Vigabatrin

James W. Wheless,* R. Eugene Ramsay,† and Stephen D. Collins‡

*University of Tennessee Health Science Center, Le Bonheur Children's Medical Center, Memphis, Tennessee; †University of Miami/Jackson Memorial Medical Center, Miami, Florida; and ‡Ovation Pharmaceuticals, Deerfield, Illinois

Summary: Refractory epilepsies such as infantile spasms (IS) and complex partial seizures (CPS) can have a severe negative impact on the neurological integrity and quality of life of affected patients, in addition to drastically increasing their risk of premature mortality. Early identification of potentially effective pharmacotherapy agents is important. Vigabatrin has been shown to be a generally well tolerated and effective antiepileptic drug (AED) in a wide variety of seizure types affecting both children and adults, particularly those with IS and CPS. A bilateral, concentric constriction of the peripheral visual field characterizes the visual field defect (VFD) associated with vigabatrin, well characterized by numerous studies. This peripheral VFD presents in 30–50% of patients with exposure of several years; however, most of these patients are asymptomatic. In well-controlled studies, the earliest onset in patients with CPS is 11 months and at 5 months in infants, with average onsets being more than 5 years and 1 year, respectively. Patients with a peripheral VFD retain an average 65° of lateral vision (normal, 90°). The fact that many patients never develop the vigabatrin-related peripheral VFD, despite long-term exposure at high doses, may support the hypothesis that the injury is an idiosyncratic adverse drug reaction (as opposed to a strict dose- or duration-dependent toxicity). Effective testing methods are available to aid in the early detection and management of the peripheral VFD. This article discusses issues of importance to clinical decision-making in the use of vigabatrin to assist the physician and patient in assessing the benefits of vigabatrin therapy and understanding the potential risks of the VFD and uncontrolled seizures. **Key Words:** vigabatrin, epilepsy, refractory epilepsy, complex partial seizures, infantile spasms, West syndrome, visual fields.

EPIDEMIOLOGY OF COMPLEX PARTIAL SEIZURES AND INFANTILE SPASMS

Epilepsy is a common medical disorder that demonstrates a cumulative incidence of 3% in the general population.[1] A significant minority of patients with epilepsy develop treatment-resistant or catastrophic variants of the disorder. partial-onset seizures with or without secondary generalization are experienced by more than 50% of patients with epilepsy.[2,3] In the united states, the incidence of complex partial seizures (cps) in people aged 60 years or less is 20 cases per 100,000 person-years.[4] for people aged 60–80 years, incidence increases to 80 cases per 100,000 person-years.[4] Complex partial seizures are characterized by complete or partial alteration of consciousness, as well as verbal or motor automatisms. some, but not all, patients also experience associated aura.

Infantile spasms (IS), also known as West syndrome, are a rare and catastrophic subtype of epilepsy with onset during infancy, characterized by myoclonic–tonic seizures and the electroencephalogram (EEG) pattern of hypsarrhythmia.[5] The incidence of IS in the United States is estimated at ≤0.60 per 1000 live births, with prevalence suggested to approximate ≤0.2 per 1000 children aged 10 years or less.[6] Of those who develop IS, 90% do so at ≤12 months of age,[7] with peak onset between ages 4 to 8 months. Infantile spasms, per se, do not usually persist into adulthood.[8] Approximately 36% of patients with a history of IS are seizure-free by adulthood[9]; however, 50–70% of patients develop other seizure types, and 18–50% develop Lennox–Gastaut syndrome.[8]

VIGABATRIN: A DESIGNER MOLECULE

Vigabatrin was synthesized in a deliberate attempt to find a molecule that would increase CNS levels of GABA, and could therefore decrease seizures by providing increased inhibition in epileptogenic circuits. Thus, vigabatrin acts as an indirect GABA agonist, which propagates its clinical effects via selective, noncompetitive

Address correspondence and requests for reprints to: Stephen D. Collins, M.D., Ph.D., Ovation Pharmaceuticals, Deerfield, IL 60015-2502.E-mail: Collins@OvationPharma.com.

inhibition of GABA transaminase, thus raising GABA levels in the brain.[10]

PHARMACOLOGY OF VIGABATRIN

The pharmacokinetic profile of vigabatrin is favorable, given its low protein-binding, lack of hepatic metabolism, renal excretion, and extended functional half-life.[11] The time to peak concentration is 2 hours, with a serum half-life of 5 to 8 hours in adults.[10] In children, the time to peak concentration is 1.3 to 2.4 hours, with a serum half-life of about 5.5 hours.[12] Serum concentrations do not correlate with efficacy, however, because enzyme binding (and the resultant elevation of GABA levels) is not correlated with circulating drug concentrations. Elimination is primarily renal; patients with renal impairment who are receiving hemodialysis typically experience reduced excretion rates of approximately 40–60%.[10]

No significant interactions occur with most antiepileptic AEDs. A reduction of serum levels of phenytoin can occur.[13–15] Phenytoin dosing decisions should be based on seizure control and clinical signs of tolerability during initiation of vigabatrin in a patient on phenytoin, rather than predetermined dose alterations.

Efficacy of vigabatrin in IS and CPS

Numerous studies have demonstrated the effectiveness of vigabatrin in patients with a wide age range and a variety of seizure types.[16–18] Approximately 60–70% of patients with CPS treated with vigabatrin, as a mono- or polytherapeutic agent, experience a significant (≥50%) reduction in seizure activity.[16,18] Furthermore, 8% of patients with CPS treated with vigabatrin in the two largest well-controlled studies experienced complete seizure cessation for up to 18 weeks.[19,20] These subjects had failed three to four previous anticonvulsants, including barbiturates, phenytoin, carbamazepine, and valproic acid. Most had also failed benzodiazepines, verifying that this was a refractory population.

Meta-analytic comparison of vigabatrin and other recently introduced AEDs has shown vigabatrin to be an effective agent for partial seizures.[21] Additional studies of varying design also contributed to the approval for treatment of CPS by the European Agency for the Evaluation of Medicinal Products (EMeA).[19,20] Two U.S. multicenter, double-blind, randomized, placebo-controlled, dose-ranging trials of vigabatrin as add-on therapy for use in patients with refractory CPS were conducted to support the new drug application approval in the United States. Ovation Pharmaceuticals is currently summarizing additional risk information requested by the U.S. Food and Drug Administration (FDA) before marketing approval can be granted. Pediatric studies in children with CPS suggest that vigabatrin may be effective in this population as well.[22–26]

Results from European randomized, controlled, placebo and active trials, open-label prospective studies, and retrospective reviews suggest that vigabatrin is safe and has effectiveness in treating subjects with IS.[27–31] One study of vigabatrin treatment in IS provided substantial evidence of its effectiveness (70% spasm-free) with greater response rates (85% spasm-free) in patients with tuberous sclerosis for periods up to 33 months.[17] The United Kingdom Infantile Spasms Study evaluated the effects of vigabatrin *versus* hormone treatment on seizure control and neurodevelopment in 101 infants followed for 1 year.[32] Significant between-group differences in seizure-freedom were not observed by the final assessment at 1 year; approximately 75% of patients from either treatment condition experienced an absence of spasms.[32] The study did not use video-EEG confirmation of spasm cessation, which may have led to a somewhat high estimate of efficacy in both treatment arms. Hormonal treatment resulted in an early onset of spasm cessation and appeared to convey greater neurodevelopmental benefits in patients without an identified seizure etiology.[32]

A large study[33,34] in 223 subjects in the United States demonstrated significant effects of vigabatrin on spasm cessation as early as 2 weeks following initiation of therapy combined with a low relapse rate. It is noteworthy that in this highly refractory patient group, 16% of patients treated with vigabatrin experienced complete seizure cessation when evaluated by video-EEG within 3 days of the end of the initial 2-week treatment period. This extremely stringent primary endpoint resulted in an inaccurate efficacy estimate, because it was not possible for most subjects to actually obtain video-EEG recording in this short time span. As the time window expanded to 9 days (a more stringent clinical condition: it now required 23 days of clinical spasm freedom prior to video-EEG evaluation), the percentages of subjects demonstrating complete control increased to 28%. Following this initial evaluation period, increasing numbers of subjects attained complete spasm cessation. Sixty-eight percent of the subjects in the high-dose group [target, 100 (mg/kg)/day] became spasm-free for the duration of the study, which in the earliest enrolling subjects was up to 3 years.

Vigabatrin was the drug of choice for IS in a 1998 consensus guideline[35]; these guidelines were revised after the discovery of peripheral visual field defects (VFDs) in vigabatrin-treated adult patients, but continued to recommend use in IS.[36] Vigabatrin has remained the drug of choice for IS for many clinicians in the United States, Europe, and Canada, especially when caused by tuberous sclerosis.[37–41]

Tolerability

Vigabatrin has established a reputation for high response rates and overall good tolerability in multiple studies over the past decade.[1,42] Vigabatrin has few adverse effects on cognition and may contribute to modest cognitive improvement secondary to cessation of spasms in patients with IS.[43,44] However, approximately 2–4% of patients treated with vigabatrin may develop behavioral side effects, characterized primarily by agitation, irritability, depression, or psychosis.[43,45–48] These effects usually occur on initiation of therapy and are reversible upon decrease of dose or elimination. Mild weight gain and possible exacerbation of absence and myoclonic seizures are other reported adverse effects.[11] No significant laboratory abnormalities have been seen in patients treated with vigabatrin in clinical studies or in postmarketing safety reports since its introduction in the United Kingdom in 1989.

VISUAL FIELD DEFECTS: THE POTENTIAL RISK

During the same year that the FDA issued an 'approvable' letter to the initial sponsor (in 1997), numerous physicians recognized visual field constriction in as many as 28–70% of the adult[49–51] and pediatric[52,53] patients on add-on or monotherapy; their publications and presentations prompted the release of a 'not approvable' letter by the FDA in 1998. One of the key factors that delayed prior recognition of this defect was the fact that approximately 90% of patients were asymptomatic when the peripheral VFD was detected by their physician. Numerous publications since 1997 have characterized the nature of vigabatrin-related VFDs, and they can now be differentiated from other visual field changes caused by epilepsy or other AEDs. Overall, the deficit appears to be due to progressive changes in the function of the retinal ganglia.

Vigabatrin VFD: what it is

A bilateral, concentric constriction of the peripheral visual field of mild to marked severity characterizes the VFD associated with vigabatrin. The nasal field is typically, though not always,[54–56] more extensively affected than the temporal field.[57–60] Unique alterations of specific electroretinographic parameters have been shown to correspond to this field defect.

An analysis of visual fields of subjects who experienced the vigabatrin VFD in a large, multinational study revealed an average peripheral (lateral) field of 65° (normal, 90°) (FIG. 1).[61] The majority of subjects in this study who had experienced a vigabatrin-related VFD retained greater than 60° of lateral visual field. Although normal fundoscopy has been described in many studies, pale disk and mild optic nerve pallor have also been reported.[56,58,60,62–65] A variety of other findings have been reported, including retinal artery narrowing, epiretinal membrane formation, an irregular sheen (or abnormal macular pigmentation), and reduction in the peripapillary nerve fiber layer.[55] These same retinal abnormalities have also been reported in non-vigabatrin-treated patients.[55,58,60] Optic disk pallor has been noted in severe cases and is associated with optic atrophy,[56,65,66] a likely irreversible change.[36,65]

Although the mechanism of action for injury is unknown, the final common pathway appears to be the retinal ganglion cell. Although some patients with peripheral VFDs experience disturbances of sufficient severity to hinder daily activities, the majority are not cognizant of their visual defect (Aventis 4020, unpublished clinical study). Morphological correlates to these ophthalmic observations are extremely limited. Children develop the same peripheral VFD defect as adults,[67] although diagnosis in very young or mentally impaired children is technically challenging given cognitive and developmental limitations on their ability to comply with perimetric tests.[68] A variety of electrophysiologic techniques exist that can be used to detect retinal effects of vigabatrin in infants, children, and adults with significant cognitive or behavioral challenges.[69–75]

VFD: what it is not

Multiple multinational studies have failed to find any evidence of central visual acuity changes secondary to vigabatrin use (Aventis 4020, unpublished clinical study and[62,64,76–80]). Increased sensitivity to glare has not been observed in vigabatrin patients; although some reports suggest a correlation between vigabatrin-induced VFD and contrast sensitivity[81,82]; others do not.[76,83] It remains similarly unclear whether vigabatrin is associated with deficits in color vision; some studies have indicated a correlation,[83–86] but this opinion remains in the minority.[55,57,60,64,76,87,88,89] In general, changes in the color vision of patients on vigabatrin and other AEDs typically are eliminated upon discontinuation of the medication.

Prevalence, onset, and progression of VFD with vigabatrin

The prevalence of the peripheral VFD in adult patients receiving vigabatrin was estimated, in early publications, at 17–70%.[55,58,60,64,77,78,87,88,90–97] The wide range of estimates is most likely attributable to differences in monitoring frequency, variable specificity of some perimetric methods, unblinded assessments, and ascertainment bias of small samples. A large and well-controlled study that applied more sensitive and specific methodologies supports a prevalence in adults of 30–50% (Aventis 4020, unpublished clinical study), which is similar to estimates from large cohort studies using very sensitive detection methodologies.[79]

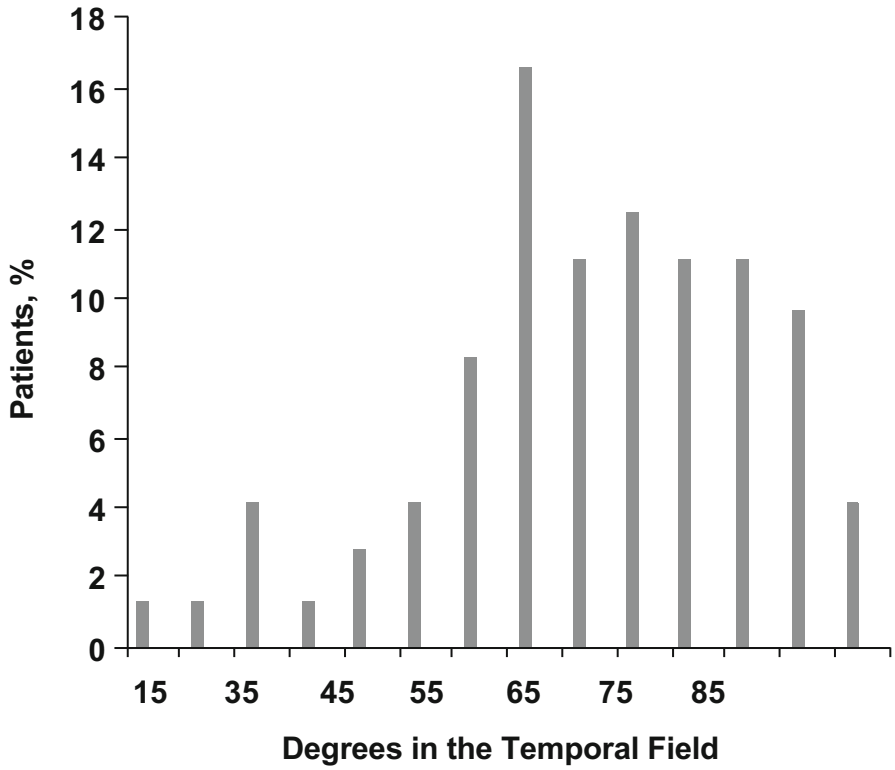

FIGURE 1. Aventis Study 402062 Histogram of degrees in the temporal field at final Goldman perimetry in subjects with peripheral VFD

The determination of prevalence in children is hindered by difficulty in performing perimetry testing before the age of 9 years. The reported prevalence in children has varied from 20%[91,96] to 65%.[59] Numerous investigators have reported the prevalence in children to be well below that of adults,[91,96,98,99] suggesting a prevalence of approximately 20% in this younger population. The best data on infants[65,71,73,100] have established a prevalence of approximately 40%, with incidence of 16% as assessed by the highly sensitive electroretinogram (ERG) 30-Hz flicker amplitude. The prevalence of cone B-wave amplitude abnormalities, the other vigabatrin-specific ERG parameter that is sensitive and specific for the vigabatrin-induced defect, is about 20%, with an incidence of 4%.[65,71,73,100–105]

The onset of peripheral defects does not occur rapidly. In the well-controlled prospective study, the earliest period at which a well-documented abnormality has been seen in patients with CPS is 11 months, with average onset from 5.5 to 8 years (Aventis 4020, unpublished clinical study). The earliest onset in infants is at 5 months, with average onset at just over 1 year.[101,103]

The risk for developing peripheral VFD from vigabatrin is reportedly approximately two-fold greater in males than in females.[57,77,78,106–109] There is as yet no agreement on risk based on dose or duration of therapy. Some studies have not found a correlation between duration of therapy, daily or total dose, and VFD[57,87,94,110–112] but others report clear "exposure" correlations.[58–60,74,84,95,97,113–115] One study found a cumulative dose effect, with the highest incidence in patients given ≥3 g vigabatrin; another study had its peak incidence at doses greater than 4 g.[97] Single doses up to 3 g do not cause the vigabatrin VFD.[116,117]

These potential risks should not affect patient selection. As already discussed, given the extreme range of doses and duration of therapy that have been shown to be associated with the defect, and given that many patients do not develop the defect even after years and many kilograms of cumulative drug administration, it is clear that this is not a simple dose-related toxicity. Best and Acheson,[118] among others,[112,119] have proposed the pathophysiology of injury to be an idiosyncratic adverse drug reaction based on the prevalence (30–40%), distal appearance, lack of progression, and lack of remission. The defect has been shown not to progress following discontinuation of drug, and not to begin after discontinuation.[112,118,119] Notably, many patients in several studies with very long vigabatrin exposure at high doses have completely normal fields (Aventis 4020, unpublished clinical study). The defect may represent an idiosyncratic adverse drug reaction, as opposed to a strict dose- or duration-dependent toxicity.[112,118]

Monitoring and testing

None of the multiple methods for testing a patient's peripheral visual fields show any superiority in assessing the presence of concentric VFD. Testing of any system other than the retina is unnecessary.[87,88,120] Standards for visual field perimetry have been established,[121] and this test can be performed in nearly all adults. Other techniques such as contrast sensitivity visual-evoked potentials (VEP), H-field VEP, and full-flash and wide-field multifocal electroretinogram have all been used to detect defects in adults and children.[73,75,79,80,100] Assessment of peripheral VFDs in children or cognitively impaired adults has been problematic, because some of the electrophysiologic parameters that change with treatment are nonspecific, and perimetric visual field tests cannot generally be performed in children aged under 9 years. A special VEP method called the H-stimulus has been validated for assessing fields in children aged 3–10 years, with a sensitivity of 75% and a specificity of 87.5%.[68,77]

To overcome difficulties with some nonspecific AED changes in the ERG, a series of vigabatrin-specific alterations have been identified and validated.[70,71,73,79,80,100–103,122] Westall and colleagues[122] investigated the evolution of retinal development in young infants and established age-adjusted normal values of all ERG parameters for infants. This group has studied more than 200 children to date (age range, 10 days to 15 years), with a subset prospectively evaluated for up to four years. The earliest onset of retinal toxicity was observed at 5 months, with the average onset of abnormalities at greater than 1 year of treatment.[122] The incidence rates (approximately 16%) support a lower risk of developing retinal injury in infants than in adults.[101,102]

In patients on vigabatrin who have the vigabatrin-VFD, cone system ERGs, the specific ERG parameters associated with the defect, demonstrate the greatest changes from initial recording. In particular, 30 Hz flicker and cone B wave amplitude showed sustained changes, as demonstrated by Harding in adults who had simultaneous perimetric and ERG testing.[74] Most alterations of early and late oscillatory potentials (OP) and flicker implicit times are more associated with a reversible drug effect and not actual retinal toxicity. Amplitude changes of the late OP4 may be associated with retinal toxicity, although data are only suggestive at this time.

TREATMENT DECISIONS IN REFRACTORY CPS AND IS

Definition of refractory epilepsy

Seizures are described as refractory when an acceptable level of control has not been attained with the resources available to the treating physician or neurologist.[123] More than 30% of patients with epilepsy may demonstrate resistance to pharmacologic intervention.[124]

TABLE 1. *Newer Antiepileptic Drugs*

Generic name of drug	Year introduced
Felbamate	1993
Gabapentin	1993
Lamotrigine	1994
Fosphenytoin sodium	1996
Topiramate	1996
Tiagabine	1997
Levetiracetam	1999
Oxcarbazepine	2000
Zonisamide	2000
Pregabalin	2005

Decreased probability of seizure-freedom has been associated with a failure of three AEDs due to lack of efficacy.[21,124] In one review, only 5% of patients who meet these criteria retain the potential for being seizure-free and the researchers felt that this estimate was further reduced when hippocampal sclerosis is present.[125] Polypharmacy in treatment-refractory patients may lead to sedative and behavioral toxicity, as well as elevating the patient's risk of cognitive decline, poor psychosocial adjustment, and perhaps sudden unexplained death in epilepsy (SUDEP).[124]

Consequences of uncontrolled seizures

The prognosis for many patients with CPS is positive. Up to 70–80% of patients with CPS will respond to appropriate AED therapy. Unfortunately, the remaining 20–30% of patients will continue to experience intractable seizures or have significant adverse reactions to AEDs.[1,126] In patients with refractory CPS, the overall risk of death (whether due to accident, suicide, or SUDEP) is very high, compared with age-matched, healthy people.[127] Heart rate abnormalities have been found to accompany CPS in drug-resistant children and adolescents, which may contribute to the occurrence of SUDEP.[128]

The prognosis for patients with IS, however, is poor. Between 70 and 90% exhibit learning difficulties or mental retardation,[8] and psychiatric symptoms are common in patients, occurring in 20–40% of adults with a history of IS.[8] Among patients with a history of IS, the reported premature death rate ranges from 2 to 31%,[7–9] with 61% of deaths occurring at or before 10 years of age, and 10% occurring after the age of 20 years.[9]

Refractory complex partial seizures and infantile spasms

Although patients with mental retardation are at greater risk of developing refractory epilepsy, it has also been observed that cognitive impairments are frequent sequelae of early-onset epileptiform activity.[125] Children with the most refractory forms of epilepsy, such as IS,

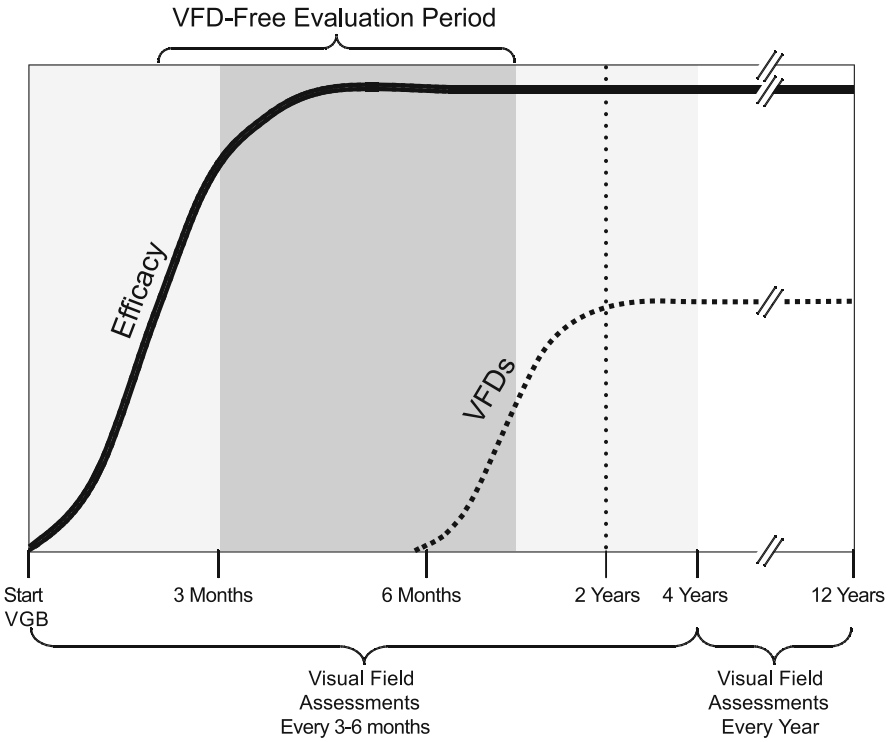

FIGURE 2. Timeline of vigabatrin therapy, typical onset of efficacy and visual field defects, and suggested visual field assessment schedule. *VFD* = visual field defect, *VGB* = vigabatrin.

demonstrate a higher frequency of profound cognitive impairment than do pediatric patients whose seizures are more amenable to treatment.[125] Researchers have found a correlation between hippocampal atrophy, cognitive decline, and extended periods of modest but chronic CPS.[125]

The desirability of rapid control to reduce secondary psychomotor regression or transition to other catastrophic seizure types (e.g., Lennox–Gastaut syndrome) is a priority in the treatment of patients with IS.[129] Corticotropin or corticosteroids are efficacious in approximately 50–75% of IS, but the adverse effects of high-dose corticosteroids are a concern.[17] Corticosteroids do not completely control spasms in all patients, are associated with appreciable relapse rates, and have serious potential side effects.[17] Valproic acid and benzodiazepines are said to be efficacious in some, but not most, patients; however, these have not been subjected to well-controlled studies.[130,131]

CURRENT CLINICAL MANAGEMENT

Ten new AEDs have been introduced to the U.S. market since 1993 (TABLE 1). The newer AEDs are more costly than their older counterparts, and there is an absence of large-scale comparative studies establishing their unequivocal superiority with regard to efficacy and safety. Differences in the side-effect profile for each drug allow latitude in changing prescribed AEDs for patients unable to tolerate their current regimen.[132] Drugs with different mechanisms of action and minimal pharmacokinetic interaction are advantageous in polytherapy regimes.[133]

BENEFIT–RISK ASSESSMENT

Refractory complex partial epilepsy is a severe, debilitating disease. Failure to effectively control seizures can severely affect the patient's quality of life and may even lead to early death. Thus, when treatments other than vigabatrin have failed to provide seizure control, this drug may be beneficial for the patient, despite the risk for or the actual loss of some peripheral vision. Vigabatrin can be evaluated for efficacy within a few months of initiation, well below the average time of onset of visual defects (FIG. 2). If no benefit has accrued for the patient, discontinuation of treatment should at a minimum greatly reduce, if not eliminate, the chance for a defect to appear. If benefit has occurred, then regular monitoring of vision along with regular evaluations of benefit will allow patients and clinicians to make ongoing decisions on risk and benefit.

For some types of epilepsy a reduction of ≥50% has been viewed as an appropriate clinical target, one that is associated with meaningful benefits for the patient.[134] For treatment of IS, however, the goal is complete sei-

zure amelioration, to improve developmental outcome, even when absolute developmental normalization is precluded by comorbid diagnoses.[134] Vigabatrin has substantially reduced or completely ameliorated seizures in many patients and may improve the developmental outcome of some IS patients, particularly those with a cryptogenic etiology, tuberous sclerosis, or localized cortical dysplasia.[32,134]

Given the catastrophic nature of IS, the risk of peripheral VFDs may be acceptable if appropriate seizure control can be achieved, thus providing an improved opportunity for normal development.[134] For this reason, many pediatric epileptologists continue to regard vigabatrin as the drug of choice in the treatment of IS, despite the risk of visual field abnormalities.[134]

Benefits from vigabatrin

Vigabatrin has been shown to be effective in decreasing or eliminating seizures in multiple, well-controlled studies, with particular efficacy in refractory epilepsies such as IS and CPS. As has been learned from multiple studies, the odds of gaining any control of seizures for a patient who has not gained effect after appropriate trials of two drugs is low, and failing three drugs puts the patient in a very refractory category. The success of vigabatrin in these refractory populations is thus all the more remarkable. Proper monitoring of vigabatrin patients may assure that the benefits are being sustained and that peripheral vision is not inappropriately compromised. The decision to stop therapy can be made as a benefit–risk decision.

Benefit–risk positioning of vigabatrin

If approved by the FDA, vigabatrin should be considered only when other treatments fail, or are not suitable for one reason or another for the individual patient. An example of such a patient would be an adult with CPS who has multiple anticonvulsant therapies (which may include both oral agents and vagus nerve stimulation) and who is not a candidate for surgical resection for epilepsy. Patients should be closely monitored before and after vigabatrin therapy is initiated. A baseline visual examination should be obtained.

Given the rapid response of most patients to vigabatrin therapy and concerns regarding the risk of peripheral VFDs, vigabatrin use should be discontinued in patients who have not benefited from treatment within about 12 weeks. For patients who continue beyond this initial trial period, follow-up visual field assessments should be conducted every 3 to 6 months thereafter for patients in whom peripheral VFDs have not been detected. If a defect is found, it is important to obtain confirmatory testing to ensure the accuracy of the findings.

CONCLUSIONS

Refractory epilepsies such as IS and CPS can have a severe negative impact on the neurological integrity and quality of life of affected patients, in addition to drastically increasing their risk of premature mortality. Early identification of potentially effective pharmacotherapy agents is important. Vigabatrin has been shown to be a generally well tolerated and effective AED in a wide variety of seizure types affecting both children and adults, particularly those with IS and CPS.

The peripheral VFD associated with vigabatrin treatment consists of a bilateral, concentric constriction of the peripheral visual field of mild to marked severity in approximately half of patients with exposure of several years. Earlier detection has been hampered by the asymptomatic presentation in approximately 90% of patients affected by VFDs. Prevalence estimates for vigabatrin-related peripheral VFDs range from 30 to 50%. The fact that many patients never develop vigabatrin-related visual problems, despite long-term exposure at high doses, may support the hypothesis that the injury is an idiosyncratic adverse drug reaction, as opposed to a strict dose- or duration-dependent toxicity. Effective testing standards are being established to aid in the early detection of vigabatrin-related peripheral VFDs; these have demonstrated sensitivities of up to 75%, with approximately 88% specificity.

With regard to clinical decision-making, the following recommendations are advanced, in the event that FDA determines that an adequate benefit–risk profile exists to approve the drug in the United States.

1. Vigabatrin should be considered for use in patients with demonstrable treatment resistance who are not candidates for other therapies.
2. Retinal function testing should be employed at baseline and throughout vigabatrin therapy.
3. The efficacy of vigabatrin should be noted within 3 months of treatment initiation, which is well below the earliest time of onset for vigabatrin-related retinopathy in well controlled studies of adults and infants.
4. Discontinuation should occur in the absence of definitive, meaningful seizure reduction during this trial period to eliminate the potential for development of peripheral defects.
5. Clinicians should continue to perform retinal function assessment and visual field testing to inform their ongoing decisions regarding the risks and benefits for patients who continue vigabatrin therapy beyond the recommended trial period.

This strategy (illustrated also in FIG. 2) should allow patients to receive vigabatrin, and the potential benefit of seizure reduction, while minimizing the risk.

REFERENCES

1. Beghi E. Efficacy and tolerability of the new antiepileptic drugs: comparison of two recent guidelines. Lancet Neurol 2004;3:618–621.
2. Berg AT, Shinnar S, Levy SR, Testa FM. Newly diagnosed epilepsy in children: presentation at diagnosis. Epilepsia 1999; 40:445–452.
3. Forsgren L, Bucht G, Eriksson S, Bergmark L. Incidence and clinical characterization of unprovoked seizures in adults: a prospective population-based study. Epilepsia 1996;37:224–229.
4. Murro AM. Complex partial seizures [Internet]. Updated: December 5, 2005. Accessed July 5, 2006. Available at http://www.emedicine.com/NEURO/topic74.htm.
5. Elterman RD, Shields WD, Mansfield KA, Nakagawa J; US Infantile Spasms Vigabatrin Study Group. Randomized trial of vigabatrin in patients with infantile spasms. Neurology 2001;57: 1416–1421.
6. Mackay MT, Weiss SK, Adams-Webber T, et al. Practice parameter: medical treatment of infantile spasms: report of the American Academy of Neurology and the Child Neurology Society. Neurology 2004;62:1668–1681.
7. Nabbout R. A risk-benefit assessment of treatments for infantile spasms. Drug Saf 2001;24:813–828.
8. Glauser TA. Following catastrophic epilepsy patients from childhood to adulthood. Epilepsia 2004;45(suppl 5):23–26.
9. Riikonen R. Long-term outcome of patients with West syndrome. Brain Dev 2001;23:683–687.
10. Product Information: Sabril, vigabatrin. Aventis Pharma Inc., Laval, Quebec, Canada.
11. Guberman A. Vigabatrin. Can J Neurol Sci 1996;23(4):S13–S17.
12. Rey E, Pons G, Richard MO, et al. Pharmacokinetics of the individual enantiomers of vigabatrin (gamma-vinyl GABA) in epileptic children. Br J Clin Pharmacol 1990;30:253–257.
13. Rimmer EM, Richens A. Interaction between vigabatrin and phenytoin. Br J Clin Pharmacol 1989;27(suppl 1):27S–33S.
14. Gatti G, Bartoli A, Marchiselli R, et al. Vigabatrin-induced decrease in serum phenytoin concentration does not involve a change in phenytoin bioavailability. Br J Clin Pharmacol 1993; 36:603–606.
15. Patsalos PN, Perucca E. Clinically important drug interactions in epilepsy: general features and interactions between antiepileptic drugs. Lancet Neurol 2003;2:347–356.
16. Garaizar C, Martinez-González MJ, Fernández-Cuesta MA, et al. Seguimiento a Largo Plazo de la Epilepsia Infantil Tratada con vigabatrina, Fuere de los Ensayos Clinicos [Long-term follow-up of childhood epilepsy treated with vigabatrin outside of clinical trials. In Spanish]. Rev Neurol 1999;29:201–207.
17. Chiron C, Dumas C, Jambaque I, Mumford J, Dulac O. Randomized trial comparing vigabatrin and hydrocortisone in infantile spasms due to tuberous sclerosis. Epilepsy Res 1997;26:389–395.
18. Satishchandra P, Kashyap B, Goverdhan S, et al. Vigabatrin in intractable complex partial epilepsy. Epilepsia 1999;40(suppl 2): 256. Abstract.
19. Data on file. Ovation Pharmaceuticals. Protocol 71754-3-C-025.
20. Data on file. Ovation Pharmaceuticals. Protocol 71754 3 C 024.
21. Cramer JA, Fisher R, Ben-Menachem E, French J, Mattson RH. New antiepileptic drugs: comparison of key clinical trials. Epilepsia 1999;40:590–600.
22. Coppola G. Treatment of partial seizures in childhood: an overview. CNS Drugs 2004;18:133–156.
23. Luna D, Dulac O, Pajot N, Beaumont D. Vigabatrin in the treatment of childhood epilepsies: a single-blind placebo-controlled study. Epilepsia 1989;30:430–437.
24. Dalla Bernardina B, Fontana E, Vigevano F, et al. Efficacy and tolerability of vigabatrin in children with refractory partial seizures: a single-blind dose-increasing study. Epilepsia 1995;36: 687–691.
25. Gobbi G, Pini A, Bertani G, et al. Prospective study of first-line vigabatrin monotherapy in childhood partial epilepsies. Epilepsy Res 1999;35:29–37.
26. Zamponi N, Cardinali C. Open comparative long-term study of vigabatrin vs carbamazepine in newly diagnosed partial seizures in children. Arch Neurol 1999;56:605–607.
27. Appleton RE, Peters AC, Mumford JP, Shaw DE. Randomised, placebo-controlled study of vigabatrin as first-line treatment of infantile spasms. Epilepsia 1999;40:1627–1633.
28. Chiron C, Dulac O, Beaumont D, Palacios L, Pajot N, Mumford J. Therapeutic trial of vigabatrin in refractory infantile spasms. J Child Neurol 1991;suppl 2:S52–S59.
29. Aicardi J, Mumford JP, Dumas C, Wood S; Sabril IS Investigator and Peer Review Groups. Vigabatrin as initial therapy for infantile spasms: a European retrospective survey. Epilepsia 1996;37: 638–642.
30. Mitchell WG, Shah NS. Vigabatrin for infantile spasms. Pediatr Neurol 2002;27:161–164.
31. Vigevano F, Cilio MR. Vigabatrin versus ACTH as first-line treatment for infantile spasms: a randomized, prospective study. Epilepsia 1997;38:1270–1274.
32. Lux AL, Edwards SW, Hancock E, et al. The United Kingdom Infantile Spasms Study (UKISS) comparing hormone treatment with vigabatrin on developmental and epilepsy outcomes to age 14 months: a multicentre randomised trial. Lancet Neurol 2005; 4:712–717.
33. Data on file. Ovation Pharmaceuticals. IND 47,707/Protocol 1A.
34. Elterman RD, Collins SD, Shields WD, Mansfield KA, Nakagawa J. Efficacy of vigabatrin in subjects with infantile spasms. Epilepsia 2005;46(suppl 8):167.Abstract.
35. Appleton RE. Guideline may help in prescribing vigabatrin. BMJ 1998;317:1322. Letter.
36. Frisen L, Malmgren K. Characterization of vigabatrin-associated optic atrophy. Acta Ophthalmol Scand 2003;81:466–473.
37. Lux AL, Edwards SW, Osborne JP, et al. Revised guideline for prescribing vigabatrin in children: guideline's claim about infantile spasms is not based on appropriate evidence. BMJ 2001;322: 236–237. Letter.
38. Vigabatrin Paediatric Advisory Group. Guideline for prescribing vigabatrin in children has been revised. BMJ 2000;320:1404–1405.
39. Riikonen R. ACTH therapy of West syndrome: Finnish views. Brain Dev 2001;23:642–646.
40. Paul SR, Krauss GL, Miller NR, Medura MT, Miller TA, Johnson MA. Visual function is stable in patients who continue long-term vigabatrin therapy: implications for clinical decision making. Epilepsia 2001;42:525–530.
41. Wheless JW, Clarke DF, Carpenter D. Treatment of pediatric epilepsy: expert opinion, 2005. J Child Neurol 2005;20(suppl 1):S1–S56.
42. Spence SJ, Sankar R. Visual field defects and other ophthalmological disturbances associated with vigabatrin. Drug Saf 2001; 24:385–404.
43. Guberman A, Bruni J; The Canadian Vigabatrin Study Group. Long-term open multicentre, add-on trial of vigabatrin in adult resistant partial epilepsy. Seizure 2000;9:112–118.
44. Jambaque I, Chiron C, Dumas C, Mumford J, Dulac O. Mental and behavioural outcome of infantile epilepsy treated by vigabatrin in tuberous sclerosis patients. Epilepsy Res 2000;38:151–160.
45. Sander JW, Hart YM, Trimble MR, Shorvon SD. Vigabatrin and psychosis. J Neurol Neurosurg Psychiatry 1991;54:435–439.
46. Aldenkamp AP, Vermeulen J, Mulder OG, et al. Gamma-vinyl GABA (vigabatrin) and mood disturbances. Epilepsia 1994;35: 999–1004.
47. Wong IC. Retrospective study of vigabatrin and psychiatric behavioural disturbances. Epilepsy Res 1995;21:227–230.
48. Thomas L, Trimble M, Schmitz B, Ring H. Vigabatrin and behaviour disorders: a retrospective survey. Epilepsy Res 1996;25: 21–27.
49. Kälviäinen R, Nousianen I, Mäntyjärvi M, et al. Initial vigabatrin monotherapy is associated with increased risk of visual field constriction: a comparative follow-up study with patients on ini-

tial carbamazepine monotherapy and healthy controls. Epilepsia 1998;39(suppl 6):72. Abstract
50. Koehler J, Thömke F, Tettenborn B, et al. Influence of new antiepileptic drugs on visual evoked potentials. Epilepsia 1999; 40(suppl 2):288. Abstract.
51. Sankar R, Wasterlain CG. Is the devil we know the lesser of two evils? Vigabatrin and visual fields Neurology 1999;52: 1537–1538. Comment.
52. Vanhatalo S, Paakkonen L, Nousiainen I. Visual field constriction in children treated with vigabatrin. Neurology 1999;52:1713–1714.
53. Iannetti P, Spalice A, Perla FM, Conicella E, Raucci U, Bizzarri B. Visual field constriction in children with epilepsy on vigabatrin treatment. Pediatrics 2000;106:838–842.
54. Krauss GL, Johnson MA, Miller NR. Vigabatrin-associated retinal cone system dysfunction: electroretinogram and ophthalmologic findings. Neurology 1998;50:614–618.
55. Miller NR, Johnson MA, Paul SR, et al. Visual dysfunction in patients receiving vigabatrin: clinical and electrophysiologic findings. Neurology 1999;53:2082–2087.
56. Choi HJ, Kim DM. Visual field constriction associated with vigabatrin: retinal nerve fiber layer photographic correlation. J Neurol Neurosurg Psychiatry 2004;75:1395.
57. Wild JM, Martinez C, Reinshagen G, Harding GF. Characteristics of a unique visual field defect attributed to vigabatrin. Epilepsia 1999;40:1784–1794.
58. Lawden MC, Eke T, Degg C, Harding GF, Wild JM. Visual field defects associated with vigabatrin therapy. J Neurol Neurosurg Psychiatry 1999;67:716–722.
59. Gross-Tsur V, Banin E, Shahar E, Shalev RS, Lahat E. Visual impairment in children with epilepsy treated with vigabatrin. Ann Neurol 2000;48:60–64.
60. Lawden MC, Eke T, Degg C, et al. Visual field defects associated with vigabatrin treatment. Epilepsia 1999;40(suppl 2):256. Abstract.
61. DeToledo JC, Westall CA, Collins SD. Vigabatrin induced visual fields defects: Update 2006. American Epilepsy Society Annual Meeting, December 1–5, 2006. Abstract 585 (poster).
62. Eke T, Talbot JF, Lawden MC. Severe persistent visual field constriction associated with vigabatrin. BMJ 1997;314:180–181.
63. Wong IC, Mawer GE, Sander JW. Severe persistent visual field constriction associated with vigabatrin: reaction might be dose dependent. BMJ 1997;314:1693–1694. Comment.
64. Daneshvar H, Racette L, Coupland SG, Kertes PJ, Guberman A, Zackon D. Symptomatic and asymptomatic visual loss in patients taking vigabatrin. Ophthalmology 1999;106:1792–1798.
65. Buncic JR, Westall CA, Panton CM, Munn JR, MacKeen LD, Logan WJ. Characteristic retinal atrophy with secondary "inverse" optic atrophy identifies vigabatrin toxicity in children. Ophthalmology 2004;111:1935–1942.
66. Wild JM, Hope-Ross M, Harding GFA, Betts TA. Vigabatrin retinopathy. Invest Ophthalmol Vis Sci 2002 43:E-abstract 238.
67. Pelosse B, Momtchilova M, Roubergue A, Doummar D, Billette de Villemeur T, Laroche L. [Study of visual field and vigabatrin treatment in children]. In French. J Fr Ophtalmol 2001;24:1075–1080.
68. Harding GF, Robertson K, Spencer EL, Holliday I. Vigabatrin: its effect on the electrophysiology of vision. Doc Ophthalmol 2002; 104:213–229.
69. Harding GFA, Wild JM, Robertson K, et al. Electroculography, ERGs, multifocal ERGs and VEPs in epileptic patients showing visual field disorder. Electroencephalogr Clin Neurophysiol 1997; 103:96. Abstract.
70. McDonagh J, Stephen LJ, Dolan FM, et al. Peripheral retinal dysfunction in patients taking vigabatrin. Neurology 2003;61: 1690–1694.
71. Morong S, Westall CA, Nobile R, et al. Longitudinal changes in photopic OPs occurring with vigabatrin treatment. Doc Ophthalmol 2003;107:289–297.
72. Morong SE, Westall CA, Buncic RJ, Snead OC, Logan WJ, Weiss S. Sweep visual evoked potentials in infants with infantile spasms before and during vigabatrin treatment. Invest Ophthalmol Vis Sci 2003;43:E-abstract 2720.
73. Westall CA, Logan WJ, Smith K, Buncic JR, Panton CM, Abdolell M. The Hospital for Sick Children, Toronto, longitudinal ERG study of children on vigabatrin. Doc Ophthalmol 2002;104: 133–149.
74. Harding GF, Wild JM, Robertson KA, et al. Electro-oculography, electroretinography, visual evoked potentials, and multifocal electroretinography in patients with vigabatrin-attributed visual field constriction. Epilepsia 2000;41:1420–1431.
75. Harding GF, Spencer EL, Wild JM, Conway M, Bohn RL. Field-specific visual-evoked potentials: identifying field defects in vigabatrin-treated children. Neurology 2002;58:1261–1265.
76. Ruether K, Pung T, Kellner U, Schmitz B, Hartmann C, Seeliger M. Electrophysiologic evaluation of a patient with peripheral visual field contraction associated with vigabatrin. Arch Ophthalmol 1998;116:817–819.
77. Hardus P, Verduin WM, Postma G, Stilma JS, Berendschot TT, van Veelen CW. Concentric contraction of the visual field in patients with temporal lobe epilepsy and its association with the use of vigabatrin medication. Epilepsia 2000;41:581–587.
78. Hardus P, Verduin WM, Postma G, Stilma JS, Berendschot TT, van Veelen CW. Long term changes in the visual fields of patients with temporal lobe epilepsy using vigabatrin. Br J Ophthalmol 2000;84:788–790.
79. Gonzalez PA, McCall A, McQuistan A, Keating D, Brodie MJ, Parks S. Assessing retinal toxicity of vigabatrin and other GABA-ergic drugs in patients with epilepsy. Association for Research in Vision and Ophthalmology, 2005, 46, 1658:B521.
80. Gonzalez PA, Parks S, Kelly K, Brodie MJ. Progression of neuro-retinal toxicity in patients on vigabatrin: objective assessment using the wide field multifocal electroretinogram. Epilepsia 2004; 45(suppl 7):188. Abstract.
81. Nousiainen I, Kälviäinen R, Mäntyjärvi M. Contrast and glare sensitivity in epilepsy patients treated with vigabatrin or carbamazepine monotherapy compared with healthy volunteers. Br J Ophthalmol 2000;84:622–625.
82. Nousiainen I, Kälviäinen R, Mäntyjärvi M. Color vision in epilepsy patients treated with vigabatrin or carbamazepine monotherapy. Ophthalmology 2000;107:884–888.
83. Bayer A, Thiel HJ, Zrenner E, Paulus W, Ried S, Schmidt D. [Sensitive physiologic perceptual tests for ocular side effects of drugs exemplified by various anticonvulsants]. In German. Ophthalmologe 1995;92:182–190.
84. Manuchehri K, Goodman S, Siviter L, Nightingale S. A controlled study of vigabatrin and visual abnormalities. Br J Ophthalmol 2000;84:499–505.
85. Besch D, Safran AB, Kurtenbach A, et al. Visual field defects and inner retinal dysfunction associated with vigabatrin. Invest Ophthalmol Vis Sci 2000;41:892S. Abstract 55.
86. Johnson MA, Krauss GL, Miller NR, Medura M, Paul SR. Visual function loss from vigabatrin: effect of stopping the drug. Neurology 2000;55:40–45.
87. Kälviäinen R, Nousiainen I, Mäntyjärvi M, et al. Vigabatrin, a gabaergic antiepileptic drug, causes concentric visual field defects. Neurology 1999;53:922–926.
88. Kälviäinen R, Nousiainen I, Mäntyjärvi M, et al. Prevalence of concentric visual field constriction in adult epilepsy patients with vigabatrin treatment. Neurology 1999;52(suppl 2):A235–A236. Abstract.
89. Gonzalez P, McCall A, McQuistan A, Keating D, Kelly K, Brodie MJ, Parks S. The assessment of neuro-retinal toxicity in patients with epilepsy on vigabatrin. Presented at: 42nd Annual Symposium, International Society of Clinical Electrophysiology in Vision, Glasgow, Scotland. August 22–26, 2005 (poster).
90. Wilson EA, Brodie MJ. Severe persistent visual field constriction associated with vigabatrin: chronic refractory epilepsy may have role in causing these unusual lesions. BMJ 1997;314:1693. Comment.
91. Wohlrab G, Boltshauser E, Schmitt B, Schriever S, Landau K. Visual field constriction is not limited to children treated with vigabatrin. Neuropediatrics 1999;30:130–132.
92. Arndt CF, Derambure P, Defoort-Dhellemmes S, Hache JC. Outer retinal dysfunction in patients treated with vigabatrin. Neurology 1999;52:1201–1205.

93. Arndt CF, Derambure P, Defoort S, et al. Is visual impairment related to vigabatrin reversible? Epilepsia 1999;40(suppl 2):256. Abstract.
94. Llerda MJ, Lasaosa SS, Juste TC, et al. Visual field defects associated with vigabatrin therapy: prevalence, characteristics and follow-up. Epilepsia 2000;41(suppl 7):240. Abstract.
95. Toggweiler S, Wieser HG. Concentric visual field restriction under vigabatrin therapy: extent depends on the duration of drug intake. Seizure 2001;10:420–423.
96. Specchio LM, Bellizzi M, La Neve A, et al. Visual impairment in adult epileptic patients treated with vigabatrin. Neurology 2000; 54(suppl 3):A308. Abstract.
97. Jensen H, Sjo O, Uldall P, Gram L. Vigabatrin and retinal changes. Doc Ophthalmol 2002;104:171–180.
98. Rintahaka P, Granström ML, Lappi M, et al. Visual field defects in vigabatrin-treated children with epilepsy. Epilepsia 2000; 41(suppl 7):196–197. Abstract.
99. Ascaso FJ, Lopez MJ, Mauri JA, Cristobal JA. Visual field defects in pediatric patients on vigabatrin monotherapy. Doc Ophthalmol 2003;107:127–130.
100. Westall CA, Nobile R, Morong S, Buncic JR, Logan WJ, Panton CM. Changes in the electroretinogram resulting from discontinuation of vigabatrin in children. Doc Ophthalmol 2003;107:299–309.
101. Westall CA, Nobile R, Buncic JR, Abdolell M. Electroretinogram indicators of toxicity in children taking the anti epileptic medication vigabatrin. Invest Ophthalmol Vis Sci 2005;46:E-Abstract 612.
102. Westall C. Visual electrophysiology to detect drug induced ocular toxicity: are abnormal results suggestive of toxicity? Presented at: 42nd Annual Symposium, International Society for Clinical Electrophysiology of Vision, Glasgow, Scotland, August 22–26, 2005 (oral presentation).
103. Westall CA, Nobile R, Buncic JR. Which factors contribute to worsening of ERGs in children taking the anti-epileptic drug vigabatrin? Invest Ophthalmol Vis Sci 2006;45:E-Abstract 775.
104. Hammoudi DS, Lee SSF, Madison A, et al. Reduced visual function associated with infantile spasms in children on vigabatrin therapy. Invest Ophthalmol Vis Sci 2005;46:514–520.
105. Predictor variable analysis to determine onset of retinal toxicity in children on vigabatrin therapy. Invest Ophthalmol Vis Sci 2005; 46:E-Abstract 611.
106. Kälviäinen R, Nousiainen I. Visual field defects with vigabatrin: epidemiology and therapeutic implications. CNS Drugs 2001;15: 217–230.
107. Committee for Proprietary Medicinal Products (CPMP), European Agency for the Evaluation of Medicinal Products (EMeA). Opinion following an article 12 referral: Vigabatrin. Report no. CPMP/1357/99. November 5, 1999. Available at: http://www.emea.europa.eu/pdfs/human/phv/135799ENB.pdf.
108. Hardus P, Verduin WM, Berendschot TT, et al. The value of electrophysiology results in patients with epilepsy and vigabatrin associated visual field loss. Acta Ophthalmol Scand 2001;79: 169–174.
109. Hardus P, Verduin WM, Engelsman M, et al. Visual field loss associated with vigabatrin: quantification and relation to dosage. Epilepsia 2001;42:262–267.
110. Benozzi JI, Jaliffa C, Nahum P, et al. Visual alterations in Argentinean patients receiving vigabatrin. Invest Ophthalmol Vis Sci 2001;42(4):S65. Abstract.
111. Newman WD, Tocher K, Acheson JF. Vigabatrin associated visual field loss: risk factors and natural history. Invest Ophthalmol Vis Sci 2001;42(4):S937. Abstract.
112. Kinirons P, Cavalleri GL, O'Rourke D, et al. Vigabatrin retinopathy in an Irish cohort: lack of correlation with dose. Epilepsia 2006;47:311–317.
113. Vanhatalo S, Nousiainen I, Eriksson K, et al. Visual field constriction in 91 Finnish children treated with vigabatrin. Epilepsia 2002;43:748–756.
114. Malmgren K, Ben-Menachem E, Frisen L. Vigabatrin visual toxicity: evolution and dose dependence. Epilepsia 2001;42:609–615.
115. Schmidt T, Ruther K, Jokiel B, Pfeiffer S, Tiel-Wilck K, Schmitz B. Is visual field constriction in epilepsy patients treated with vigabatrin reversible? J Neurol 2002;249:1066–1071.
116. Steinhoff BJ, Freudenthaler N, Paulus W. The influence of established and new antiepileptic drugs on visual perception. 1. A placebo-controlled, double-blind, single-dose study in healthy volunteers. Epilepsy Res 1997;29:35–47.
117. Tiel-Wilck K, Jokiel B, Zinser P, et al. Afferent visual function after single dose application of gamma-vinyl-GABA. Neuroophthalmology 1995;15:305–310. Abstract.
118. Best JL, Acheson JF. The natural history of vigabatrin associated visual field defects in patients electing to continue their medication. Eye 2004;19:41–44.
119. Newman WD, Tocher K, Acheson JF. Vigabatrin associated visual field loss: a clinical audit to study prevalence, drug history and effects of drug withdrawal. Eye 2002;16:567–571.
120. Mauguiere F, Chauvel P, Dewailly J, Dousse N; PMS Study Multicenter Group. No effect of long-term vigabatrin treatment on central nervous system conduction in patients with refractory epilepsy: results of a multicenter study of somatosensory and visual evoked potentials. Epilepsia 1997;38:301–308.
121. American Academy of Ophthalmology. Automated perimetry. Ophthalmology 1996;103:1144–1151.
122. Westall CA, Panton CM, Levin AV. Time courses for maturation of electroretinogram responses from infancy to adulthood. Doc Ophthalmol 1998;96:355–379.
123. National Institutes of Health Consensus Conference. Surgery for epilepsy. JAMA 1990;264:729–733.
124. Brodie MJ, Kwan P. Staged approach to epilepsy management. Neurology 2002;58(8 suppl 5):S2–S8.
125. Meador KJ. Cognitive outcomes and predictive factors in epilepsy. Neurology 2002;58(8 suppl 5):S21–S26.
126. French JA, Kanner AM, Bautista J, et al. Efficacy and tolerability of the new antiepileptic drugs, II: Treatment of refractory epilepsy: report of the TTA and QSS Subcommittees of the American Academy of Neurology and the American Epilepsy Society. Epilepsia 2004;45:410–423 [Erratum in: Epilepsia 2004;45:1299].
127. Tomson T, Walczak T, Sillanpaa M, Sander JW. Sudden unexpected death in epilepsy: a review of incidence and risk factors. Epilepsia 2005;46(suppl 11):54–61.
128. Mayer H, Benninger F, Urak L, Plattner B, Geldner J, Feucht M. EKG abnormalities in children and adolescents with symptomatic temporal lobe epilepsy. Neurology 2004;63:324–328.
129. Kivity S, Lerman P, Ariel R, Danziger Y, Mimouni M, Shinnar S. Long-term cognitive outcomes of a cohort of children with cryptogenic infantile spasms treated with high-dose adrenocorticotropic hormone. Epilepsia 2004;45:255–262.
130. Guerrini R, Parmeggiani L. Practitioner review: use of antiepileptic drugs in children. J Child Psychol Psychiatry 2006;47:115–126.
131. Mackay M, Weiss S, Snead OC 3rd. Treatment of infantile spasms: an evidence-based approach. Int Rev Neurobiol 2002;49: 157–184.
132. Van Ness PC. Therapy for the epilepsies. Arch Neurol 2002;59: 732–735.
133. Devinsky O. Patients with refractory seizures. N Engl J Med 1999;340:1565–1570.
134. Shields WD. Infantile spasms: little seizures, big consequences. Epilepsy Curr 2006;6:63–69.