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REVIEW

Safety and Efficacy of Vigabatrin for the Treatment of Infantile Spasms

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Abstract: In 2009, vigabatrin became the first FDA approved medication for the treatment of infantile spasms in the United States. There are few well-designed prospective studies comparing the drug to placebo or other modalities used in the treatment of infantile spasms. The available data have demonstrated that vigabatrin is efficacious in the treatment of infantile spasms regardless of underlying etiology, but that it is particularly beneficial in patients with a diagnosis of tuberous sclerosis. Adrenocorticotropic hormone (ACTH), the only other medication with robust efficacy data, has been used as first line therapy for infantile spasms associated with other etiologies, and in general controls spasms sooner than vigabatrin, though relapse is common with both therapies. Vigabatrin is generally well tolerated. However, use has been associated with permanent loss of peripheral vision in some patients. In children with tuberous sclerosis, vigabatrin should be considered as initial therapy for infantile spasms. It is a viable alternative for patients with suboptimal response, contraindications or intolerance to ACTH.

Keywords: ACTH, infantile spasms, hypsarrhythmia, tuberous sclerosis, vigabatrin

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Introduction

Approximately 2% of childhood epilepsy is comprised of a seizure type known as infantile spasms (IS).[1] These spasms occur in approximately one child for every 2000–6000 live births. The initial seizure typically occurs within the infant's first year of life, and peak onset is between the ages of three and five months of age.[2] The explicit pathogenesis of IS remains unknown. One potential cause that is frequently mentioned is a non-specific reaction of the juvenile brain to insult. However, while this might explain the mechanism underlying a diffuse pathology, IS can also arise from focal insults. Abnormalities of the brainstem and hypothalamus have both been implicated in cases of IS.[3]

There are several classifications of IS. Symptomatic IS, which comprises the majority of diagnoses, may result from a variety of identifiable prenatal, perinatal and postnatal causes.[4] Included within the prenatal subgroup are infants with genetic disorders, in particular tuberous sclerosis (TS) which is a neurocutaneous syndrome that results in IS in up to 50% of patients.[5] TS, which is the underlying cause of up to 30% of prenatal cases, is known to result in some of the most difficult to treat instances of IS.[1,6] Additional prenatal causes include sequelae from infection or other issues arising while in utero, and abnormalities of metabolism. Perinatal causes arise primarily due to difficulties during delivery, including hypoxia of the brain and trauma, whereas postnatal causes are primarily trauma and infection related. The majority of infants with IS have some degree of mental retardation.[7] Autistic spectrum disorders have been noted in children who suffered from IS. There is also a subset of patients with cryptogenic IS (a term sometimes used interchangeably with idiopathic IS) which implies that an underlying cause has not been identified. Many infants with cryptogenic IS have family members with epilepsy.[8] IS can be devastating, and has been associated with premature death rates of five to more than 30%.[12] Of those with no identifiable underlying cause, more than half are noted to have normal or near normal cognitive development prior to the onset of spasms. However, at the time of diagnosis, the vast majority of patients will experience arrest of psychomotor development, or may actually regress from their baseline.[1,9] Children who show such regression typically have a more negative long-term outcome than do those who respond quickly and completely to treatment.[8] Though IS may disappear with age, over half of surviving patients will develop other seizure types.[7,10]

IS are variable in their presentation from infant to infant. Spasms are most commonly a mix of flexor and extensor responses, but each may also exist alone. The spasms are most often described as sudden trunk and limb contractions that are tonic in nature, may last up to ten seconds, and typically occur in clusters of 20–30. However, there have been cases where clusters consist of up to as many as 100 spasms.[2] Intensity can also vary with outward signs manifesting as something seemingly benign (eg, a brief rolling back of the eyes), to a relatively violent presentation that is more like a muscular shock.[11] Onset of clusters may be temporal in nature, frequently occurring just prior to the onset of sleep or upon awakening.[1] The characteristic EEG pattern associated with IS is called hypsarrhythmia, and consists of random high voltage slow waves and spikes that are variable in both their location and length.[7] When IS, hypsarrhythmia and mental retardation occur together, a diagnosis of West Syndrome is made. Though some studies have evaluated drug efficacy by measuring cessation of spasms only, there is evidence that the termination of the EEG abnormalities is important in determining long-term outcome.[7]

Medication Therapy of Infantile Spasms

As is often the case in efficacy studies of medications used to treat epilepsy, there are difficulties designing robust trials of drugs for IS. The ethical dilemmas are even more apparent due to the pediatric status of IS subjects. Delay of spasm control via inclusion of a placebo study arm may be construed as unethical.[2] Additionally, adrenocorticotropic hormone (ACTH), which is one of the most commonly used medications for the treatment of IS, is given by injection. Subjecting an infant to dummy injections in a clinical trial might be considered ethically questionable. As such, there is a paucity of well-designed randomized controlled trials in the area of IS. Most prospective trials have enrolled a small number of subjects. Much of the available efficacy data have been collected and evaluated retrospectively. A Cochrane review (last updated in 2009) found most available

studies were weak methodologically, and the authors of the practice parameter put forth by the American Academy of Neurology and the Child Neurology Society (AAN/CNS) conceded that published trials have generally been poorly designed without come measures exhibiting great variance from study to study.[2,12] As such, conclusions about optimal therapeutic regimens have been hard to draw.

Currently the only two treatments with enough data to suggest proven efficacy in the treatment of IS are ACTH and vigabatrin, though other medications are sometimes used.[7] In particular, the AAN/CNS has found insufficient evidence to recommend topiramate, levetiracetam, valproic acid, lamotrigine, zonisamde or benzodiazepines as viable options for first-line treatment of IS.[1] Additionally, oral corticosteroids (particularly prednisolone) are not generally recommended for initiation of therapy, though there is some evidence that they may possess some ability to control IS at high doses.[13,14]

The exact mechanism by which ACTH exerts its effects on IS remains elusive. It is hypothesized that IS may arise from an abnormality involving the brain-adrenal axis.[15] Abnormal amounts of corticotropin releasing hormone (CRH) in the brain of infants with IS may cause spasms. ACTH has been shown to cause the down regulation of excessive CRH expression. (This mechanism would also explain the efficacy of prednisolone).

Vigabatrin is currently the only drug approved in the US for use in IS, (though ACTH is currently undergoing regulatory hearings at the FDA).[11] It has been available in the United Kingdom and Ireland since 1989, and has been used widely throughout Europe for the treatment of IS. The drug is a suicide substrate used to inhibit the enzyme gamma-aminobutyric acid-transaminase, or GABA-T. This irreversible binding decreases conversion of the inhibitory neurotransmitter GABA to succinic semialdehyde. The result is an increase in brain GABA concentrations which has been linked to suppression of seizure activity. Unlike many other antiepileptic medications, vigabatrin has no strong propensity for inducing or inhibiting hepatic enzymes, and is virtually unbound to serum protein making drug interactions unlikely. There have been reports of phenytoin concentration decreasing with concomitant administration, however breakthrough seizure activity has not been linked to these changes.[16–19] No other clinically relevant drug interactions have been routinely noted with vigabatrin use. The drug may be taken without regard to meals, and is easily absorbed achieving bioavailability of up to 70% of a dose due to its high degree of solubility.

Efficacy Studies of Vigabatrin

A total of six prospective, randomized controlled trials designed to assess the efficacy of vigabatrin have been identified (Table 1). Three of these trials were submitted to the FDA as part of the drug's approval process. As previously discussed, most enrolled a small number of subjects, and only one was placebo-controlled. The earliest of these studies were published in 1997.

A clinical trial conducted by Vigevano and colleagues was the original prospective study comparing vigabatrin and ACTH for the treatment of IS.[20] Forty-two subjects were enrolled, 15 with cryptogenic IS, and the remaining 27 with symptomatic IS. The study was designed in two phases. During the first phase, subjects were randomized to receive either vigabatrin at 100 mg/kg/day (with subsequent titration of 25 mg/kg/day in three day increments to a total of 150 mg/kg/day), or a constant 10 iu dose of ACTH depot injection. In the case of non-response or intolerance due to medication side-effects, cross over to the alternate therapy occurred at day 20. Twenty-three subjects were randomized to the vigabatrin arm initially. Eleven met the endpoint of spasm cessation (four with cryptogenic IS, four with symptomatic IS not otherwise specified, and all three subjects with TS). The difference in initial response rates was not different between the two medications ($P = 0.12$). In total, 13/28 infants given vigabatrin over the duration of the trial became spasm free in comparison to 25/31 of those treated with ACTH ($P = 0.007$). However, at three months, six of the subjects responding to ACTH experienced relapse compared to one who had responded to vigabatrin. Earlier EEG normalization favored ACTH with >50% exhibiting no abnormalities at 10 days vs. none receiving vigabatrin. At the end of 20 days 78% and 36% of EEG readings had normalized in the ACTH and vigabatrin groups respectively. The authors note that vigabatrin use results in evolution of hypsarrhythmia cessation, whereas ACTH

Table 1. Prospective studies evaluating the efficacy of vigabatrin in infantile spasms.

Study	Participants	Design	Outcomes
Vigevano and Cilio[20]	n = 42 (n = 3 TS) age 2–9 mo.	R (AA), NB, circumstantial CO 20 days × 2 phases, vigabatrin 150 mg/kg/day vs. ACTH depot 10 iu/day	No difference in initial response ($P = 0.12$), spasm-free status at study end favored ACTH ($P = 0.007$) EEG normalization = 78% (ACTH) and 36% (vigabatrin) at day 20, 100% response in TS patients with vigabatrin
Chiron et al[21]	n = 22 (n = 22 TS) age 1–24 mo.	R, NB, circumstantial CO 1 month × 2 phases, vigabatrin 150 mg/kg/day vs. hydrocortisone 15 mg/kg/day	Spasm-free status favored vigabatrin (100% response, $P < 0.01$) EEG normalization = 100%
Appleton et al[22]	n = 40 (n = 0 TS) age 1–20 mo.	Blinded with switch to OL 5 day PC (phase 1), 24 week OL (phase 2), vigabatrin 50–150 mg/kg/day	Significant decrease in spasm frequency with vigabatrin in phase 1 ($P = 0.02$) with 7 spasm free ($P = 0.063$) 15 spasm free on vigabatrin at study end, EEG normalization = 5 vigabatrin patients in phase 1, not monitored in OL phase
Elterman et al[23,24]	n = 142 (n = 25 TS)-first cohort n = 221-second cohort age < 24 mo.	R, SB, circumstantial CO 2 weeks, vigabatrin low dose (18–36 mg/kd/day) vs. high dose (100–148 mg/kg/day) titrated to response	(first cohort) Seizure free status (including normalization of EEG) favored high dose vigabatrin ($P < 0.001$), 65% spasm free by study end, 92% response in TS patients; (second cohort) High dose favored ($P = 0.0375$), 59.7% seizure free by study end (both dosing groups)
Askalan et al[25]	n = 9 (n = 1 TS) age 3–16 mo.	R, OL, circumstantial CO 2 weeks × 2 phases, vigabatrin 150 mg/kg/day (18 month taper) vs. ACTH 150 iu/m^2/day (12 week taper)	None seizure free in phase 1 (cessation of spasms + normalization of EEG), 4/9 responded by study end (2 on each drug), TS patient result not reported
Lux et al[13]	n = 107 (n = 0 TS) age 2–12 mo.	R, OL, circumstantial CO 2 weeks, vigabatrin 100–150 mg/ kg/day vs. prednisolone 10 mg qid-20 mg tid vs. tetracosactide depot 0.5 mg–0.75 mg qod (2:1:1 randomization)	73% spasm reduction with prednisolone + tetracosactide vs. 54% with vigabatrin ($P = 0.043$) Longer median seizure free period with prednisolone + tetracosactide ($P = 0.038$), EEG normalization = 81% vs. 56% ($P = 0.024$)

Abbreviations: TS, tuberous sclerosis; R, randomized; AA, alternate allocation; CO, crossover; NB, non-blinded; OL, open label; SB, single blinded.

produces rapid normalization early, but is more likely to result in relapse.

A study by Chiron et al was among those submitted to the FDA. The study population consisted of 22 subjects with symptomatic IS due to underlying TS.[21] Subjects were randomized to receive either vigabatrin at a dose of 150 mg/kg/day, or the comparator drug, hydrocortisone, at a dose of 15 mg/kg/day. Spasm-free status was assessed during a one-month timeframe. In the case of non-response, the alternative drug was given for an additional month. Vigabatrin was significantly more efficacious for spasm control than hydrocortisone ($P < 0.01$) achieving remission in 100% of subjects. Six subjects originally receiving hydrocortisone were crossed over to vigabatrin therapy due to lack of response. Each of these individuals ultimately achieved spasm-free status. Response to vigabatrin therapy occurred rapidly (mean of four days) compared to hydrocortisone ($P = 0.058$), but due to the small sample size in the study, the mean difference of 8.8 days did not reach statistical significance. All nine infants with hypsarrhythmia (four of whom were randomized to vigabatrin) had normalization of EEG by the end of the study.

In 1999, Appleton and colleagues published an international multicenter study which was also submitted to the FDA as proof of vigabatrin's efficacy in IS.[22] This study was the first to look at response to vigabatrin in newly diagnosed IS. Forty infants were originally randomized to receive vigabatrin (50–150 mg/kg/day titrated in 50 mg/kg/day intervals according to response) or placebo in blinded fashion for five days. Of the symptomatic IS patients, none had been diagnosed with TS. At the end of the blinded phase, 77.9% and 25.9% of vigabatrin and placebo users respectively had a reduction in spasm frequency compared to pre-treatment baseline ($P = 0.02$). Seven vigabatrin-treated patients were spasm free at the end of the blinded period (five of whom had cessation of hypsarrhythmia) compared to two receiving placebo ($P = 0.063$). Four infants failed vigabatrin in the first five days leaving 16 to receive open-label vigabatrin for the next 24 weeks along with the twenty subjects originally randomized to placebo. Twenty-nine subjects completed the trial, with 15 achieving spasm cessation on vigabatrin monotherapy. EEG monitoring was not undertaken during the open-label phase.

Elterman et al evaluated high vs. low dose vigabatrin in treatment naïve infants with IS in a single-blind trail.[32] High dose vigabatrin (100–148 mg/kg/day) was administered to 67 subjects, while the remaining 75 received low dose vigabatrin (18–36 mg/kg/day) for two weeks. A seizure free period of seven days (by caregiver report and absence of hypsarrhythmia for an eight-hour monitoring period) during this time-frame was defined as the primary outcome. Those receiving the low dose who had not responded were crossed over to the high dose regimen. If spasms had not subsided within the following seven days, a final titration to 200 mg/kg/day was allowed. Eight infants on low dose vigabatrin met the primary endpoint compared to 24 in the high dose group ($P < 0.001$). By the end of a three-month evaluation period, 65% of subjects were spasm free, though 16% of patients relapsed. Twenty-three of 25 patients who met the end point at three months had an underlying diagnosis of TS. A follow-up to this original study was published in 2010.[24] The total number of subjects enrolled in the intent-to-treat group (including those in the original study) was 221. High dose therapy continued to be better in achieving the primary end point ($P = 0.0375$), and there was no observed difference between patients when stratified by etiology of IS in this follow-up study ($P = 0.0736$).

In 2003, Askalan and colleagues conducted an open label trial of vigabatrin vs. ACTH in nine subjects.[25] Responders were those with cessation of both spasms and hypsarrhythmia as evidenced by EEG at either week one or week two of the study. The first 14 day trial phase saw subjects randomized to ACTH 150 iu/m^2/day for seven days (n = 3), followed by a dose decrease of 50% for the following seven days. The vigabatrin group (n = 6) received 100 mg/kg/day which was increased to the maximum dose of 150 mg/kg/day on the third day of the study. Non-responders to initial treatment were crossed over to the opposite arm after the first week. The second phase saw subjects tapered off of their medications (over 12 weeks in the case of ACTH, or 18 months if on vigabatrin). None of the subjects demonstrated normalization of EEG by the end of the first phase, however four subjects (one randomized to vigabatrin, one crossed over to vigabatrin, and two crossed over to ACTH) responded by study end. (Of note, this study was actually designed to assess the

incidence of epilepsy and autism in patients exposed to medications for IS).

The final prospective 14-day comparison study of vigabatrin was conducted by Lux and colleagues, and compared the drug to prednisolone or tetracosactide (a synthetic analog of ACTH).[13] One hundred seven subjects, none of whom were diagnosed with TS, were randomized in a 1:1:2 ratio with the larger group (n = 52) given vigabatrin. The vigabatrin regimen consisted of treatment initiation at a dose of 50 mg/kg/day, then 100 mg/kg/day with an additional increase to 150 mg/kg/day if spasms were not controlled at 96 hours. Individuals given prednisolone took 10 mg four times daily for two weeks with titration to 20 mg three times daily if spasms were still not under control at the end of week one. The tetracosactide depot injections were given every other day at an initial dose of 0.5 mg (equivalent to ACTH 40 iu), with an increase to 0.75 mg (60 iu) in the case of non-response at one week. The primary outcome measure was cessation of spasms for a period of at least 48 hours per caregiver diary, with cessation of hypsarrhythmia considered a secondary outcome. Crossover due to non-response occurred in two subjects given prednisolone (vigabatrin substitution), and three subjects randomized to vigabatrin (two of whom received prednisolone, and one who received a benzodiazepine). Considered together, the two hormonal treatments resulted in cessation of spasm in 73% of study participants compared with 54% of those given vigabatrin ($P = 0.043$). The median seizure free period also favored hormonal treatments (9 days vs. 2.5 days with vigabatrin, $P = 0.038$). EEG normalization occurred in 81% and 56% of those receiving hormones and vigabatrin respectively ($P = 0.024$).

Safety and Tolerability of Vigabatrin

When vigabatrin first came to the European market, it quickly became the drug of choice for IS due to its ease of use and seemingly benign side-effect profile in comparison to ACTH.[11] The side-effects associated with hormone/steroid use are well known, and can be serious in nature. They include weight gain, edema, excessive irritability, elevated blood pressure, heart failure, derangements in regulation of blood glucose, an increase in risk of opportunistic infection and kidney calcifications.[14] It is recommended that patients undergo MRI evaluation prior to the start of ACTH as transient abnormalities approximating brain atrophy may occur.[26] Many ACTH side-effects are dose and duration dependent, and for this reason the drug is typically tapered off within several weeks of a positive response.[27] However, unlike some side-effects associated with vigabatrin, hormone-related side-effects tend to be transient, and resolve with drug discontinuation.

Most side-effects associated with vigabatrin use in infants are relatively benign. The most commonly reported side-effects in drug studies include psychomotor agitation, hyperexcitability and axial hypertonia.[21,23] There have been reports of MRI abnormalities in patients using vigabatrin. Changes consistent with reversible cytotoxic edema have been noted in infants.[28] A retrospective study of MRI data in patients with a mean age of 19.1 months demonstrated that approximately one in three presented with changes in signal intensity or restricted diffusion-weighted imaging.[29] The duration of vigabatrin exposure did not correlate with these changes. MRI aberrations tend to normalize after drug discontinuation, but may also in some cases normalize while the patient is still using the drug.[29] These changes seem to be exclusive to patients with IS as opposed to other seizure types.[28,30]

The ultimate delay in approval of vigabatrin in the US was the emergence of permanent visual field defects (VFD) in users. As a condition of approval for vigabatrin the FDA stipulated that a risk evaluation and mitigation strategy (REMS) be put in place to minimize the risk of symptomatic vision loss. As part of the REMS, patients are required to undergo visual field testing every three months while on the medication, as well as have a final evaluation after cessation if therapy is withdrawn. The risk of VFD in infants is smaller than the risk in adults, which is believed to be anywhere from one in four to half of patients on chronic therapy.[31,32] Though estimates vary anywhere from 15%–40%, at present, we do not know how likely patients under the age of one year are to develop VFD.[6,33,34] Part of the reason for this is the difficulty that exists regarding visual testing in young patients. Though the REMS provides for visual field testing, there is no standardization for the type of evaluation that must be used in children. In general, static perimetry is the preferred method of testing, but it is questionable whether a patient below the age of

about nine years would be able to participate in such testing in order to garner an accurate result.[11] Ability to participate in testing may be further impaired in patients with residual cognitive dysfunction.

One method used in infants is electroretinography (ERG) which requires an electrode to be placed on the cornea. One study of patients with IS treated with vigabatrin utilizing ERG results showed that one in 20 had some degree of impairment.[35] Other visual field tests (behavioral testing or Goldman perimetry (which is kinetic in nature rather than static)) administered to 25 patients revealed abnormalities in seven.[35] It should be noted that the authors relate the controversial nature of behavioral testing (used in 22 patients) due to its low sensitivity in detecting smaller defects. Goldman perimetry testing was utilized in another study of 16 children who began vigabatrin use at a mean age of 7.6 months.[36] Only one of the 16 showed mild visual impairment. However, all of the included subjects experienced good seizure outcomes and were considered to be in generally good health, so it is not known if the data can be applied to others with IS.

When discussing the risks vs. the benefits of vigabatrin exposure as they relate to potential loss of peripheral vision, it is important to consider that most visual field loss is asymptomatic.[36] In addition, there are data to show that changes in vision are common in IS even in the absence of vigabatrin exposure. A retrospective chart review of 10 patients defined as having profound visual inattention was completed by Castano and colleagues.[37] Despite obvious symptoms, the patients' ocular exams were all normal. The authors note that most patients with IS do present with visual inattention of varying degrees. This is true particularly if there is evidence of hypsarrhythmia on EEG. In general, children who present with visual inattention are more likely to have ongoing visual difficulties as they age. Those children with IS seem to have more difficulty with vision associated with their condition than do those with other seizure types.[38] Since patients with IS exposed to vigabatrin tend to have worse visual outcomes than those using vigabatrin for other diagnoses, and ocular problems are frequently evident in IS patients before drug exposure, it is difficult to determine how much of the impairment is drug-related vs. related to the underlying condition. It can also be argued that if hypsarrhythmia is associated with poor visual outcomes, and poor outcomes in general, the risk of using vigabatrin to normalize EEG patterns may be justified.

Cognitive outcomes after medication exposure are also of concern in patients with IS. In the study by Askalan previously described, 33% of patients (3/9) developed Autism Spectrum Disorders (ASD) confirmed at 20 months.[25] All three patients were exposed to vigabatrin. A follow-up study to the trial by Lux evaluated developmental outcomes in their study subjects at 14 months.[39] They found no difference regardless of study arm. The same patients were evaluated again at four years.[9] The lack of difference in developmental outcomes was reconfirmed when all subjects were considered together, though symptomatic patients exhibited better median behavior scores with hormonal treatment. An additional study carried out in subjects with TS, all of whom were considered to have moderate to severe mental retardation, was completed by Jambaqué et al.[6] All seven were complete responders to vigabatrin therapy, and none relapsed. Five were exhibiting autistic behavior. With treatment, the developmental quotient (measured using three distinct diagnostic tools) increased by 10–40 points in all but one subject ($P = 0.03$). The results were reconfirmed in the four patients who were re-tested at least two years later. This trial provides evidence that the underlying cause of IS likely influences cognitive and behavioral outcomes in those exposed to vigabatrin.

Place of Vigabatrin in the Treatment of Infantile Spasms

In general, favorable prognostic outcomes for infants with IS include a cryptogenic classification of spasms, onset after the age of four months, the absence of a mixed seizure disorder, bilateral changes on EEG (if noted), and rapid, sustained treatment response.[1] Most studies show that seizures are controlled more quickly and more often with hormonal therapy than with vigabatrin when spasms are not stratified by underlying etiology, though there are exceptions.[2] However, it remains to be seen if the more rapid response translates into better outcomes overall. Regardless of the treatment used, relapses after treatment are frequent necessitating a second course of therapy.[8,33] Due to the possibility that ongoing seizure

activity is related to negative long-term outcomes, based on current evidence it is probably prudent to initiate therapy with ACTH in patients without TS who do not have conditions that may be exacerbated with hormone use. However, the evidence for the use of vigabatrin as primary therapy for patients with TS as the underlying etiology for their spasms is robust. The National Institute for Clinical Excellence, the Scottish Intercollegiate Guideline Network and the 2005 US Pediatric Epilepsy Survey all support vigabatrin for this purpose.[40–42] If the use of ACTH does not result in spasm control and EEG normalization within 14 days, vigabatrin is a viable alternative therapy for IS of any etiology.[7]

Conclusion

Vigabatrin is the drug of choice for IS occurring in conjunction with a diagnosis of TS. Furthermore, it has shown efficacy in patients with symptomatic IS resulting from other underlying diagnoses, and in patients with cryptogenic IS alike. In general, it has a mild side-effect profile. However, vigabatrin may cause permanent loss of vision in the peripheral field in some patients. Given the current evidence which suggests that rapid control of spasms and normalization of EEG is imperative for the best chance at positive long-term cognitive outcomes, the use of vigabatrin as first line therapy in patients with TS, and in those who have failed ACTH therapy, is warranted. Additional data will need to be evaluated to determine if rapidity of IS cessation definitively correlates with better long term outcomes as patients move toward adulthood.

Disclosures

Author(s) have provided signed confirmations to the publisher of their compliance with all applicable legal and ethical obligations in respect to declaration of conflicts of interest, funding, authorship and contributorship, and compliance with ethical requirements in respect to treatment of human and animal test subjects. If this article contains identifiable human subject(s) author(s) were required to supply signed patient consent prior to publication. Author(s) have confirmed that the published article is unique and not under consideration nor published by any other publication and that they have consent to reproduce any copyrighted material. The peer reviewers declared no conflicts of interest.

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