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Visual Field Defects and Other Ophthalmological Disturbances Associated with Vigabatrin

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Abstract

Vigabatrin has been an important anticonvulsant drug for over 10 years with a reputation for high efficacy and excellent tolerability. However, since 1997, there have been over 25 reports in the literature of visual field defects attributable

to the use of this agent. Most are case reports and many have only been reported as abstracts or posters or as letters or short communications. Only a small number of papers give details of patient characteristics. Typically, case reports detail ophthalmological tests such as visual acuity, funduscopic examination, integrity of colour vision, and the nature of the field cut. Many also include various electrophysiological tests which were performed in an attempt to further describe the nature of the visual changes. In order to shed light on the mechanism underlying these visual field changes, many investigators also tested various electrophysiological parameters. However, because electrophysiological testing requires considerable expertise on the part of the technician, this could be a source of variability in results and may also pose a challenge with data interpretation.

The magnitude of the problem is difficult to assess. The manufacturer's estimate of incidence of visual field defects with vigabatrin was approximately 0.1%, but incidences estimated in the literature range from 6 to 30%. Since the majority of the published data are in case report form, proof of causation is also very difficult. Two papers that used proper scientific methodology to investigate this condition suggest that vigabatrin causes these changes; however, there needs to be further studies with larger populations to answer this question definitively. There is a lack of data on the dose-response characteristics of vigabatrin and the development of visual field defects. The only available data are reports of trends that implicate duration of therapy or cumulative dose. Perhaps the most important area to elucidate is whether or not the visual field defects are reversible. Data are scare on this subject, but we can hope that data will emerge as follow-up periods become more substantial.

There is a need for more complete information regarding several aspects of the mechanistic basis of visual field defects associated with vigabatrin that will allow rational clinical decision making. The treatment choices, both pharmacological and nonpharmacological, for patients with refractory epilepsy have grown substantially in the last few years. Thus, it is doubtful that the clinical positioning of vigabatrin is likely to change in the future from that of a very valuable 'niche drug', with emphasis on paediatric usage.

Vigabatrin, a structural analogue of γ-aminobutryric acid (GABA), was synthesised in 1974 as the first 'designer' anticonvulsant drug. It acts as an irreversible inhibitor of GABA transaminase, the enzyme that degrades GABA, thus increasing GABA levels in the brain. Since GABA is the principal inhibitory neurotransmitter in the CNS the increased levels would be expected to increase the threshold for seizures. Indeed, this has been demonstrated in experimental models of seizures in animals.[1]

The drug was first licensed in Britain and Ireland in 1989 and is currently in use in clinical practice in over 40 countries. Since its introduction it has proved effective in treating seizures in both adult and paediatric patients. It is especially successful in treating infantile spasms, a catastrophic form of childhood epilepsy. The drug's approval in the US was initially delayed because of concerns regarding toxicity to the white matter in the brains of experimental animals.[2,3] However, this appears to be species specific and has not been demonstrable in humans either by magnetic resonance imaging (MRI), electrophysiological measures,[4] or direct neuropathological examination.[5-7] More recently there has also been evidence that this toxicity is in-

creased in the developing rat brain (e.g. compared with the adult animals),[8] but that it is also partially reversible upon drug withdrawal.[9]

However, in 1998 the US Food and Drug Administration notified the manufacturer, Hoechst Marion Roussel (now Aventis), that the drug was 'not approvable'. This stems from concerns about recent data regarding visual field defects associated with and possibly attributable to the drug, since the first case report published in 1997. Eke and colleagues described 3 patients taking vigabatrin with severe and persistent concentric visual field defects.[10] Over the next 12 to 24 months, many more case reports appeared in the literature and were presented at various scientific meetings in neurology, epilepsy, and ophthalmology. Only in the last year have more papers been published attempting to further elucidate this problem by looking at possible mechanisms, trying to estimate its prevalence, and finally proving the causal relationship to vigabatrin.

This review examines published data ranging from simple case reports (published as letters or in abstract form) to papers presenting detailed visual field analyses and electrophysiological data in symptomatic and asymptomatic patients. As these data emerge, many questions regarding the future of vigabatrin are raised: has a causal relationship been proved; what is the true incidence; are there risk factors for developing visual problems, and if so what are they; how might these problems be monitored for development or progression in patients who are asymptomatic and/or cannot cooperate with behavioural testing; are the deficits progressive; and further are they reversible upon discontinuation of the drug; are there age related differences in risk of occurrence and or reversibility; and finally what are the analyses regarding risks versus benefits?

1. History and Nature of the Visual Problems Associated with Vigabatrin

Since 1997, there have been over 25 reports in the literature of visual field defects attributable to the use of vigabatrin. Most are single or small sample case reports and many appear as abstracts of papers or posters presented at scientific meetings or as letters or short communications. There are only a small number of papers that give details of patient characteristics and specific ophthalmological tests (including electrophysiological tests) that were done to further describe the defects and elucidate possible mechanisms.[10-16] The results are highly variable even in these studies.

Obviously, there has been great concern over the existence of asymptomatic cases, especially after the rather sudden appearance of so many symptomatic cases, years after widespread use of the drug. Historically, it has been known from diseases such as retinitis pigmentosa or tumours that compress the optic chiasm that symptoms of visual field loss are discerned by the patient only at a relatively advanced stage of the disease. Prevalence and causality, using reasonably large patient populations and nonvigabatrin-exposed control groups, have been investigated in only a small number of studies.[14,17-21]

2. Ophthalmological Assessments

Typically, case reports detail ophthalmological tests such as visual acuity, funduscopic exam, integrity of colour vision, and the nature of the field cut. These data will be described in general in the following sections and are detailed in table I. Many also include various electrophysiological tests which were performed in an attempt to further describe the nature of the visual changes. These data are summarised in the next section and detailed in table II.

2.1 Visual Acuity

There are many studies where 'blurred vision' is given as the presenting symptom to physicians, but only a small number report significant visual acuity change. One paper described 2 of 25 patients with acuity outside the normal range.[18] In another case report of diminished visual acuity the patient also had bilateral optic atrophy and maculopathy.[22] Since there was no mention of whether the patients had had formal visual assessment prior to taking

Table I. Ophthalmological assessments of patients receiving vigabatrin reported in case reports and abstracts

Reference	No. of patients	Acuity	Funduscopic	Colour	Symptoms	VFD
Eke et al.[10]	3	Normal	Slightly pale optic discs in 2	NA	Tunnel vision, constriction of peripheral fields, bumping into objects	Concentric in 2, nasal predominance in 1
Wilson & Brodie[22]	1	Impaired	Bilateral optic atrophy	NA	Blurred, loss of peripheral vision	Full, but only tested by confrontation
Wong et al.[23]	1	NA	Optic disc pallor	NA	Bumping into things	Restricted temporal fields by optician, marked constriction by ophthalmologist
Blackwell et al.[24]	1	NA	Normal	NA	Bumping into people	'Less severe than Eke et al. 1997'
Harding[25]	2 (plus the 3 original Eke pts)	NA	NA	NA	NA	Constriction 'similar to' Eke et al. 1997
Mackenzie & Klistorner[26]	2	NA	NA	NA	None	Subtle binasal defect by Humphrey with additional superior defect by Goldman in 1, binasal by Humphrey in 1
Rao et al.[27]	11	NA	NA	NA	None	'Appreciable changes' by Humphrey
Beran et al.[28]	5	NA	Acute macular neuroretinopathy in 1, optic atrophy in 1, elevated intraocular pressure in 1, others NA	NA	None	Gross concentric constriction of VF in 1, others NA
Baulac et al.[29]	3	NA	NA	NA	Pts with pre-existing VFDs complained of VF narrowing	VF narrowing confirmed by perimetry (Goldman and/or automated)
Acheson[30]	5	NA	NA	NA	NA	Major field defects outside 25 deg nasally and 40 deg temporally
Kramer et al.[31]	4	NA	NA	NA	NA	Bilateral concentric VFD
Vanhatalo & Paakkonen[32]	2 paediatric	NA	NA	NA	None in 1, not able to assess the other	Bilateral concentric VFD (superimposed on known hemianopsia in 1)
Versino & Veggiotti[33]	1 paediatric	Normal	Normal	NA	Bumping into objects	Severe bilateral VF constriction by automatic testing
Krauss et al.[13]	4	20/20 to 20/50	Normal in 2, surface wrinkling retinopathy in 2	Normal	Bumping into things in 1, blurred in 1, constriction of peripheral vision in 1	Constricted by both static and kinetic perimetry in 2, normal by static but constricted by kinetic in 1, normal by static in 1
Ruether et al.[34]	1	Normal	Normal	NA	Constriction of VF	Concentric constriction of 20-30 deg by Humphrey & Goldman

deg = degrees; **NA** = not assessed; **pts** = patients; **VF** = visual field; **VFD** = visual field defect.

Table II

vigabatrin, it is impossible to state that the visual acuity was related to vigabatrin usage. In the sample from The Johns Hopkins Hospital reported by Miller et al.[14] and Johnson et al.,[35] decreased acuity was noted to have developed during treatment with vigabatrin. However, in the majority of studies visual acuity was reported as normal or unaffected.

2.2 Other Testing

In the few studies which specifically mention colour vision, there are only rare reports of abnormalities associated with vigabatrin use.[14,35] In a study where disturbances in colour vision were reported in nearly one-third of patients taking vigabatrin, a similar incidence was observed in patients taking carbamazepine.[36] The same authors also reported in another paper that while vigabatrin had no effect on glare sensitivity, abnormalities in contrast sensitivity could be discerned in those patients that had sustained a visual field defect.[37]

2.3 Funduscopic Examination

While most authors described normal fundoscopy, there are several reports of abnormal retinal exams in the literature. The most commonly reported abnormality was a 'pale disc' or mild optic nerve pallor.[10,12,18,23] There are also rare reports of retinopathy.[13,28] Miller and colleagues describe 'nonspecific retinal abnormalities' in 72% of their patients including retinal artery narrowing, epiretinal membrane formation, an irregular sheen (or abnormal macular pigmentation) and reduction in the peripapillary nerve fibre layer.[14] Since patients had not been formally tested prior to starting the drug, it is impossible to attribute any of these changes to vigabatrin *per se*. However, the report by Miller[14] does state that there were no funduscopic abnormalities in any of their 10 nonvigabatrin-exposed control patients.

2.4 Visual Fields

The majority of case reports are descriptions of patients who presented with symptoms referable to

Table II. Electrodiagnostic testing of patients on vigabatrin reported in case reports and abstracts

Reference	No of patients	VEP	EOG	ERG
Eke et al.[10]	3	Normal	Low Arden indexes in 2 of 3	Reduced oscillatory potentials in 2 of 2 tested
Wilson & Brodie[22]	1	Normal	Flat	Subnormal rod & cone ERGs
Wong et al.[23]	1	'Similar to Eke'	'Similar to Eke'	'Similar to Eke'
Blackwell et al.[24]	1	NA	Normal	Normal
Harding[25]	2 plus the 3 Eke	NA	Normal	Normal
Mackenzie & Klistorner[26]	2	NA	NA	Multifocal ERG with decreased summated action potential, particularly b-wave, mild-moderate decreased b-wave amplitude
Kramer et al.[31]	4	NA	Decreased Arden in 1	NA
Krauss et al.[13]	4	Delayed in 1, normal in 3	NA	Decreased b-wave in all 4, decreased oscillatory potentials in all 4
Ruether et al.[34]	1	Normal	Normal Arden	Standard ERG basically normal, low b/a ratio, reduced 2nd oscillatory potential, cone and 30Hz flicker at low end of normal, multifocal ERG with abnormal wave forms in the affected areas

EOG = Electro-oculogram; **ERG** = Electroretinogram; **NA** = not assessed; **VEP** = Visual evoked potential.

visual field defects (e.g. tunnel vision, bumping into things). These patients were subjected to formal visual field testing with some investigators using static or automated perimetry testing (e.g. Humphrey) and others using kinetic perimetry testing (e.g. Goldmann). Static or automated perimetry testing only extends to 60 degrees (sometimes only to 30 degrees). Kinetic testing may be preferable for evaluating the far periphery. It should be noted that perimetry testing, whether static or kinetic, is dependent both on the expertise of the examiner and the cooperation of the patient.

Most patients were found to have bilateral concentric constriction of the visual fields. There were also some reports showing relative sparing of the temporal portion of the fields or more selective involvement of the nasal portion.[15,18,19] There have also been reports of selective involvement of temporal fields.[13,14]

Issues of operator expertise and participant cooperation are important to consider when evaluating data quality in the literature. There is bound to be variability in the expertise of the examiners, and there will almost certainly be cooperation errors among a population of patients with long-standing epilepsy, many of whom have subnormal mental capacity. (This excludes testing a large population of children who are not old enough to be considered reliably cooperative.)

3. Electrodiagnostic Testing

In order to shed light on the mechanism underlying these visual field changes, many investigators also tested various electrophysiological parameters including visual evoked potentials (VEP) or responses, electro-oculograms (EOG), and electroretinograms (ERG). Because electrophysiological testing requires considerable expertise on the part of the technician, this could be a source of variability in results and may also pose a challenge with data interpretation. The larger studies are discussed in detail in the text that follows. Data from the case reports and abstracts are summarised in the following sections and in table II.

3.1 Visual Evoked Potentials

Many investigators have evaluated the integrity of VEPs because of the white matter toxicity that had been reported in experimental animals. The majority report normal results suggesting that vigabatrin has no toxicity on optic nerve or tract function.[4,10,22,34,38] There are some reports of abnormal results. One of the 4 patients reported by Krauss and associates[13] and 22% of the 32 patients reported by Miller et al.[14] (note that this group includes the 4 patients from the Krauss paper) had abnormal VEPs. Gross-Tsur and colleagues[15] also found 5 of their 15 paediatric patients (33%) had abnormal VEPs. There were 30% of patients in the Daneshvar et al.[12] study with abnormal VEPs; however, the authors suggest that this abnormality may still be a reflection of a retinal phenomenon and not optic nerve toxicity *per se* because these were the same patients who showed deficits in the central visual field.

There is 1 paper in the literature where vigabatrin is specifically implicated as the cause of optic nerve damage.[39] The authors present a case report of optic neuropathy in an 8-year-old girl receiving vigabatrin therapy which reversed with corticosteroid treatment and removal of drug. Interestingly, there was no report of visual field testing, which means the phenomenon may have been a case of optic neuritis that responded well to corticosteroids, with no vigabatrin component.

3.2 Electro-Oculogram

Some investigators have reported abnormalities in the EOG. The EOG tests the integrity of the retinal pigment epithelium (RPE) and RPE-photoreceptor outer segment complex. Perhaps the most frequently reported measure in the EOG is the Arden index or ratio. This is obtained by calculating the difference from the peak amplitude during light adaptation (light peak) and the minimal potential during dark adaptation (dark trough). This index was below normal in 2 of Eke's original 3 patients[10] and in a patient described by Kramer et al.[31] A 'flat' EOG was described in a patient reported by Wilson

and Brodie.[22] However, there are just as many reports of normal EOGs in patients with proven visual field defects who are symptomatic.[24,25,34] In fact, the low Arden indexes were not confirmed when the same patients reported by Eke were retested by Harding.[25] The relationship of this finding to the visual field defects must therefore be questioned.

The data appears to be similarly ambiguous among larger groups of patients. Arndt et al.[11] report a decreased Arden index in 14 of 20 patients, but not all of these patients had documented visual field defects. While all of the patients with severe visual field defects did show abnormal Arden ratios, there were a number with abnormal EOGs that had normal visual fields and a number with mildly abnormal fields with normal EOGs.[11] The authors demonstrated that there was no linear relationship between severity of visual field defect and reduction of the Arden ratio.

Daneshvar and colleagues[12] reported abnormal Arden ratios in 5 of their 10 patients, all of whom had abnormal fields. However, the other 5 patients with normal EOGs also had abnormal fields.[12] Lawden and colleagues[18] reported abnormal Arden ratios in all patients in their cohort who were receiving vigabatrin at the time of testing, but again, not all of these patients had abnormal visual fields. Also interesting is that these abnormalities were consistently reversible upon withdrawal of the drug. However, the Arden index change was not related to the degree or the reversibility of the actual visual field defect. This suggests that the changes in Arden index merely reflect vigabatrin's influence on GABAergic cells in the retina, and have no causal relationship to the development of visual field defects.[18]

Harding and colleagues[40] tested this theory in healthy volunteers exposed to a short course of vigabatrin. They found that while there were no changes in visual field (measured with a Humphrey analyser) there was a significant decrease in the group mean Arden index between baseline and day 9. This occurred only with vigabatrin and not with carbamazepine or placebo. They suggest that this result is simply a reflection of altered GABA levels in the retina.

In summary, EOG changes occur after a short exposure time, are reversible upon drug withdrawal and do not correlate with the presence or severity of a visual field defect (especially the absence of any abnormality even in the presence of visual field defect). Therefore, there appears to be insufficient evidence that an alteration in Arden index is the mechanism for visual field defect development in patients exposed to prolonged use of vigabatrin. Unfortunately, it also makes EOG less useful as a tool for following the asymptomatic patients or those that cannot participate in detailed visual field testing (e.g. young children or patients with an intellectual handicap).

3.3 Electroretinogram

Other studies have reported abnormalities in the ERG. As with the EOG, there are some reports of normal results even in the face of visual field defects.[15,18,24,25] Abnormal responses have been reported using a special technique of multifocal ERG,[18] particularly the b-waves.[26] However Ruether and colleagues[34] found abnormalities in the various measures of the conventional ERG but not when using the multifocal technique.

There is also conflicting evidence to support which individual measure in the ERG is abnormal. In some of the reports of small numbers of patients with abnormalities, normal a- or b-wave responses were found (the a-wave chiefly reflects the functional integrity of the rods and the cones, while the b-wave represents the functioning of the middle retinal layers) but with decreased oscillatory potentials (which represents the activity of the amacrine cells).[10,34] Arndt and colleagues[11] tested 20 consecutive patients and found normal a- and b-wave potentials in all participants but abnormal oscillatory potentials in 50%. The potentials were absent in all of the cases of severe visual field defects, but were normal in some cases of mild visual field defect. There were also abnormal potentials in patients without any visual field defect. The absence or reduction of oscillatory potentials is thought to

be related to the effect of vigabatrin on the activity of highly GABA-ergic amacrine cells in the retina and may suggest midretinal layer dysfunction.[11]

Other papers report normal oscillatory potentials but abnormalities in the a- and b-waves; and these vary whether they are tested in photopic (e.g. cone) or scotopic (e.g. rod) conditions. Daneshvar and colleagues[12] screened a sample of 41 consecutive patients who were taking vigabatrin. There were 12 patients with visual field defect. In 10 of the 12 patients who were studied further, oscillatory potentials were normal, but there were reduced amplitudes of b-waves to scotopic (e.g. rod) testing in 4 and to photopic flicker testing in 1. Conversely, Krauss and colleagues[13] tested 4 symptomatic patients and found abnormal fields in 3 of them. Oscillatory potentials and cone response amplitudes were reduced in all 4 patients. Rod response amplitudes were decreased in 1 eye in 2 patients. The authors suggest that dysfunction in the cone system, the inner retinal layers and especially the amacrine cells was the cause. In a later paper by the same investigators, they suggest that the absence of significant changes seen by the Daneshvar group[12] may have been related to the use of different or 'nonstandard' methodologies of recording oscillatory potentials.[35]

Miller and co-workers[14] evaluated 32 patients exposed to vigabatrin (including the 4 patients reported by Krauss) and found that all of them had severely depressed oscillatory potentials and b-waves for rod and cone systems. They further report that 1 specific parameter of the ERG, the reduction in the amplitude of the flicker responses of the cones, actually showed a significant correlation with the degree of visual field constriction. They suggest that this represents inner retinal dysfunction.

Kälviäinen and associates[17] performed ERGs on patients found to have visual field constriction and report that all of those with severe visual field defect and 60% of those with mild visual field defect had reduced oscillatory potentials. Patients with severe visual field defect also had reduced a-and b-wave amplitudes in both cone photopic and rod scotopic testing.

In the most recent study, specifically designed to separate electrophysiological changes related to current use of vigabatrin from those actually attributed to vigabatrin-associated visual field defect, Harding and colleagues[16] tested patients presently or previously exposed to vigabatrin and compared them to vigabatrin-naïve patients with epilepsy and to normal controls. They found that the latencies of the scotopic a-wave and the second oscillatory potential were prolonged in current compared to past vigabatrin users, all with significant visual field defect. This suggests that these measures are more related to current vigabatrin use than to the presence of the visual field defect.

Using receiver operator characteristics curves, they went on to look at the variables related to the presence and severity of vigabatrin visual field defect. They report that the predictive values of the photopic a-wave latency and a-b amplitude, the 30Hz a-wave latency and a-b amplitude and the latency of the first oscillatory potential all increased with increasing severity of the visual field defect. They conclude that the ERG variable most consistently associated with the presence of vigabatrin visual field defect is the 30Hz flicker amplitude. Using a threshold value of <0.52 microvolts they report a sensitivity of 100% and specificity of 75%. Adding the presence of an abnormality in either the photopic a-b wave or the first oscillatory potential, made the specificity rise to 83%.

Whilst abnormalities in ERG may be the most consistent electrophysiological abnormality in the literature, there have also been reports of a high percentage of abnormal ERGs in the absence of any visual field defects in patients receiving vigabatrin.[16] In the most recent study, Harding and colleagues[16] found increased latency of the second oscillatory potential in the vigabatrin-exposed group compared to the nonvigabatrin-exposed epilepsy patients. However, this was in the absence of any visual field defect. In another study, Harding[40] tested healthy participants with short exposure to vigabatrin and found normal scotopic ERG, normal oscillatory potentials, but significantly al-

tered b-waves in the photopic ERG. Again this was in the absence of any change in visual field.

The presence of abnormalities in the absence of any visual field change calls into question the clinical significance of these findings. Obviously, there is the hope that they could be used as a harbinger of the emergence of the deficits.

While there are not any prospective studies designed to directly test this hypothesis, there are some data suggesting that it may be true. Duckett and colleagues[41] tested a large number of patients taking vigabatrin with ERG and found abnormalities in 36 of 140 of them. Specifically, there were delayed latencies and reduced amplitudes in the b-waves as well as reduced oscillatory potentials in the light-adapted (e.g. cone) condition. Only 1 of these patients actually had a change in visual field. It should be noted that these data are only available in abstract form and the details of the visual field testing are not included. Given that this was a paediatric sample, it could be argued that visual field testing was not adequate to detect some abnormalities because of poor cooperation.

Importantly, further follow-up on some of these same patients suggests a strong relation between the presence of visual field defects and progressive ERG changes. Brigell and colleagues[42] found that in 14 patients in the open-label extension trial with visual field defects, there were 11 who had progression of ERG abnormalities over time, thus giving ERG changes a 78% sensitivity. However, they also found that 23 of the 46 patients without any field constriction also had progression of ERG changes, which limited specificity. Unfortunately, both data sets are presented in abstract form, which makes it difficult to examine them critically. However, this is probably the most compelling evidence of the use of the ERG to predict the emergence of visual field defects.

Thus, there appears to be more data with the ERG than with other tests, to support that various measures in the ERG may correlate with the presence and/or severity of the visual field defect. There is even some evidence that this may be useful in predicting the occurrence of the vigabatrin-visual field defect. However, there is still enough conflicting data regarding which specific part of the measure really shows the defect to be wary of using the ERG as the definitive electrodiagnostic measure to follow or predict the emergence of visual field defect with vigabatrin.

4. Estimates of Prevalence

The first estimates of prevalence of vigabatrin-associated visual field defects were made by the manufacturer. They used information on the adverse drug event registry about patients with symptomatic visual field defects. At the start of 1997, the manufacturer had received very few reports of any visual disturbance associated with the use of vigabatrin and they estimated the prevalence at 0.14%. However, increasing numbers of cases were documented after the first report appeared in the literature.[10] It is not clear why this happened; however, the reports garnered the attention of the neurological community, which may have led to more systematic investigation.

Since it is impossible to base true prevalence estimates on case reports, several investigators began more widespread testing of all patients receiving vigabatrin therapy. This brought the first asymptomatic cases to light and prompted the design of a few prospective studies in order to investigate rigorously the actual prevalence of visual field disturbances in patients treated with vigabatrin.

4.1 Symptomatic Visual Field Deficits

According to the manufacturer, by June 1997 there had been 92 cases of visual disturbance reported among 170 000 treated patients (i.e. incidence of 0.05%), but 7 among the 1941 in clinical trials (0.4%) [numbers cited by Black].[43] After the Eke report, Wong and colleagues[23] were prompted to review results of their large long term efficacy study and found only 1 case with suspected constriction of visual fields in 713 patients (0.14%). Based on epidemiological data reported to the manufacturer from 1990 to 1997, Harding also reports an incidence estimate of 0.14% or 14.5/ 10 000 patients per year with symptomatic visual field dis-

turbance[44] (citing an internal report from the company).

Black attempted to make an estimate of symptomatic cases in Australia using the number of reports collected via the adverse drug response database and found only 20 cases (10 severe, 10 mild) in the entire country.[43] A follow-up paper, supported by the manufacturer cited 136 spontaneous reports of visual field loss associated with vigabatrin reported to the manufacturer by March 31, 1998[19] making an additional 44 cases in less than a year.

Beran and colleagues[28] presented preliminary results at the Third European Epilepsy Congress in 1998 showing visual field defects in only 2 of 28 unselected patients receiving vigabatrin therapy only 1 of whom was symptomatic. Krauss and colleagues[13] report 4 patients with visual complaints (2 with field constriction and 2 with blurred vision) in a sample of 38 patients taking vigabatrin through a research study. Interestingly only 3 of these 4 patients had abnormal visual fields when formally tested with kinetic perimetry. Five of 19 patients (26%) studied by Arndt and associates had complained of visual symptoms.[11] The 2 patients complaining of constricted fields had verified severe visual field constriction on testing. The other 3 patients presented only with blurring and were in the mild visual field deficit group (1 unilateral and 2 bilateral).

Perhaps because of the increasing awareness of the visual toxicity associated with vigabatrin, the fraction that is symptomatic among those with measurable visual field defect seems to be increasing. In a recent report by Manuchehri et al.,[20] 45% of the patients complained of blurred vision. Many of these patients also had intracerebral lesions. Even though the study corrected the diagnosis of visual field defects for the lesions on an anatomic basis, it is difficult to ascertain whether the symptoms experienced by these patients were a result of the preexisting cerebral lesion, the effect of vigabatrin on the expected 'normal' field, or both. Another recent report[21] detailing a high prevalence of peripheral constriction with nasal predominance (one-third of the 18 patients studied) does not indicate how many were symptomatic.

4.2 Asymptomatic Visual Field Deficits

In a brief letter in the *BMJ* in 1998, Rao and colleagues[27] presented preliminary data of a much higher estimate of patients with asymptomatic deficits. Prompted by the report from Eke et al.[10] to look for visual field defects in all patients taking vigabatrin, they report that 11 of the first 15 patients (73%) receiving long term vigabatrin therapy screened showed 'appreciable visual field deficits' on Humphrey field analysis.[27] Unfortunately, no other details are given to assess the validity of this extremely high rate of visual field defects in asymptomatic patients.

There have been 9 major studies published in the last 2 years which could be used to assess the prevalence of asymptomatic visual field defects in patients taking vigabatrin. Despite similar designs, the results varied widely from 17 to 65%.[11,12,14,15,17-19,45,46]

Arndt et al.,[11] evaluated 20 consecutive patients with partial seizures (17 adults and 3 children) who had been treated with vigabatrin for longer than 6 months. They found 11 out of 19 testable patients (58%) had abnormal fields (5 bilateral severe constriction, 3 bilateral mild constriction, 3 unilateral mild constriction). These investigators used both static and kinetic perimetry and a relatively strict criterion for reliability of visual field testing. Note that the percentage of symptomatic patients in their group (26%) is much larger than the estimates of symptomatic prevalence previously reported in the literature. The reason for this is unclear.

Daneshvar and colleagues[12] tested 41 consecutive adult patients taking vigabatrin who were referred by their neurologists for screening based on the 'prevailing concern about the possible visual effects of vigabatrin.' They found 12 (~35%) with visual field defects on automated Humphrey field analysis and 4 of the 12 were symptomatic (~6% of the total sample). It is surprising that this prevalence is lower than Arndt's sample, especially as it is a patient population that is subject to bias since

they were referred for ophthalmological evaluation only after the first cases had been reported.

Gross-Tsur and colleagues[15] retrospectively examined a sample of asymptomatic paediatric patients in their clinic who had been taking vigabatrin for at least 6 months. They found 11 of 17 (65%) had visual field constriction using static or kinetic perimetry. This is the highest prevalence estimate in the literature, and is of special concern because it involves paediatric patients. Perhaps, the developing retina is more sensitive than the developed retina to vigabatrin toxicity. Alternatively, there may be an over-estimation of visual field defects because of issues related to reliability of testing paediatric patients.

Hardus and colleagues[46] examined 157 patients with drug-resistant epilepsy who had been selected for epilepsy surgery and compared the incidence of visual field defects in the vigabatrin-treated versus vigabatrin-naïve patients. They found that 20 of the 118 patients (17%) who had been exposed to vigabatrin had concentric visual field constriction compared to none of the 39 patients never exposed to vigabatrin. These patients were first screened with static perimetry and those with defects received confirmatory testing using the kinetic technique. The examiner was blinded (e.g. the examining ophthalmologist was unaware of patients' anticonvulsant regimens).

Kälviäinen and colleagues[17] analysed data from a clinical trial and identified 32 patients with asymptomatic visual field defects who were taking vigabatrin monotherapy. There were 13 patients (~40%) who had abnormal fields (3 severe and 10 mild) [kinetic (Goldman) perimetry]. The examiner was also blinded in this study and an independent neuro-ophthalmologist verified their visual field results in 25% of the patients.

Lawden et al.[18] screened 31 vigabatrin patients (29 adults and 2 children) from their neurology and epilepsy clinics using static perimetry (Humphrey). There were 16 patients (52%) with abnormal visual fields. Other reasons for abnormal fields were stated for 4 patients; thus, 12 patients (39%) had visual field defects attributable to vigabatrin. Of the 12, three complained of tunnel vision and another 5 complained of blurring. Thus, the prevalence of symptomatic cases was ~30% of the total sample. The ophthalmologist who examined the visual field data in this study was also blinded to drug treatment. They also used extremely strict criteria for cooperation and had a low threshold for deeming a patient 'unreliable' on field testing. Despite this rigorous methodology and relatively low estimate of asymptomatic cases, the high percentage of symptomatic patients relative to other studies, raises the question of patient selection bias.

Miller and colleagues[14] performed complete neuro-ophthalmological evaluations on 32 clinical trial patients receiving vigabatrin and compared them with 10 control patients who had not been exposed to vigabatrin.[14] Almost all patients underwent both static and kinetic perimetry. Their paper does not report the percentage of patients with visual field defects but gives the mean visual field constriction as assessed in degrees of vision compared to controls. Their tables do contain data presenting the number of patients with a given deviation from normal in visual field measurements. Based on kinetic perimetry they found 7 of 20 patients outside the range of control patients. Using static perimetry they found 9 of 19 patients outside the range of the control participants. The prevalence of visual field defects in this study appears to be similar to others reported in the literature.

Wild and colleagues[19] examined data from an open-label extension trial in Japan. Of 102 patients who underwent ophthalmological assessment screening, 33 were judged to have abnormal fields (3 had alternate explanations). Overall prevalence was judged to be 29%.

Similar to Gross-Tsur et al,[15] Wohlrab and colleagues[45] looked exclusively at visual impairment in children.[45] After excluding patients younger than 5 or those who were intellectually handicapped, they found 12 testable patients out of a cohort of 153 paediatric patients who had been treated with vigabatrin. All were asymptomatic for visual field defects. Using Goldmann perimetry, they report abnormalities in a total of 5 patients (~42%). There

were 2 of the 5 patients who had intracranial lesions that could account for visual field defects (temporal lobe resection or parieto-occipital lesion). Therefore, abnormalities that could be directly attributable to vigabatrin were observed in 3 patients (25%). Interestingly, only 3 of the 12 testable patients were still receiving vigabatrin therapy at the time of evaluation, the others had stopped therapy because of primary lack of efficacy or loss of efficacy. Note that this estimate of prevalence in the paediatric population is much lower than the 65% reported by Gross-Tsur et al. (see earlier in this section).[15]

5. Is There a Causal Relationship?

Perhaps the most important question to ask is whether or not the reported visual field defects are causally related to the use of vigabatrin. A review of the literature shows that most studies are not designed to answer this question and may only suggest an association. Many studies have used MRI data and have ruled out obvious structural lesions as the cause of visual field defects. However this still does not prove that the defects are caused by vigabatrin. In fact, very few studies reported any *a priori* symptomatic visual field defects except those in patients who had undergone lobectomy for epilepsy or tumour surgery. In general there was no comprehensive visual assessment before introducing vigabatrin. One can posit many other explanations for the apparent association including that the defects are related to the longstanding epilepsy itself or that the defects are caused by a combination of anticonvulsant drugs and might be more prevalent when vigabatrin is included.

It is very difficult to calculate the effect of other antiepileptic drugs given the variability of drug combinations, duration of use and dosing. Many studies reported other anticonvulsant use in their patients, but few detailed all of the past combinations. Since vigabatrin is a relatively new medication, the majority of patients used it as an add-on to their current regimen, hence the confounding variables. However, there are some data on visual field defects with other antiepileptic drugs. There is also some suggestion that combining vigabatrin with some other antiepileptic drugs may be an important factor in the development of the defects.[10,19,22,24,34]

In an attempt to prove or disprove causality, Leach[47] evaluated a small cohort of patients with epilepsy, some of whom were exposed to vigabatrin and others who were not. They found a very high percentage of 'some degree of visual defect' in both groups (85% in the vigabatrin group and 70% in the non-vigabatrin group). Unfortunately, this was published in abstract form only and details of the nature of these visual abnormalities were not given; however, the presence of visual changes without vigabatrin exposure does implicate other factors.

Schmidt and colleagues[48] studied a cohort of 64 patients with intractable epilepsy prospectively by ophthalmological and visual field testing at baseline and then again at follow-up. They found 16 patients who developed visual field defects over time, 13 of whom had been exposed to vigabatrin. They also report that the patients who developed visual field defects were significantly older and suggested that increasing age may be a predisposing factor to vigabatrin-related visual field defects.

In another prospective study from the same group, Schmitz et al.[49] monitored visual field changes in 37 patients with intractable epilepsy over 12 months, testing them with kinetic perimetry before treatment, at 6 weeks and at 12 months. There were 15 patients receiving antiepileptic drugs at the time of enrolment who received add-on therapy with vigabatrin. Another 22 had never received any antiepileptic drug before and were given monotherapy with carbamazepine or valproic acid (13 or 9 patients, respectively). There was a statistically significant constriction of the visual fields in the vigabatrin group over time, most prominent after 6 weeks. There was also a change in the carbamazepine group, although smaller than that in the vigabatrin group, which reached statistical significance in 1 case. As this study looked at add-on therapy only, it may be concluded that the visual field defect developed as a reaction to multidrug therapy and not to any one drug.

There are 2 large studies which implicate vigabatrin as the cause of visual field defects. The first is the report by Kälviäinen and colleagues,[17] who show a significant difference between the prevalence of visual field defects in patients taking vigabatrin compared to those taking carbamazepine.

The authors examined a subset of a cohort of 135 patients with new-onset complex partial seizures who had been randomised originally to receive monotherapy with either vigabatrin or carbamazepine. (This is the only peer reviewed paper we are aware of where the confounding variable of previous use of, or combination use with, other antiepileptic drugs is removed.) The authors examined 50 asymptomatic patients from their cohort: 32 patients taking vigabatrin and 18 patients taking carbamazepine. They also included a group of healthy participants as controls. Detailed ophthalmological exams were performed by a physician who was blinded to the drug regimen.

There were no significant differences among the 2 drug groups and the controls on any of the demographic variables, the type of epilepsy, or length of treatment (mean 69 months on vigabatrin and 60 months on carbamazepine). The results showed abnormal visual fields (by kinetic perimetry) in 13 of the 32 vigabatrin patients (40%; 3 severe and 10 mild) but none in the carbamazepine or control groups.

This estimate is perhaps the strongest data of the true prevalence of visual field defects associated with vigabatrin. The fact that these patients were newly diagnosed seizure patients and did not have a history of longstanding uncontrolled seizures or antiepileptic drug use is strong evidence that visual field defects are caused by vigabatrin use. However, the authors showed that there is no statistically significant correlation between the degree of the visual field defect and either the duration of therapy, the dosage or the cumulative dosage of vigabatrin.

Hardus and colleagues[46] compared a similarly large group of 157 patients with intractable epilepsy, some of whom had been exposed to vigabatrin (118) and some of whom had not. They found a prevalence of visual field defects of only 17% in the vigabatrin group, compared to zero prevalence in the control group. Whilst these patients were not naïve to antiepileptic drug therapy (as in the Kälviäinen et al. study), the authors did statistically investigate the contribution of all of the other drugs. The only drug that correlated significantly with the presence of visual field defects was vigabatrin. There was also a significant correlation between the severity of the visual field defect and the length of treatment with vigabatrin: the visual field defect was more extensive in those patients with 2 to 4 or 4 to 6 years' exposure compared with 0 to 2 years' exposure.

5.1 Evidence of Visual Problems with Drugs Other than Vigabatrin

There are case reports scattered in the literature which describe visual problems, including visual field defects, attributed to other anticonvulsant drugs. As might be expected, most have actions on the GABA system but others do not.

5.1.1 Non-γ-Amniobutyric Acid (GABA) Drugs

Carbamazepine

Nielsen and Syversen[50] reported 2 cases of retinopathy attributable to carbamazepine, whose mechanism of action is Na^+ channel blockade, both of which reversed upon discontinuation of the drug. Of note, in the 1 patient where fields were tested they were normal. Carbamazepine has also been implicated in visual field dysfunction. In the report by Kälviäinen et al., the group taking carbamazepine showed significant visual field constriction in superior fields compared with the controls, though not as large as the vigabatrin group.[17]

5.1.2 GABA Drugs

Diazepam

Elder[51] described a case of an elderly caucasian female with bilateral concentric visual field constriction (by Humphrey analysis) in association with a high dosage of diazepam (25mg 4 times daily). She was retested at 6 months after dosage reduction and the visual field defect was much improved. At 12 months after discontinuation of the

drug, there was a marked improvement in her condition.

Progabide

Baulac et al.[52] reported a case of a patient with tunnel vision who was found to have a severely constricted visual field (by automated analysis) whilst receiving progabide and phenobarbital. Progabide was replaced by valproic acid and fields improved over time.

Valproic Acid

Whilst there are no studies specifically looking at the effect of valproic acid on visual field defects, there are several reports on vigabatrin that show its combination with valproic acid may be particularly toxic.[10,22,24,34] Arndt and colleagues[11] state that the only patients in their study who were symptomatic with visual field constriction, showed severe visual field changes and had abnormal electrophysiological responses, were 2 patients treated with this combination. One group of the cohort reported by Wild and colleagues[19] who were receiving vigabatrin plus valproic acid, had a higher percentage of visual field defects than the groups who were on other drug regimens. This suggests a higher incidence or severity of visual field defects when vigabatrin is combined with valproic acid than with other antiepileptic drugs. However, these results were not confirmed in the group from the open label extension trial where carbamazepine in combination with vigabatrin produced the highest percentage of visual field defects.[19]

In the study by Wohlrab and colleagues,[45] there was 1 patient in their non-vigabatrin exposed control group with visual field defects who was taking lamotrigine and valproic acid. This patient had been treated previously with ethosuximide and clobazam. However, in another study there were no instances of visual field defects in patients taking valproic acid monotherapy.[49]

Obviously, these reports do no more than suggest an association and are not statistically reliable. A drug-drug interaction that enhances retinal toxicity is certainly possible and needs to be studied in a more scientific manner.

Tiagabine

If we are to posit that visual field defects are a result of increased GABA levels in the retina, then the other designer drug which acts as a GABA reuptake inhibitor, tiagabine, should show similar effects. However, a literature review does not reveal much evidence for this. Collins and colleagues[53] examined the data from all tiagabine phase II and III clinical trials in the US (>2500 patients) and found there were only 8 instances in the adverse events reports of visual changes that could be related to visual field defects. Two of these patients had fixed visual field defects that were not related to tiagabine, 4 had only transient problems, which self-resolved and the last 2 resolved after reduction of either carbamazepine or tiagabine.

Since then other researchers have looked more carefully for asymptomatic cases. Fakhoury and colleagues[54] tested 11 patients who had a mean of 2 years' exposure to tiagabine and no exposure to vigabatrin. They found none had a selective peripheral visual field constriction; although they do report that 4 had 'nonspecific visual field changes' which could not be reproduced. Kälviäinen and colleagues[55] tested patients receiving tiagabine monotherapy with Goldmann perimetry and found no evidence of visual field constriction in 2 groups: 22 patients who were previously naïve to antiepileptic drug therapy and had mean exposure of 21 months, and 34 who had switched from another antiepileptic drug.[56]

The absence of visual field defects in patients taking tiagabine suggests that the mechanism of visual field constriction is not just the increase in synaptic GABA in a retinal layer, but that other factors, such as the physicochemical properties of the vigabatrin molecule may be involved.

6. Evidence Regarding the Reversibility of the Defects

The studies in this article have only appeared in the literature in the last 3 to 4 years. Thus, there is no true long term follow-up of individual cases. Also, the quality of the data regarding reversibility or progression is highly variable. Many studies fail to

mention the length of the follow-up period or how the patients were reassessed. In the earlier case studies, most reported no significant change in the condition.[10,22,23] Arndt and colleagues[57] tested 25 patients and found visual field defects in 15 of them. These patients were then divided into 2 groups; 1 group continued with vigabatrin therapy and the other did not. Retests after 6 months showed there was no difference between the first and second tests, which suggests there was no progression or reversal of the visual field defect.

6.1 Reversibility

There are reports of some improvement of visual field defects after vigabatrin therapy is ceased. Acheson[30] reported improvement in 3 of 5 patients. Krakow and associates[58] reported that visual field defects improved significantly in 2 patients when retested 6 months after discontinuation of the drug. One case report documented significant improvement in both symptoms and visual field testing after withdrawal of the drug in a 10-year-old patient.[33] These authors suggest that the repair mechanisms in children might be better than in adults. However, others have suggested that this may have simply been a practice effect of repeated visual field testing.[25] Data from a paediatric cohort reported by Wohlrab and colleagues[45] do not support the idea that children have better ability to recover than adults. While they did not include follow-up data *per se*, they do note that 4 of their 5 patients with visual field defects had discontinued the drug anywhere from 1 month to 2.5 years prior to the time of assessment. This suggests that the deficits are at least persistent and not easily or quickly reversible in all paediatric patients.

Several larger studies have also reported improvement of visual field defects after withdrawing vigabatrin. In the study by Lawden and colleagues,[18] there was modest improvement upon withdrawal of the drug in 3 of 16 of their patients. However, those with severe defects have shown no improvement over a 3-year follow-up period. Two of their patients with deficits remained on vigabatrin. In 1 patient, the condition remained stable over 3 years, and in the other there was a slight deterioration over 11 months.[18]

In a series of patients with temporal lobe epilepsy,[59] visual field defects did not improve after discontinuation of vigabatrin. Similarly, in another study[35] there was no significant change in visual fields, visual acuity, or colour vision in 9 of 13 patients who had experienced visual changes on vigabatrin treatment 3 to 9 months after discontinuation of the drug. Some small but significant changes in various parameters of the ERG were noted; however, the authors state that these may have been an artifact of the fitting algorithm used to measure the responses. Overall there was no significant improvement of the ERG amplitude reductions or the oscillatory potential amplitudes, although they did note large improvements in individual patients. Because the patients who showed the largest improvement were those with no or minimal visual field defects, the authors suggest that the progression to visual field defect may signify permanent injury. Those same patients were among the youngest in their sample, which suggests that age may be a factor in recovery.

6.2 Progression

The analysis by Wild et al.[19] of 1 of the long term extension cohorts, presents the data regarding the prevalence of vigabatrin-related visual field defects as a function of length of treatment. They found that there was no significant difference in the occurrence of visual field defects in those treated for greater than or less than 4 years (32 *vs* 28%). This suggests that either there was no significant progression of the defects over time or that the defects appear prior to 4 years if they are going to appear at all. Similarly, the Hardus et al.[46] study showed a significantly increased severity of deficit in those treated for more than 2 years compared to less than 2 years, but they did not find a significant difference between those treated for 2 to 4 or 4 to 6 years. Conversely, 1 of the patients in the Lawden et al. study[18] did have a slight deterioration of their condition over an 11-month follow-up period.

Unfortunately, there have been no large prospective trials with frequent examination to truly document progression. Clearly, the deficits must appear at a certain period of time and it is probably a gradual process. It may be concluded that this time period was present in the studies where progression was noted. The question remains whether or not there is a plateau in the condition. Information from at least 2 studies would support this,[19,46] although a subsequent report by 1 of the same groups,[59] suggests that a slight but measurable progression could be seen in the visual field of 11 patients who continued taking vigabatrin after the diagnosis of visual field defects.

7. Conclusion

Vigabatrin is an extremely effective anticonvulsant that has been in widespread use outside the US. The authors have attempted to review all of the clinical studies related to visual problems associated with, and thus often attributed to, vigabatrin use. Our goal was to use these data to conclude the truth about whether these effects are in fact causally related to vigabatrin and if so how frequent and severe these problems are. We also hoped to use the data to make recommendations about the safety of using the drug and how patients might best be monitored during its use. However, what became clear is that there is such a tremendous amount of variation in the data published in the current literature that it is difficult to achieve our goal.

7.1 The Nature of the Defects

There are numerous papers suggesting that vigabatrin use is associated with a variety of visual changes. The most frequent change is an asymptomatic visual field constriction but reports of decreased acuity, colour vision and abnormal funduscopic examination also exist.

7.2 Causality

The majority of the published data is in case report form, which makes proof of causation very difficult. The 2 papers that used proper scientific methodology to investigate this condition seem to support the notion that vigabatrin causes these changes;[17,46] however, there needs to be further studies with larger total populations to answer this question definitively. Currently, we believe that most practitioners are operating on the premise that vigabatrin is the causal factor of visual field defects.

7.3 Incidence

The rapid appearance of all of the symptomatic cases in the literature is still unexplained. Where were all of these patients in the first 10 years of using this drug? The manufacturer's estimate of incidence of visual field defects with vigabatrin was approximately 0.1%, but the case reports of reportedly unselected samples cite incidences anywhere from ~6[12] to 30%.[18]

More puzzling is the discrepancy in the numbers reported in the literature from the few papers that attempted to estimate prevalence of the asymptomatic cases, which ranged from 17[46] to 65%[15] or even 73%.[27] Possible explanations for these discrepancies include various biases and methodological issues. Selection biases and reporting biases would tend to increase the estimates of incidence. Conversely, problems with patient cooperation and/or technical difficulties in measurement of the visual field defect would tend to decrease the estimates of incidence. More or less of each of these types of biases in a given sample could greatly influence the overall number reported.

7.3.1 Monitoring the Patient

There needs to be many more studies to fully define the role of vigabatrin in visual field constriction; however, the drug is still prescribed in many countries. For this reason, we make the following recommendations for monitoring patients during vigabatrin use.

7.3.2 Visual Field Testing

Both static and kinetic methods of visual field testing are highly operator and patient-dependent. This is an important issue when the patient populations who might be monitored is considered (e.g. those with mental retardation or uncooperative chil-

dren). Krauss and colleagues[60] have reviewed the relative benefits and problems of each technique. There is literature to suggest that kinetic perimetry is more sensitive than static methods and should be preferred for this reason. One patient in the study by Krauss et al.[13] was shown to have a deficit only when tested with kinetic methodology. Miller and colleagues[14] found that kinetic perimetry produced larger differences compared with controls than static testing. The differences were only statistically significant in 1 eye using the static methodology.

The sensitivity difference between static and kinetic methodology may be responsible for some of the discrepancies in the literature regarding the percentage of patients with visual field deficits. For instance, Hardus and colleagues[46] screened with static perimetry then used kinetic perimetry for confirmation of the visual field defect. It is possible that this resulted in some undetected cases and could account for the overall lower percentages in their study compared with others.

7.3.3. Electrophysiological Measurements

Given the number of problems with detecting visual field defects and questions about their reversibility once present, it would be beneficial to follow their development objectively by use of electrophysiological measures. Unfortunately, there does not appear to be 1 measure that consistently corresponds to either the presence or the severity of the visual field defect. The literature cites many patients with abnormal fields yet normal electrophysiological tests, and vice versa.

The basic science data suggests that the various retinal abnormalities that can be seen in tissue preparations is easily explained by the presence of increased GABA,[61] but this does not necessarily mean that there is a causal relationship to the visual field defect. If it were that simple then there should routinely be abnormal electrodiagnostic measures with every abnormal visual field detected; and this is clearly not the case.

The VEP appears to be the electrophysiological test that is least correlated to visual field defects: most studies have reported normal VEPs. This is not surprising since the visual field defect is thought to represent retinal toxicity and the VEP is a measure of optic nerve integrity.

The EOG is more promising since it does measure the function of various cell layers in the retina. Unfortunately, the abnormalities are not closely coupled to appearance of the visual field defect, appear to be an epiphenomenon of the increased GABA, and are completely reversible upon cessation of the drug regardless of the presence or absence of the visual field defect.

Data are perhaps best for the use of the ERG in following or perhaps even predicting the development of visual field defects while using vigabatrin. Johnson and colleagues[35] suggested this was the most important electrodiagnostic test because the changes become irreversible once the visual field defects appear. Harding and colleagues[16] specifically implicate 1 measure of the ERG, the amplitude of the 30Hz flicker response, as being predictive of the presence and severity of the vigabatrin-visual field defect with a 100% sensitivity and 75% specificity. Brigell and colleagues[42] tried to use the progression of ERG changes over time as a predictor of the appearance of visual field defects but found a much lower specificity of ~50%. Nevertheless, there does appear to be consensus between ophthalmologists at Johns Hopkins Medical Center[62] and at Aston University, Birmingham, England,[16] that the ERG is the best option for a potential mechanism for screening (i.e. rather than the VEP or the EOG). Obviously, the overall specificity of the ERG and its individual variables need to be confirmed if it is to be used as a screen. A false positive test result could mean that patients would be taken off their medication, yet have no visual field defect.

7.4 Dose Response

There is a lack of data on the dose-response characteristics of vigabatrin and the development of visual field defects. The only available data are reports of trends that implicate duration of therapy[15] or cumulative dose[16,17] with the presence or severity of visual field defects. Either these stud-

ies are not large enough to provide sufficient power to detect a significant difference, or the effect is truly not very strong. Regardless, there is no definitive evidence regarding dose-response at this time.

This issue is especially important in the paediatric population where vigabatrin is used to treat infantile spasms. If the length of treatment before development of visual field defects was known then the drug could be used for that length of time to control this typically age dependent catastrophic form of epilepsy, after which the child would automatically be switched to another anticonvulsant. For a baby with infantile spasms attributable to tuberous sclerosis, even a clear risk of an asymptomatic visual field defect may be acceptable compared to the potential for severe long-term morbidity from the lack of uniquely effective treatment or management with other risky and ineffective modes.[63]

7.5 Reversibility

Perhaps the most important area to elucidate is whether or not these changes are reversible. Data is scarce on this subject; however, we can hope that data will emerge as follow-up periods become more substantial. There are some intriguing suggestions that increasing age may reduce the likelihood of reversibility. If proven correct, this would have major implications on the use of vigabatrin in children with infantile spasms. It will be challenging to obtain good data, even with long term follow-up, because of the complexity of the issues involved (e.g. cumulative dose, duration of treatment, combination of other antiepileptic drugs, seizure type and severity, age and gender).

We have documented and assessed the available data and have stated the need for more complete information regarding several aspects of the mechanistic basis of visual field defects associated with vigabatrin that could facilitate rational clinical decision making. The treatment choices, both pharmacological and nonpharmacological, for patients with refractory epilepsy have grown substantially in the last few years. Thus, it is doubtful that the clinical positioning of vigabatrin is likely to change in the future from that of a very valuable 'niche drug,' with emphasis on paediatric usage.

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