is to be published, have attempted to overcome these methodological deficiencies and provide the best estimates that we have to date. They adopt two different approaches. The first was based on the 10 patients who had convulsions during treatment with amitriptyline and the seven who had seizures during treatment with imipramine reported by Toone & Fenton (1977). These were inpatients at the Maudsley and Bethlem Royal Hospitals during the seven year period 1967–73. During this time 10 153 patients were discharged and approximately 40% of patients admitted to these hospitals had a diagnosis of depressive psychosis or depressive neurosis. This meant that an approximate total of 4000 patients were treated for depression between 1967 and 1973. On the assumptions that the retrospective search of Toone and Fenton found all the patients who had seizures and every patient with a depressive illness received a tricyclic antidepressant (the use of MAOIs in the two hospitals at the time was small) the incidence of seizures would be at least 0.4 to 0.5%.

Peck and his colleagues also reviewed the papers studied by Smith *et al.* (1969). These appeared in the medical literature between 1955 and 1966. Two thousand articles had been screened and 918 were included in the survey. Of these, 473 dealing with drug efficacy were abstracted. One hundred and forty-three dealt with imipramine and 67 with amitriptyline. Peck and his associates excluded papers that did not indicate that side-effects were sought, those that did not state the number of patients taking the drug and those that did not provide adequate information concerning the dose, route of administration and concomitant medication. From the 98 papers that were included

they calculated the incidence of seizures in the 958 patients who received more than 200 mg of imipramine a day as 0.63% and in the 2986 patients who were taking 200 mg a day or less as being 0.10%. Only one of the 1811 patients treated with 200 mg or more of amitriptyline had a convulsion giving an incidence of 0.06%, while no cases were recorded in 1038 patients receiving less than 200 mg a day.

To obtain comparable data for mianserin, again one has to refer to the medical literature. Two extensive reviews (de Ridder, 1979; Pinder & Fink, 1982) indicate that to date 1792 patients have received mianserin in clinical studies, but not a single case of convulsions has been reported. If mianserin had the same epileptogenic potential as imipramine, using the figures of Peck *et al.* (unpublished) one would expect between two and 11 cases of convulsions, and if as epileptogenic as amitriptyline, only one case. In so far as none has been reported, it suggests that mianserin is no more epileptogenic than conventional tricyclic antidepressants.

Predisposition to mianserin-induced convulsions

Whatever the relative epileptogenic properties of mianserin it is important to identify predisposing factors as an aid to the prevention of convulsive seizures. In the present study the sex ratio of women to men might have suggested that women are more susceptible to convulsions but there was a similar sex ratio in the control group. This indicates that mianserin is prescribed more often for women either due to a higher prevalence of depression in females (Slater & Roth, 1970) or due to a greater tendency for doctors to prescribe psychotropic drugs, including antidepressants, for women (Shepherd *et al.*, 1966; Dunnell & Cartwright, 1972). It also appeared that younger subjects were more vulnerable until it was revealed in the control group that mianserin is prescribed more often for younger patients.

A positive family history of epilepsy or of a condition that predisposes to epilepsy is clearly relevant. Two patients in the convulsions group but none in the control group had a family history of epilepsy. Although the difference is not statistically significant it is probably clinically significant. A past history of epilepsy or of conditions that predispose to epilepsy is even more important and we were able to demonstrate a significant difference between the convulsions and control group.

Convulsions occurred during treatment with conventional doses of mianserin in all but one

patient who was receiving 180 mg a day. Most patients were receiving 30 mg a day and the majority of these were taking mianserin in divided doses three times a day. This dose and frequency of administration probably reflects the extent to which 30 mg a day is given in general medical practice and physicians' habit of prescribing on a thrice-daily basis. The majority of patients in the control group were taking mianserin as a single daily dose at night. This could well be the result of local teaching on the advantages of the total daily dose of antidepressants being taken at night.

Significantly larger numbers of patients in the convulsions group than in the control group had a change in dose of mianserin in the week preceding the attack. This is in keeping with the findings of Toone & Fenton, (1977) who found a marked increase in drug prescribing in the week preceding the seizure.

More patients in the convulsions group than in the control group had been taking mianserin for two weeks or less. This difference could be determined at least in part by the method of selection of controls or be due to the fact that convulsions occurring during the early days of treatment are more likely to be reported than those occurring later. But it is also possible that convulsive seizures, like many other unwanted effects, are more liable to occur early in treatment.

A larger number of other drugs were being taken concurrently by patients in the convulsions group than in the control group. This is partly determined by the fact that many of the patients had concurrent physical and psychiatric illnesses requiring drug treatment, but the large number of drugs prescribed in both groups also reflects the tendency of doctors to use combined drug treatment. Some of the drugs that were being taken concurrently are themselves alleged to induce convulsions but others, for example benzodiazepines that have anticonvulsant properties, could have conceivably decreased their occurrence.

Some of the drugs, for example norethisterone and antipsychotic agents such as chlorpromazine (though not necessarily in the low doses used) are documented as having epileptogenic properties, while many of the drugs have been notified to the CSM as being associated with convulsions. In some cases, such as with benzodiazepines, it is possible that patients had withdrawal effects rather than adverse reactions occurring during continuing treatment. There are also anomalies, notably seizures allegedly occurring during treatment with the anticonvulsant, phenytoin. This drug was clearly not the cause of the seizures but was presumably being taken alongside some other offending agent notified to the CSM.

Withdrawal from benzodiazepines (Hollister *et al.*, 1961; Barten, 1965; Vyas & Carney, 1975; Fruensgaard, 1976; Rifkin *et al.*, 1976), including lorazepam (Einarson, 1980; Howe, 1980), is not a well established cause of seizures. Although only two patients had a benzodiazepine discontinued during the week prior to the convulsions in the present study, there could possibly have been others. Benzodiazepines are the most widely prescribed of all psychotropic drugs and, although antidepressants are often given in addition to benzodiazepines, in many cases the latter are discontinued when the antidepressants are introduced. With medical record keeping leaving much to be desired this can easily be overlooked and the antidepressant may be erroneously incriminated as the cause of benzodiazepine-withdrawal convulsions.

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Discussion

M. Trimble

I would like to congratulate Dr Edwards—I know he has been working on this subject for some time and it is an extremely important field. I certainly agree with him on a number of points. The first is the difficulty in dealing with the CSM data. However I think it is valid in the sense that it is randomly collected and that it is clinical information sent in by clinicians, and I would agree with his general conclusions that to date mianserin is no more or no less epileptogenic than certainly the tricyclic antidepressants. One of the problems of dealing with the data that Dr Edwards looked at is, of course, the non-random nature of the presentation to the CSM. I would just like to reflect here that when the story of seizures associated with maprotiline broke forth. I analysed in a similar way all the case reports of seizures associated with maprotiline and discovered that out of well over 100 cases some 45 or 50% of them were reported between two years. Most of the cases came from the UK and 10 cases came from one physician. This struck me as showing the rather non-random nature of these problems and it is still a mystery to me how maprotiline has stood out in this sense and why suddenly between 1976 and 1978 there was a rush of reports which have now diminished.

Professor Richens highlighted perhaps the most important clinical aspects of this from the point of

view of epilepsy, and the reason that we set up the trial looking at nomifensine and mianserin was because we felt that it was important to establish whether the newer non-tricyclic antidepressants were less inclined to provoke seizures. Also the pharmacokinetic interactions between the antidepressants and the anticonvulsants were something that needed to be looked at. The main message must be that if you prescribe antidepressants to patients with epilepsy who are on enzyme-inducing drugs, then you must look very carefully at the possibility that they may not respond because they have very low serum levels. Tailoring of dosage may be very important in this group; indeed this may be one subgroup of patients where one could clearly justify the availability of antidepressant monitoring of serum levels.

So what is this peculiar relationship between seizures and epilepsy? We have a fascinating biological inter-relationship. Seizures in patients with depression improve the depression. ECT is still a very effective treatment for depression. Conversely, in my patients with epilepsy who developed psychiatric disorders there was absolutely no doubt clinically that some patients developed a psychosis when the frequency of their seizures diminished. I have numerous patients, who when they became psychotic ceased having seizures. Then we have this fascinating fact that in patients who are depressed the majority of drugs that have been