

REVIEW

Open Access



Peripheral visual field defect of vigabatrin in pediatric epilepsy: A review

Umme Habeeba A. Pathan^{1*} , Navapreetha Shetty¹, Safiya Anhar¹ and Reshma Mayya¹

Abstract

Vigabatrin is the medication used for the treatment of infantile spasms and refractory complex partial seizures, but its usage has always been contradictory due to its effect on vision. This review focuses on the registry, mechanism of injury, animal study, pharmacokinetics, risk factors, efficacy, safety and precautions of vigabatrin. The first visual defect with vigabatrin use was detected in 1997. This led to initiation of many trials including compulsory registration of patients in Sabril registry. The site of toxicity is found to be inner retina where vigabatrin tends to inhibit densely gamma amino butyric acid-C (GABA-C) receptors resulting in intoxication of visual field and also genetic variations held responsible for the injury. The toxicological studies of vigabatrin on various animals reveal different physiology, deficiency of taurine and light can effect on visual field and its related cells. Only thing need to be monitored with use of vigabatrin is visual field because it is well absorbed, with zero protein binding and no necessary dosage adjustment. The effect of vigabatrin is seen to vary with age, duration of therapy, cumulative dose and gender. The efficacy differs in various studies for different forms of epilepsy and so does the safety. Precautions are needed to be followed regarding use of vigabatrin by considering the risk versus benefit ratio for each and every individual and also discussing with the patient's caregivers. The ultimate goal in treating with vigabatrin for any form of epilepsy is the good clinical response.

Keywords Vigabatrin, Visual field defects, Pediatric epilepsy, Sabril registry

Background

Vigabatrin (VGB) is one of the first 'designer medications' to be discovered in the 1980s and 1990s which is highly selective irreversible inhibitor of gamma-aminobutyric acid (GABA) transaminase, the enzyme responsible for the metabolism of GABA at the synaptic cleft [1–5]. It is a second generation anti-epileptic drug (AED) which aims to increase GABA, a major inhibitory neurotransmitter in brain [6, 7]. VGB is the first Food Drug Administration (FDA) approved treatment for infantile spasms [8]. It is a novel effective approved drug after valproate in the treatment of refractory partial and tonic-clonic

seizures and is found to be effective as monotherapy in infantile spasms (IS) also known as West syndrome [1, 8]. In prolonged and experimentally induced seizures, VGB has shown to protect neurons and neuronal function [9]. Response to therapy is usually seen within first 12 weeks of duration of treatment with the dose of 100–150 mg/kg/day [6]. Recently, VGB was designated as "fast track" according to FDA in treating cocaine and methamphetamine dependence [5].

IS were first described 160 years ago and are rare severe seizure disorder that is characterized by epileptic spasms, hypersarrhythmia on electroencephalogram (EEG) and developmental regression [10, 11]. According to International League Against Epilepsy (ILAE) IS are classified as an "epileptic encephalopathy" [12, 13]. The incidence ranges from 2 to 3.5 cases per 10,000 live births, with a peak onset at 3–7 months of age [10]. Due to safety concerns including peripheral visual field defects, VGB's

*Correspondence:

Umme Habeeba A. Pathan
ummehabeeba777@gmail.com

¹ Department of Pharmacy Practice, Bapuji Pharmacy College, SS Layout
Shamnur Road, Davangere 577004, Karnataka, India

development in United States (US) was delayed and was approved only in 2009 [2]. In 1997, cases with visual field defects were identified in patients treated with VGB [14]. IS are catastrophic epilepsy affecting infants, hence prompt recognition and treatment within 3–4 weeks after onset using effective therapy is essential for good seizure control and developmental outcome. Effective treatments include VGB and hormonal agents like Adrenocorticotropic hormone (ACTH) or prednisolone [15]. In the United Kingdom Infantile Spasms Study (UKISS) trial, hormonal treatments showed better spasms cessation compared to VGB therapy [16].

The first severe symptomatic visual field defect constriction was reported in 1997 and later asymptomatic binasal visual field defects (VFDs) became common after administration of VGB [17]. Trials were adjourned for a short period of time when intramyelinic edema was seen in animal studies in 1983. The VGB associated visual field loss was first evident in Italian [6]. It has become prominent after reports that VGB may cause permanent concentric visual field loss, injury to retinal photoreceptors, retinal ganglion and their axons [3]. The prevalence rate of VFDs induced by VGB is 15–31% in infants, 15% in children and 25–50% in adults [18]. The incidence rate of visual field constriction (VFC) is higher and usually present with no symptoms [19]. VGB can induce phototoxicity due to taurine deficiency in photoreceptors of retina [1]. A post-mortem report with use of VGB has revealed vacuolar myelinopathy including brainstem, inferior cerebral peduncle, optic nerves, chiasms, hypothalamus and dentate nucleus [17]. VGB is often prescribed with higher doses and longer duration of time [20]. The visual field loss is usually asymptomatic until loss is severe, it is considered to be slowly progressive and irreversible [21]. The pattern of defect is typically a bilateral, absolute concentric constriction of visual field and the severity measures from mild to severe [3]. The association between VGB and VFDs has been documented in several reports and few possible explanations for this have been put forth. The visual field defects may be associated with other AED, as VGB is usually given as additional therapy along with other AED. The defects can also be associated with the disease that is, seizures or with VGB monotherapy. There is lack of evidence for determining the cause of these VFDs [19]. At lower doses, VGB acts as an anxiolytic agent without any addiction and protect against both tolerance and dependence of diazepam intake [22].

A Sabril registry is maintained in the United States of America (USA) and participation is mandatory for all VGB consumers as well as prescribers. During the monitoring of Sabril registry, a total of 1200 adults received VGB therapy and were enrolled. It was reported by clinicians that, total five patients who were

naive to VGB discontinued the treatment because of VFDs. The VGB exposures of those patients were from 13 months to 3.3 years [23]. Only a minority of registry patients received ACTH or other related steroid therapies prior to VGB, even though ACTH is the preferred initial treatment option. According to registry data, some prescribers do use VGB as first-line agent. A notable proportion of patients were also treated with levetiracetam and topiramate, which is a non-evidence based and non-FDA approved therapy for IS [24].

The risk associated with VGB led the FDA to institute the implementation of a comprehensive Risk Evaluation and Mitigation Strategy (REMS). In USA, VGB is only accessible by means of Support, Help And Resources for Epilepsy (SHARE), a restricted distribution program which should be included in registry. This strategy was designed to reduce the risk of vision loss and it includes baseline and regular vision monitoring, frequent assessments of effectiveness and education. If the patients fail to show improvement in seizures within 3 months then, it is suggested to discontinue the medication. There were three major parts of REMS, first label which include black box warning on packaging to guide patient, second to plan on education and communication disseminating key messages and third by conducting programs on safety use including restrictions on prescribing and dispensing to physician or pharmacies considering benefit risk, ophthalmic evaluation and enrolling patient in a registry database [23]. This review focuses on the VFDs with the use of VGB in pediatric population. The data source for this review include PubMed search articles with various keywords as Vigabatrin, Visual Field defect, Pediatric epilepsy, Infantile spasms, loss of vision, and seizures. The date of last search was March 2023 and time period of studies were from 1980's to 2022. The eligibility criteria for selection of articles were original research articles and reports on VGB and associated factors which are discussed briefly below in separate subheadings.

Mechanism of injury induced by VGB

Neurons produce GABA through glutamate decarboxylation from glutamate [19]. The site of toxicity has been put forward to be at the inner retina. As GABA is an established neurotransmitter, it is associated with horizontal, interplexiform and amacrine cells of the inner retina [25]. VGB may also imbalance the excitatory and inhibitory effects of the amacrine cells [19]. VGB inhibits the enzyme GABA transaminase resulting in increased GABA levels in the central nervous system [19, 23]. Systemic VGB cross the blood retinal barrier and can be detected immunocytochemically in retina and it cause accumulation of GABA in the retinal muller cells [19].

GABA may have a role in modulation of phototransduction from the retinal photoreceptor cells to the ganglion cells. Lower density of ganglion cells in the peripheral retina is related to cause VFD. A glutamatergic effect is counteracted by VGB action on reducing glutamate or glutamine cycling between astrocytes and neurons [7]. The retinal nerve fiber layer (RNFL) thinning is due to ganglionic cell loss and strongly associates with visual field loss. VGB associated visual defects is irreversible [15].

There are 3 GABA receptors namely GABA-A, GABA-B and GABA-C. GABA-A receptors gates chloride channels and are binding sites for benzodiazepines and barbiturates, GABA-B is G protein receptors which couples to calcium and potassium channels and GABA-C receptors are dense in retina specifically in amacrine cells, bipolar cells, photoreceptors, muller and ganglion cells and axon terminals [15]. The visual field abnormality can be explained by inhibition of GABA-C which is densely found on rod bipolar cells of inner retina [19]. GABA is anabolized by GAD enzyme through decarboxylation and catabolized by GABA-aminotransferase (GABA-T enzyme) and then GABA interacts with its 3 receptors of which GABA-A control inhibitory action through chloride channel [26]. VGB is intended to accumulate in amacrine and muller cells by 5–18 times than in brain which results in decrease in activity of GABA transaminase in retina [15]. The intoxication effect on visual field and electrophysiological effect is due to anatomical differences and intra-individual distribution of these receptors [25]. Genetic variations have also been found in development of VAVFL, and 3 candidate genes have association with the risk of VAVFL and they are one gene coding GABA-B receptors (GABRR1/2) and two genes coding GABA-transporters (GAT1/3 and GAT2) [27].

Research shows that children with different form of epilepsies showed abnormal eye movements and impairment in oculomotor and neurocognitive functions [28]. Hence children suffering from epilepsy in conjunction with the use of VGB become more vulnerable to vision problems.

Toxic effects in animals

Toxicological studies in rats, mice and dogs revealed that VGB is concentrated on white matter microvacuolation in myelin sheaths [14, 19]. When the drug was first introduced it did not show any toxic effects, however in mice and rodents, intramyelic edema and brain vacuolation were reported [29]. Retinal tissues of VGB exposed animals showed severe disorganization and degeneration of photoreceptors whereas in human it was seen conversely through electrophysiology data that post-receptor

cone system of inner retina was more affected [27]. An *in vivo* study examined effect of VGB on function and morphology in mouse retina through electroretinopathy (ERG), spectral domain optical coherence tomography (SD-OCT) and optokinetic testing. The study revealed a close relationship between retinal toxicity and exposure to light. The mice which were reared in darkness had significantly better visual function than compared with mice exposed to light [30].

Taurine has antioxidant and membrane stabilizing properties which works by protein phosphorylation and calcium uptake and depletion in this can lead to retinal toxicity of VGB and has been evident in rats [15]. In VGB exposed neonatal rats, retinal ganglion cells (RGC) loss was significantly associated with VGB-induced taurine deficiency and consequence of VGB toxicity [27]. VGB competitively inhibits taurine protein transporters and reduces taurine level [5]. It also stated that dietetic taurine supplements can partially alleviate morphological and functional discrepancies induced by VGB [30]. GABA has effect on cone synaptogenesis in newborn rabbits as a regulator and VGB is associated with retinal cone system dysfunction [29]. High doses of VGB lead to death in pregnant mice whereas low doses did not result in maternal toxicity [31]. Developmental disorders were found in malformed babies due to abnormal cortical and hippocampal linkage to cell migration defects. After acute and chronic ingestion of ethanol with VGB in rats showed increment of GABA-T activity by twofold and it is said that VGB may potentiates ethanol [32].

Pharmacokinetics

VGB upon oral administration is completely absorbed, widely distributed and excreted through renal excretion. VGB do not bind to plasma protein and dosage adjustment is not necessarily required [33]. Plasma peak concentration reaches within 2 h and rapidly as 1 h. The absorption half-life and mean terminal half-life ranges from 10 to 35 min and 5 to 7 h, respectively. The assumption of linear model is based on that RGC axon components loss of RNFL is constant and it does not contribute in the alteration of visual function [27]. The oral form of VGB exists as a racemic mixture of the S (+) and R (–) enantiomers, and S (+) enantiomers is held responsible for drug activity and this enantiomer binds irreversibly to GABA-T. The factors which affect plasma pharmacokinetics are individual factors like age and renal clearance and due to these factors, bioavailability of VGB is lesser in younger patient than adults, hence higher doses of VGB is required in infants and children [34]. Use of VGB in pregnant women has teratogenicity effect on fetus and results in congenital malformation [32] (Table 1).

Table 1 Pharmacokinetics of VGB [34]

Pharmacokinetic parameters	Observed value
Oral bioavailability	> 60%
Concentration range	0.8–36 mg/L
T _{max}	1–2 h
T _{1/2}	5–8 h
Protein binding	0%
Volume of distribution	0.6 L/kg
Compliance (trough serum range)	6 to 278 mol/L at dose 1000–3000 mg/day

Risk factors

Age Several studies have shown that the development of VFDs is seen in older patient than in younger patient taking VGB [35]. But few studies show that there is no relationship between age and RNFL thickness [27]. After 18 months of VGB treatment more boys were affected than girls according to an observational cohort study [36]. The exposure to VGB during infancy does not significantly increase the risk of visual loss and children are too young to perform visual field assessment with perimetry [35].

Duration of therapy Longer exposure of VGB can lead to accumulation of GABA in muller cells [3]. Thirty patients out of 146 showed VGB-induced retinal damage and reason for less prevalence of damage was attributed to shorter duration of treatment in maximum number of patients [36]. In one study, children were classified according to duration of VGB treatment into first, second and third group of less than 1 year, 12–24 months and more than 2 years, respectively. In first group, 1 out of 11 children suffered from mild VFD, in second group, 3 out of 10 children suffered mild (1 child) and severe (2 children)

VFD and in third group, 7 out of 11 children suffered mild (3 children) and severe (4 children) VFD [20]. It is very uncommon to develop visual defects within 3 months of VGB treatment [15].

Cumulative dose The Market Authorization Holders (MAH) evaluated the association between cumulative dose of VGB and VFD in cohort of 219 patients. The prevalence of VFD among this cohort was found to be 30.2% [3]. But there was no significant correlation found between cumulative dose of VGB and VFD [20]. The prevalence of VFDs by VGB rises steeply between cumulative doses of 1–3 kg, with a cumulative risk plateau of 5 kg [35]. Cumulative dose was higher after 18 months of treatment and is attributed to toxicity of retina [15].

Gender Male gender is two times at risk for developing VFD with the use of VGB [20]. But in clinical study conducted showed no significant difference was found between male and female for MRD or RNFL thickness [27].

Efficacy of VGB therapy

The details of efficacy on VGB are shown in Table 2 [6, 19, 29, 37–40] and Table 3. [8, 10, 12, 13, 16, 20, 21, 23, 24, 41–45].

Safety of VGB

In 1998, long-term study revealed that VGB had low rate of side effects and children in study experienced hyperactivity and irritability which dissolved after dose reduction and no child withdrew VGB due to side effects [37]. Another study revealed, 5 out of 66 patients discontinued the study on advent of 3 patients developing adverse events whereas 2 patients lost follow up. Before the end of phase II, 3 patients left the study due of worsening of seizures. The most common side effects were

Table 2 Studies regarding efficacy of VGB

Year	Authors	Disease	Results
1998	Seimes [37]	Refractory IS	VGB is effective both in short-term and long-term treatment
1999	Daneshwar [19]	Seizures	12 out of 41 showed peripheral visual field constriction
2000	Elterman [6]	IS	Three years study conducted on patients age below 2 treated with VGB without any AEDs for 3 months. The response increased well after 2 weeks but later time to response became shorter for high dose VGB
	Kaul [29]	Epilepsy	Four children who were on VGB as add-on therapy had developed eye changes in the form of retinal pigmentation, hypopigmented retinal spots and optic atrophy
	Nicolson [38]	Seizures	Visual fields were normal, abnormal and non-identifiable cause among tested individuals and confirmed possibility of higher incidence of asymptomatic VFDs with the exposure to VGB
2006	Werth [39]	Epilepsy	VGB induced visual constriction is not more frequent in children younger than 6 years and mentally handicapped than compared with VGB induced VFDs in school age children
	Ko [40]	Epilepsy	Type and severity of VFD was determined. In terms of type 15 had VGB-related VFDs, had nasal arcuate, 1 had nasal and temporal constricted type and 1 had nasal constricted. In terms of severity, VGB attributed VFDs were graded in 4 categories, Grade I was minimal (25–30°), Grade II was moderate (20–30°), Grade III was moderate to severe (< 20°) and Grade IV was severe with ring scotoma. In this study 7, 5, 2 and 1 patients had Grade I, II, III and IV of severity related with VGB use

Table 3 Last decade data on efficacy of VGB

2014	Riikonen [20]	IS	The results revealed that out of 32 children 34% had mild or severe VFC. The study concluded to use benefit versus risk ratio if planning to use VGB
2016	Sergott [41]	rCPS	This study evaluated ocular changes with adjuvant VGB therapy in naive adults suffering from rCPS revealed almost every patient in study experienced RNFL thickening after intake of VGB and this thickening progressed with duration of exposure and total daily dose of VGB
	Krauss [23]	IS	Five year results of Sabril in adults revealed 70% were naive to VGB who continued the treatment even after 3 months and only 5 patients discontinued due to the development of VFDs
	Pellock [24]	IS	Five year results of Sabril in pediatrics revealed in which majority of participants failed to undergo ophthalmic evaluation because of age
	Sckwarz [8]	IS	Risk of development of VAVFL was clinically significant only in 3.2% with VGB treatment in infantile spasm. Among patients participated in study, vision loss was seen in 31% with VGB exposure whereas 32% without VGB exposure and also vision discrepancies were not characterized as peripheral and loss was better explained by other etiologies. Clinical risk of vision loss was apparently low in young children treated with VGB for IS
	Collaghan [16]	IS	After UKISS trial, an International Collaborative Infantile Spasms Study (ICISS) aimed to test hypothesis in combination of hormonal therapy with VGB in cessation of spasms compared to hormonal therapy alone. The study showed spasms cessation with combination therapy compared to hormonal therapy alone
2017	Chtsuka [12]	IS	It was a phase III trial, single-blind study with inclusion criteria being diagnosis of IS with hypsarrhythmia on EEG, greater or equal to 4 weeks and less than 2 years of age at the start of VGB. 8 patients had more than 50% of decrease in seizure frequency whereas no VGB induced VFDs were found and no serious drug events were seen even after discontinuation of VGB
	Hussain [13]	IS	Risk of VGB associated brain abnormalities on Magnetic Resonance Imaging (MRI) (VABAM) was evaluated. Among 104 patients, four showed symptomatic VABAM which was highly co-related with the high amount of dosage and concomitant hormonal therapy
2019	Hahn [10]	IS	Analyzed and compared the efficacy of VGB and steroid combination with first-line treatment. They divided into four groups of VGB, prednisolone, combination therapy with VGB and prednisolone and non-standard therapy. The primary outcome was response to therapy. But, the response rate to combination therapy (prednisolone with VGB) was significantly better than VGB monotherapy alone
	Wild [21]	Refractory seizures	This study made the model to check the appearance and ensuing staging of VAVFL derived with European Medicines Agency approved protocol. This model showed that there were 6 stages of VAVFL, and these stages can provide assistant to clinician or pediatricians in analyzing risk-benefit ratio in treatment of epilepsy
2021	Xu and Dressler [42, 45]	IS	A study aimed to further discover the risk factors and incidence of VABAM in children suffering from IS. Out of 77 children selected 25 developed VABAM and 23 among them were given with peak dose of VGB between 50 to 150 mg/kg/day and observed for 30 days
2022	Dzau and Schein [43, 44]	Epilepsy	This study described the ophthalmic assessments in children, incidence of ocular related toxicity and regular screening in children with VGB therapy from the medical records of Children's Hospital of Philadelphia, San Francisco from May 2010 to May 2021. Ophthalmic observations used were Visual Field (VF), ERG, OCT and funduscopy examination. Over period of ten years rate of examination and ERGs per child decreased. Two children out of 284, showed definitive VGB-related ocular toxicity on ERG

psychomotor agitation, hyperexcitability, axial hypertension and reversible cytotoxic edema [45].

Modified signal detection methods (SDMs) was used to evaluate differences in adverse events occurring between children and adults. The study included Green Forms (GFs) through which all patient's demographics along with VGBs initial dose, reason to stop (RS), adverse events were recorded and reported to regulatory authorities coded by Drug Safety Research Unit (DSRU) database. Over 30% of patients were children which were taken from dispensed VGB prescription orders issued between 1991 and 1995 while median observation was 299 days for children and 330 days for

adults. The most common RS in children was attributed to psychiatric disorders and only 3 patients showed abnormal ophthalmic events. In adults, there were 31 patients showing VFD in which 4 were possibly related to VGB use along with other AEDs [46]. In phase IV trial study the most common side effects reported were convulsion, suicidal thoughts, fall, weight gain, dizziness, depression, blurred vision, diarrhea, fatigue, somnolence and vagus nerve stimulation [41]. Movement disorder in infants was an unusual adverse drug reaction found in ICISS trial that is both in hormonal therapy group and combination of hormonal therapy with VGB [16].

In 2019, a case report on VGB induced encephalopathy in a baby girl of age 5 and half months suffering from IS due to TCS. She was suffering from TCS and hence VGB was started initially, but the therapy did not respond in the child hence ACTH was added which resulted in reducing 5 spasms per day to 2 spasms per day. Despite improvement she showed the signs and symptoms of encephalopathy with psychomotor regression. An EEG was carried out on the patient and showed hypsarrhythmia so the VGB was discontinued immediately and follow up EEG showed improvement with normal rhythms after withdrawal of VGB [47].

Precaution needed to be taken before administering VGB

Before starting the treatment with VGB, it is responsibility of the prescribing doctor to discuss with patient's caregivers about the risk of VFDs [36]. In the treatment for pediatric infantile spasms, VGB has been primary alternative agent and comparatively it has outstanding safety profile. The only downside is that there is lack of data on long-term effects of VGB therapy in pediatrics [37]. In the initial treatment of infantile spasms, VGB and ACTH showed no significant difference. On considering the monotherapy, patients receiving ACTH were 1.2 times more likely to relapse when compared to patients taking VGB [11]. A clinician can use qualitative assessments to quickly analyze the visual field defects [48].

The ophthalmologists or neuroophthalmologists should conduct the age-appropriate testing and repeat the qualitative screening if necessary [48]. Before managing the ocular adverse effects with oral administration of VGB, includes referring patient to ophthalmic screening, baseline visual field should be obtained [47]. During VGB therapy, achieving improved seizure control can be observed within 2–4 weeks after attaining the therapeutic dosage in patients with infantile spasms. Hence, clinical response can be evaluated at the starting of the therapy itself. If substantial response has not yet been achieved in the particular duration of time, discontinuation of VGB is a better option to avoid the visual field defects. If the efficacy of VGB is substantial, continuation of therapy with regular vision monitoring is preferred [6].

VGB given to treat IS are more vulnerable to VFD than given for other indication, since visual problems are evident in IS before any exposure of drug hence it becomes ambiguous that visual problems are due to drug intake or related with the disease [7]. The regulatory procedures in US require parents or guardians to give a written statement that, "about one in three patients taking vigabatrin has vision damage". It also contradicts with the studies that show that VFD risk is lower in pediatrics who undergo short duration of therapy. The physicians must consider the risk–benefit ratio during the VGB

therapy. The benefits of decreased number of seizures and improved quality of life versus the potential risk of developing VGB induced visual field defects should be assessed [35].

Evaluation of VFDs with the use of VGB

In one of the study, the prevalence of VFDs with the use of VGB was 22% against other use of anti-epileptic drugs [40]. One study revealed PK data of VGB enables to know the exposure and response of the drug, but attaining this data is quite challenging in pediatric population. Several pediatrics dosing regimens were developed mimicking adult data, however there is a huge gap between two population and differences in anatomical, physiological, child-specific biochemical characteristics, ethical issues, and only few subjects being eligible for study. It also extrapolated the data of adults on pediatrics with age greater than 2–4 years and VGB exposure was evaluated [49].

Conclusion

Cumulative dose of VGB can be the reason for visual field loss and hence it is recommended to undergo frequent visual field checkups, if the duration of VGB intake is long. In order to continue VGB, evaluation of clinical response during the early onset of treatment is necessary and it depends on individual risk and benefit ratio. Evaluation of clinical response to VGB and identification of risk associated can be done by implementation of a risk evaluation mitigation strategy (REMS). Overall management should be the monitoring of visual field and minimal defects with the use of VGB besides proper communication between treating physician, ophthalmologist and pharmacist. The ultimate goal is good clinical response and better patient care in children using VGB.

Abbreviations

AED	Antiepileptic drug
ACTH	Adrenocorticotrophic hormone
DSRU	Drug Safety Research Unit
EEG	Electroencephalogram
ERG	Electroretinogram
EOG	Electrooculogram
FDA	Food Drug Administration
GABA	Gamma-aminobutyric acid
GFs	Green Forms
IS	Infantile spasms
ILAE	International League Against Epilepsy
ICISS	International Collaborative Infantile Spasms Study
MAH	Market Authorization Holders
MRI	Magnetic resonance imaging
REMS	Risk Evaluation and Mitigation Strategy
OCT	Optical coherence tomography
RNFL	Retinal nerve fiber layer
RGC	Retinal ganglion cells
rCPS	Refractory complex partial seizures
RS	Reason to stop
SHARE	Support, Help And Resources for Epilepsy

SD-OCT	Spectral domain optical coherence tomography
SDMs	Signal detection methods
TSC	Tuberous sclerosis complex
UKISS	United Kingdom Infantile Spasms Study
VGB	Vigabatrin
VF	Visual field
VFD	Visual field defects
VFC	Visual field constriction
VAVFL	Vigabatrin associated visual field loss
VABAM	VGB associated brain abnormalities on magnetic resonance imaging

Acknowledgements

None.

Author contributions

UHAP*, NS, SA, RM; writing original draft. UHAP; critically reviewed the manuscript. UHAP*; supervision. All authors have read and approved the final version of manuscript.

Funding

This study received no funding.

Availability of data and materials

Not applicable.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The author declares that he has no competing interests.

Received: 24 October 2022 Accepted: 22 June 2023

Published online: 07 July 2023

References

- Fecarotta C, Sergott RC. Vigabatrin-associated visual field loss. *Int Ophthalmol Clin*. 2012;52(3):87–94.
- Hussain AS. Treatment of infantile spasms. *Epilepsia Open*. 2018;3(s2):143–54.
- Tuğcu B, Bitnel MK, Kaya FS, Güveli BT, Atakh D. Evaluation of inner retinal layers with optic coherence tomography in vigabatrin-exposed patients. *Neurol Sci*. 2017;38:1423–7.
- Sergott RC. Vigabatrin-associated visual field loss: past, present and future. *Expert Rev Ophthalmol*. 2014;9(3):145–8.
- Foroozan R. Vigabatrin: lessons learned from the United States experience. *J Neuroophthal*. 2018;38(4):442–50.
- D'Alanzo R, Rigante D, Mencaroni E, Esposito S. West Syndrome: a review and guide for paediatricians. *Clin Drug Investig*. 2018;38:113–24.
- Golec W, Solowiej E, Strzelecka J, Jurkiewicz E, Jozwiak S. Vigabatrin—new data on indication and safety in pediatric epilepsy. *Neurol Neurochir Pol*. 2021;55(5):429–39.
- Schwarz MD, Li M, Tsao J, Zhao R, Wu YW, Sankar R, et al. A lack of clinically apparent vision loss among patients treated with vigabatrin with infantile spasms: the UCLA experience. *Epilepsy Behav*. 2016;57:29–33.
- Meng X-F, Yu J-T, Song J-H, Chi S, Tan L. Role of the mTOR signaling pathway in epilepsy. *J Neurol Sci*. 2013;332:4–15.
- Hahn J, Park G, Kang H-C, Lee SJ, Kim HD, et al. Optimised treatment for infantile spasms: vigabatrin versus prednisolone versus combination therapy. *J Clin Med*. 2019;8(10):1591.
- Takahashi Y, Ota A, Tohyama J, Kirino T, Fujiwara Y, Ikeda C, et al. Different pharmacoresistance of focal epileptic spasms, generalized epileptic spasms, and generalized epileptic spasms combined with focal seizures. *Epilepsia Open*. 2022;7(1):85–97.
- Ohtsuka Y. Efficacy and safety of vigabatrin in Japanese patients with infantile spasms: primary short-term study and extension study. *Epilepsy Behav*. 2018;78:134–41.
- Hussain SA, Tsao J, Li M, Schwarz MD, Zhou R, Wu JY, et al. Risk of vigabatrin-associated brain abnormalities on MRI in the treatment of infantile spasms is dose-dependent. *Epilepsia*. 2017;58(4):674–82.
- Menachem B. Mechanism of action of vigabatrin: correcting misperceptions. *Acta Neurol Scand*. 2011;122(Suppl. 192):5–15.
- Kotagal P. Limiting retinal toxicity of vigabatrin in children with infantile spasms. *Epilepsy Curr*. 2015;15(6):327–9.
- Callaghan FJKO, Edwards SW, Alber FD, Hancock E, Johnson AL, Kennedy CR, et al. Safety and effectiveness of hormonal treatment versus hormonal treatment with vigabatrin for infantile spasms (ICISS): a randomized, multicentre, open-label trial. *Lancet Neurol*. 2017;16:33–42.
- Biswas A, Yossofzai O, Vincent A, Go C, Widjaja E. Vigabatrin-related adverse events for the treatment of epileptic spasms: systematic review and meta-analysis. *Expert Rev Neurother*. 2020;20(12):1315–24.
- Barrett D, Yang J, Sujirakul T, Tsang SH. Vigabatrin retinal toxicity first detected with electroretinographic changes: a case report. *J Clin Exp Ophthalmol*. 2014; 5(5).
- Daneshvar H, Racette L, Coupland SG, Kertes PJ, Guberman A, Zackon D. Symptomatic and asymptomatic visual loss in patients taking vigabatrin. *Ophthalmology*. 1999;106(9):1792–8.
- Riikinen R, Renner-Primec Z, Carmant L, Dorofeeva M, Hollody K, Szabo I, et al. Does vigabatrin treatment for infantile spasms cause visual field defects? An international multicenter study. *Dev Med Child Neurol*. 2015;57:60–7.
- Wild JM, Smith PEM, Knupp C. Objective derivation of the morphology and staging of visual field loss associated with long-term vigabatrin therapy. *CNS Drugs*. 2019;33(8):817–29.
- Miziak B, Borowicz-Reutt K, Rola R, Blaszczyk B, Czuczwar M, Czuczwar SJ. The prophylactic use of antiepileptic drugs in patients scheduled for neurosurgery. *Curr Pharm Des*. 2017;23(42):6411–27.
- Krauss G, Faught E, Foroozan R, Pellock J, Sergott R, Shields W, et al. Sabril® registry 5-year results: characteristics of adult patients treated with vigabatrin. *Epilepsy Behav*. 2016;56:15–9.
- Pellock J, Faught E, Foroozan R, Sergott R, Shields W, Ziemann A, et al. Which children receive vigabatrin? Characteristics of pediatric patients enrolled in the mandatory FDA registry. *Epilepsy Behav*. 2016;60:174–80.
- van der Torren K, Graniewski-Wijnands HS, Polak BC. Visual field and electrophysiological abnormalities due to vigabatrin. *Doc Ophthalmol*. 2002;104(2):181–8.
- Carver CM, Reddy DS. Neurosteroid interactions with synaptic and extrasynaptic GABA(A) receptors: regulation of subunit plasticity, phasic and tonic inhibition, and neuronal network excitability. *Psychopharmacology*. 2013;230(2):151–88.
- Clayton LM, Devile M, Punte T, Kallis C, de Haan GJ, Sander JW, et al. Retinal nerve fibre layer thickness in vigabatrin-exposed patients. *Ann Neurol*. 2011;69(5):845–54.
- Lunn J, Donovan T, Litchfield D, Lewis C, Davies R, Crawford T. Saccadic eye movement abnormalities in children with epilepsy. *PLoS ONE*. 2016;11(8): e0160508.
- Koul R, Chacko A, Ganesh A, Bulusu S, Riyami KA. Vigabatrin associated retinal dysfunction in children with epilepsy. *Arch Dis Child*. 2001;85:469–73.
- Tao Y, Yang J, Ma Z, Yan Z, Liu C, Ma J, et al. The vigabatrin induced retinal toxicity is associated with photopic exposure and taurine deficiency: an in-vivo study. *Cell Physiol Biochem*. 2016;40:831–46.
- Verrotti A, Scaparrotta A, Cofini M, Chiarelli F, Tiboni GM. Developmental neurotoxicity and anticonvulsant drugs: a possible link. *Reprod Toxicol*. 2014;48:72–80.
- Fan HC, Lee HS, Chang KP, Lee YY, Lai HC, Hung PL, Lee HF, Chi CS. The impact of anti-epileptic drugs on growth and bone metabolism. *Int J Mol Sci*. 2016;17(8):1242.
- Verrotti A, Lapadre G, Donato GD, Francesco LD, Zagaroli L, Matricardi S, et al. Pharmacokinetic considerations for anti-epileptic drugs in children. *Expert Opin Drug Metab Toxicol*. 2019;15(3):199–211.
- Jacob S, Nair AB. An updated overview on Therapeutic Drug Monitoring of recent Antiepileptic drugs. *Drugs R D*. 2016;16(4):303–16.

35. Riikonen R. Infantile spasms: outcome in clinical studies. *Pediatr Neurol*. 2020;108:54–64.
36. Westall CA, Wright T, Cortese F, Kumarappah A, Snead OC, Buncic JR. Vigabatrin retinal toxicity in children with infantile spasms: an observational cohort study. *Neurology*. 2014;83(24):2262–8.
37. Siemes H, Brandl U, Spohr H-L, Völger S, Weschke B. Long-term follow-up study of Vigabatrin in pretreated children with west syndrome. *Seizure*. 1998;7(4):293–7.
38. Nicolson A, Leach JP, Chadwick DW, Smith DF. The legacy of vigabatrin in a regional epilepsy clinic. *J Neurol Neurosurg Psychiatry*. 2002;73:327–9.
39. Werth R, Schädler G. Visual field loss in young children and mentally handicapped adolescents receiving vigabatrin. *Invest Ophthalmol Vis Sci*. 2006;47(7):3028–35.
40. You SJ, Ahn H, Ko TS. Vigabatrin and visual field defects in pediatric epilepsy patients. *J Korean Med Sci*. 2006;21:728–32.
41. Sergott RC, Johnson CA, Laxer KD, Wechsler RT, Cherny K, Whittle J, et al. Retinal structure and function in vigabatrin-treated adult patients with refractory complex partial seizures. *Epilepsia*. 2016;57(10):1634–42.
42. Xu Y, Li W, He W, Wang Y-Y, Wang Q-H, Luo X-M, et al. Risk of vigabatrin-associated brain abnormalities on MRI: a retrospective and controlled study. *Epilepsia*. 2021;63(1):120–9.
43. Dzau W, Cheng S, Snell P, Fahey M, Scheffer IE, Harvey AS, et al. Response to sequential treatment with prednisolone and vigabatrin in infantile spasms. *J Paediatr Child Health*. 2022;58:2197.
44. Schein Y, Miller KD, Han Y, Yu Y, Compomanes AG, Binenbaum G, et al. Ocular examinations, findings, and toxicity in children taking vigabatrin. *J AAPOS*. 2022;26(4):187.e1-187.e6.
45. Dressler A, Benninger F, Trimmel-Schwahofer P, Gröppel G, Porsche B, Abraham K, Mühlebner A, Samuelli S, Male C, Feucht M. Efficacy and tolerability of the ketogenic diet versus high-dose adrenocorticotropic hormone for infantile spasms: a single-center parallel-cohort randomized controlled trial. *Epilepsia*. 2019;60(3):441–51.
46. Aurich-Barrere B, Wilton L, Brown D, Shakir S. Paediatric post-marketing pharmacovigilance: comparison of the adverse event profile of vigabatrin prescribed to children and adults. *Pharmacoepidemiol Drug Saf*. 2011;20:608–18.
47. Ahmad R, Mehta H. The ocular adverse effects of oral drugs. *Aust Prescr*. 2021;44(4):129–36.
48. Conway ML, Hosking SL, Zhu H, Cuppidge RP. Does the Swedish Interactive Threshold Algorithm (SITA) accurately map visual field loss attributed to vigabatrin? *BMC Ophthalmol*. 2014;14(166).
49. Rodrigues C, Chiron C, Ounissi M, Dulac O, Gaillard S, Nabbout R, et al. Pharmacokinetic evaluation of vigabatrin dose for the treatment of refractory focal seizures in children using adult and pediatric data. *Epilepsy Res*. 2019;150:38–45.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Submit your manuscript to a SpringerOpen[®] journal and benefit from:

- Convenient online submission
- Rigorous peer review
- Open access: articles freely available online
- High visibility within the field
- Retaining the copyright to your article

Submit your next manuscript at ► [springeropen.com](https://www.springeropen.com)
