CNS Drugs (2014) 28:279–290
DOI 10.1007/s40263-014-0139-5

CURRENT OPINION

Recent Advances in the Pharmacotherapy of Infantile Spasms

Raili Riikonen

Published online: 7 February 2014
© Springer International Publishing Switzerland 2014

Abstract Adrenocorticotrophic hormone (ACTH), oral corticosteroids and vigabatrin are now first-line treatments for infantile spasms in the US and Europe. There is now increased knowledge regarding the role of ACTH, corticosteroids and vigabatrin (e.g. efficacy, doses, side effects, treatment in specific aetiological subtypes of infantile spasms), and other antiepileptic drugs (i.e. topiramate, valproate, zonisamide, sulthiame, levetiracetam, lamotrigine, pyridoxine, ganaxolone), as well as adjunctive flunarizine and novel drugs not yet in clinical use for infantile spasms (i.e. pulse rapamycin and melanocortin receptor agonists). The existence of a latent period, weeks to months following a precipitating brain insult, raises the possibility of preventive interventions. Recent experimental data emerging from animal models of infantile spasms have provided optimism that new and innovative treatments can be developed, and knowledge that drug treatment can affect long-term cognitive outcome is increasing. The aim of this article is to review recent developments in the pharmacotherapy of infantile spasms and to highlight the practical implications of the latest research.

1 Introduction

Infantile spasms, or West syndrome, consists of epileptic spasms, hypsarrhythmia or modified (atypical) hypsarrhythmia. The hypsarrhythmic EEG pattern reflects chaotic, high-voltage, interictal epileptic activity, and could be known as electrical status epilepticus. On positron emission tomography (PET) scan, expansion of glucose hypometabolism can be seen with persistent epilepsy [1]. Infantile spasm syndrome is an epileptic encephalopathy. Epileptic activity itself contributes to behavioural and developmental consequences, therefore if spasms are not controlled, cognitive outcome is always poor. Thus, it is important to stop this damaging activity without delay.

Genetic, structural, metabolic, and unknown aetiological groups represent modified concepts to replace idiopathic, symptomatic and cryptogenic aetiology, according to the International League Against Epilepsy (ILAE) Commission on Classification and Terminology in 2010 [2].

Underlying aetiology is the most important factor affecting developmental outcome [3], and more than 200 potential aetiological factors for infantile spasms have been reported [4]. After careful aetiological investigations, some specific aetiological subgroups can be identified for which specific therapy is recommended. Such groups include metabolic diseases [5], cytomegalovirus infection [6], cryptogenic group of infantile spasms [7] and tuberous sclerosis (TS) [8]. The number of genes associated with infantile spasms are rapidly increasing (*ARX, CDKL5, FOXG, GRIN1, GRIN 2A, MAGI, MEF2C, SLC25A22, SPTANI, STXBP1* and *15q11q13*) [9], therefore genetic therapy might be possible in the future.

In evidence-based reviews, infantile spasms are divided into two traditional groups: (i) cryptogenic—normal development before the spasms and no cause can be found by careful aetiological investigations [magnetic resonance imaging (MRI) being normal]; and (ii) symptomatic—a pre-, peri- or postnatal cause can be identified. The cryptogenic group may have a normal outcome in up to 100 % of patients if the effective treatment has been started within 1 month [10]. The symptomatic group can have a favourable outcome in approximately 20 % of patients [11].

R. Riikonen (✉)
Children's Hospital, University of Eastern Finland,
Puijonlaaksontie 2, P.O. Box 1627, FI-70211 Kuopio, Finland
e-mail: raili.riikonen@kuh.fi; raili.riikonen@kolumbus.fi

The number of cases in the cryptogenic group is decreasing because chromosomal abnormalities and cortical dysgenetic malformations can be found by modern genetic testing and neuroradiological methods. In this review, the traditional classification has been used because it was used in the clinical studies discussed.

The aim of this article was to review recent developments in the pharmacotherapy of infantile spasms and to highlight the practical implications of the latest research. Large excellent reviews have been recently published [7, 12]; however, many questions (such as the safety profile of approved and experimental therapies) still remain unanswered [13]. The author's own experience and search for other relevant studies from the world literature has supplemented the present review.

2 What is the Most Effective Treatment for Infantile Spasms?

Infantile spasms are usually resistant to conventional antiepileptic drugs (AEDs) and adrenocorticotrophic hormone (ACTH) has been the preferred treatment since 1958 [14]. Corticosteroids, such as prednisone, prednisolone and hydrocortisone are used less often. Until now, data on the efficacy of AEDs other than vigabatrin have been scarce.

Clinicians currently choose therapy for infantile spasms on published studies, or less objective measures such as personal experience, costs or side effect profile and availability of a drug. A through critical review was published in 2004 by the American Academy of Neurology Central Nervous System group to provide guidelines to clinicians in the treatment of infantile spasms [15]. In a recent paper published in *Neurology*, the same group provides an update to these guidelines [7]. The researchers carried out database searches of MEDLINE and EMBASE for relevant studies conducted during the period 2002–2011, and place their findings in the context of pre-2002 evidence [15]. The searches identified 1,935 articles. Sixty-eight articles were selected for detailed review, and 26 were included in the analysis. Evidence-based criteria are shown in Table 1.

The aim of the 2012 guidelines update was to address five questions that could not be answered in 2004 because of insufficient data:

1. Are low-dose ACTH regimens effective for short-term treatment of infantile spasms?
2. Is ACTH more effective than vigabatrin for short-term treatment of infantile spasms?
3. Are corticosteroids as effective as ACTH for short-term treatment of infantile spasms?
4. Is there a role for AEDs other than vigabatrin and for a ketogenic diet in managing infantile spasms?
5. Does the successful early treatment of infantile spasms lead to long-term improvement of neurodevelopmental outcomes or decreased incidence of epilepsy?

Most recent studies only deal with short-term effects of drugs and lack some outcome measures. Outcome measures should include the following: cessation of the spasms with resolution of hypsarrhythmia, relapse rate, absence of epilepsy and epileptiform EEG, and cognitive and behavioural outcome [16]. Furthermore, the dropout rates of the studies should be given because some studies include a majority of patients with primarily favourable outcome. Effective treatment is now defined as complete cessation of the spasms plus abolition of hypsarrhythmia ('all-or-none response') [15]. Parental reports are insufficient and EEG should always be included for interpretation of response.

There have been more than 150 trials for the treatment of infantile spasms. The data of patients treated with first-line agents and in studies with evidence-based criteria I–III are seen in Tables 2 and 3.

Table 1 Recommendations graded in a 4-tier scheme according to the strength of evidence supporting them [15]

Level of evidence	Description
A	Strong research-based evidence (requires at least two Class I studies)
B	Moderate research-based evidence (requires at least one Class I study or two consistent Class II studies)
C	Limited research-based evidence (requires at least one Class II study or two consistent Class III studies)
U	Data are conflicting or insufficient to support the treatment = no scientific evidence
I	Prospective, randomised controlled trial
II	Prospective, controlled trial, lacking one of the following criteria: (a) primary outcome; (b) exclusion criteria; (c) dropouts; (d) baseline characteristics clearly defined
III	Controlled trial in a representative population
IV	Evidence from uncontrolled studies

Table 2 Prospective (Class I–III) ACTH and oral glucocorticoid studies

Class of evidence	No. of patients	SIS vs. CIS (% of patients)	ACTH dose	Duration at full dose (weeks)	Total treatment duration (weeks)	Spasms stopped (%)	EEG resolution (%)	Follow-up (months)	References
III	105	65 vs. 35	110/m^2	3	8	49	39	6 years	[48]
I	59	49 vs. 78	150/m^2	3	12	54	22	NS	[27]
		45 vs. 75	20 IU/m^2	3	12	58	21	NS	
I	15	52 vs. 80	150 IU/m^2	2	4	87	87	15	[24]
	12	92 vs. 67	Prednisone 2 mg/kg	2	4	33	33	16.9	
III	19	64 vs. 88	10 IU/day	3–5.5	5–6	74	78	9–44	[39]
III	25	52 vs. 48	Tetracosactide 0.5 mg every second day	2	NS	76	70	NS	[22][a]
	30	57 vs. 43	40 mg/day prednisolone	2	10	70	EEG not done in all	10 weeks	
NS	97	86 vs. 14	20–40 IU/day	3	5–6	64	77	10.4 years	[29]
	54	77 vs. 13	120 IU/day	3	5	54	74	10.4 years	

ACTH adrenocorticotrophic hormone, *NS* not stated, *SIS* symptomatic infantile spasms, *CIS* cryptogenic infantile spasms

[a] Tuberous sclerosis excluded

Table 3 Prospective (Class I–III) vigabatrin studies

Class of evidence	No. of patients	SIS vs. CIS (% of patients)	Vigabatrin dose (mg/kg/day)	Duration at full dose (weeks)	Spasms stopped (%)	EEG resolution (%)	Follow-up (months)	References
I	20	32 vs. 50	150	5 days	35	23	12	[31]
III	75	79 vs. 31	18–32	12	23	NS	3–38	[40, 41]
	67	77 vs. 33	100–150	12	11	NS	3–38	
III	23	44 vs. 57	150	NS	48	36	14–44	[39]
III	52	40 vs. 60	100–150	14	54	50	14	[22, 50]

SIS symptomatic infantile spasms, *CIS* cryptogenic infantile spasms, *NS* not stated

2.1 Adrenocorticotrophic Hormone (ACTH)

Different forms of ACTH are available. Corticotrophin, so-called 'natural ACTH' (e.g. corticotrophin gel and carboxymethyl cellulose) is naturally occurring and the therapeutic product is derived from a bovine or porcine source. Corticotrophin acts for 12–18 h [17]. Its synthetic derivate, tetracosactide, consists of 24 amino acids occurring in ACTH, and acts for 24–48 h [17]. Duration of action of the depot tetracosactrin is twice that of corticotrophin [17]. The international units (IU) of ACTH and tetracosactide are believed to be equivalent: corticotrophin 80–100 IU is equivalent to 1 mg Zn tetracosactide. Zn tetracosactide is used on alternate days because of its prolonged action. The relatively serious side effects of tetracosactide are probably due to its prolonged action [18]. Natural ACTH (Achtar®) is not available in Europe, and synthetic ACTH, tetracosactide, (Synacthen Depot®, S-Cortrophin Z®) is not available in the US. The former drug is more than 200 times more expensive than the latter [19]. There are no studies comparing the effects of natural ACTH and synthetic derivates in the treatment of infantile spasms.

Doses of ACTH vary in different countries: Japan, 0.1 mg/day [20]; Finland, 0.25 mg/day (=0.5 mg every second day) [21]; UK, 0.5 mg every second day [22]; and US 60–80 IU/day (=0.6–0.8 mg/day) [23]. It is not clear why infants in the US would need considerably larger doses than in Japan.

Recently, in a large US review [23] it was concluded that ACTH is the preferred therapy, but the optimal dose is still unknown. High-dose ACTH (80 IU/m^2) had a better response than low-dose prednisone (2 mg/kg) for the treatment of infantile spasms in a randomised controlled trial (RCT) including 29 children [24] (Class I evidence) (Table 2). In a large US consensus statement published in 2011, it was concluded that early recognition and diagnosis, initiation of short-term therapy with first-line treatment, timely EEG evaluation of treatment effectiveness, and

prompt treatment modification [25] were beneficial strategies for the treatment of infantile spasms. However, there has been no consensus on dosage or duration of therapy. Spasms should be completely stopped. EEG evolution should be an 'all-or-none' response. Unless hypsarrhythmia or multifocal spikes resolve, cognitive recovery is likely to be incomplete and disease progression is likely [26].

2.1.1 *Are Low-Dose ACTH Regimens Effective for Short-Term Treatment of Infantile Spasms?*

A Class I study ($N = 50$) showed similar efficacy (cessation of the spasms) between low-dose (20–39 IU/day), given for 3 weeks, and high-dose (150 IU/day) natural ACTH given for 2–6 weeks [27]. A Class II study ($N = 25$) likewise showed similar efficacy (cessation of the spasms) between the low-dose (20 IU/m^2) and high-dose (150 IU/m^2) treatments [28]. Combining these two studies revealed that high-dose ACTH stopped the spasms in 79 % of subjects compared with 76 % of subjects with low-dose ACTH [12]. An older, prospective, large Finnish study showed no difference in response rate (cessation of infantile spasms and resolution of hypsarrhythmia) or relapse rate comparing low-dose (20–40 IU/day) [$N = 54$] and high-dose (80–120 IU/day) [$N = 97$] regimens; however, long-term cognitive outcome was better with the low-dose regimen [29, 30].

Recent evidence also suggests that low-dose ACTH is probably as effective as high-dose ACTH for short-term treatment of infantile spasms (Class I and II evidence) [7]. Therefore, the following recommendation was given in 2012: "Low-dose ACTH should be considered as an alternative to high-dose ACTH for treatment of infantile spasms (Level B)" [7].

2.2 Vigabatrin

Vigabatrin is an inhibitor of GABA transaminase, which elevates GABA levels in the brain, leading to seizure inhibition. Vigabatrin has been used in Europe since the late 1980s and in Canada since 1994. It has gained popularity because of its ease of use and efficacy. Opinions are divided in Europe with regard to vigabatrin as initial treatment. In the US, vigabatrin was approved by the FDA in 2009, and vigabatrin and ACTH are now considered to be the first-line therapies [23]. Clinical studies (Class I) have shown that vigabatrin is superior to placebo in decreasing the frequency of infantile spasms [31].

Determining how long the therapy should be maintained is one of the great current challenges. Recently, it has been recommended that if spasm improvement is not achieved within 12 weeks of initiation, vigabatrin should be discontinued because of the risk of visual field defects [32]. Vigabatrin might be withdrawn without relapse in infants who have been spasm free for 6 months [33].

Hormonal treatment may be stopped after only 1 month, and vigabatrin after 6 months, according to a US consensus statement [23]. It is not known why vigabatrin treatment should be much longer than ACTH treatment, which can have a permanent effect after 2–4 weeks of therapy [24, 34]. Effective short-duration treatment may avoid major side effects associated with the treatment of infantile spasms [35].

Open questions still remain: can the relapses be avoided with prolonged corticosteroid or vigabatrin treatment, or will prolonged treatment cause glucocorticoid-induced dementia [36] or vigabatrin-induced visual field defects and apoptosis in the brain [37, 38]. It is known that glucocorticoid stimulation induced by mild stress has positive effects on the hippocampus, but severe stress induces apoptosis, which would favour the use of small doses of corticosteroids or ACTH.

2.2.1 *Is ACTH More Effective than Vigabatrin for Short-Term Treatment of Infantile Spasms?*

There are only a few prospective studies comparing vigabatrin and ACTH. In one prospective, randomised study from Italy [39] (Class III), 42 infants received vigabatrin 100–159 mg/kg/day or ACTH depot 10 IU intramuscularly once daily for 20 days. The effects (cessation of the spasms) were 48 % versus 74 % in favour of ACTH ($p = 0.007$). EEG response was faster with ACTH treatment than with vigabatrin.

In the largest open randomised prospective study (the United Kingdom Infantile Spasms Study; UKISS) including 107 children (excluding TS), the effects (cessation of the spasms) of ACTH and vigabatrin were 76 % and 52 % at day 14 of treatment, respectively ($p < 0.043$) [22] (Class III). Relapse rates did not differ significantly between the treatment groups.

A Cochrane analysis included prospective studies comparing ACTH (or other hormonal treatments) against vigabatrin. Results from two Class III studies ($N = 107$ and 28, respectively) indicate that hormonal therapy leads to resolution of spasms three times more rapidly and in more infants than vigabatrin [22, 39].

In a Finnish prospective crossover study, vigabatrin (50–100 mg/kg/day) was given as the first-line drug to all 42 patients with all aetiological groups. In total, 26 % responded to vigabatrin (total cessation of the spasms and resolution of hypsarrhythmia). ACTH was then offered in combination with vigabatrin. The starting ACTH dose was 3–5 IU/kg; however, if the spasms continued, the dose was doubled after 2 weeks. The total response rate was 60 %. Patients were monitored by video EEG Class IV. [11].

In the study of 179 infants by Elterman et al. [40] (Class III), which also included video EEG, the response rates with vigabatrin were very similar to the Finnish study: 23 % at day 14 but 60 % at 3 months. Thus, the response to vigabatrin seems to come later and in fewer infants than ACTH. Large doses of vigabatrin (100–140 mg/kg/day) were more effective than the small doses (18–36 mg/kg/day) in the study by Elterman et al. [40, 41].

In a multicentre retrospective study in Israel in children with idiopathic West syndrome [42] (Class IV), 14 children were treated with vigabatrin (100–180 mg/kg/day) and 14 with ACTH (100 IU on alternate days). Spasm cessation with vigabatrin at 2 weeks was 80 % and with ACTH was 88 %. Cognitive outcome at 9 years was normal in all subjects in the early (within 1 month) ACTH-treated group, 67 % in the late ACTH group and 54 % in the vigabatrin group ($p = 0.03$).

In a Pakistan study including 56 infants (excluding TS), the response rate (cessation of the spasms) to initial therapy was 55 % for vigabatrin and 50 % for ACTH [43] (Class IV).

In a UK study by Mohamed et al. [44] (Class IV) including 75 infants (24 with cryptogenic spasms and 51 with symptomatic spasms), 61 % of subjects responded to prednisolone 40 mg/day and 42 % to vigabatrin [44] (Class IV). Corticosteroids yielded a significantly better response in the cryptogenic group than in the symptomatic group. Spasms stopped significantly more rapidly after corticosteroid therapy (8 days) than after vigabatrin treatment (16 days) [44].

After pooling the data of eight separate prospective and retrospective studies, vigabatrin had a good response on spasms in 44 % of 478 patients [11, 22, 31, 39, 40, 45–47]. In the pooled data of nine separate prospective and retrospective studies, ACTH had a good response on spasms in 59 % of 476 patients [22, 24, 26–29, 34, 48, 49].

Early cessation of the spasms was attained significantly more often with hormonal therapy (ACTH/prednisolone) than with vigabatrin in the UKISS study, which included 107 subjects (excluding TS) [21] (Class III). As a continuation of the aforementioned study, the same study group published the results of follow-up at 14 months and 4 years [50, 51] (Class II and Class I, respectively). At 14 months of treatment, there was only a minimal difference in the relapse-free response rate between vigabatrin and hormonal treatments and in terms of seizure frequency [50]. However, cognitive outcome was better after initial ACTH than vigabatrin in the unknown aetiology subgroup, but not in the identified aetiology subgroup [50, 51]. This might be explained by earlier cessation of the spasms in the ACTH/hormone group.

2.3 Different Forms of Corticosteroids

Other forms of corticosteroids include hydrocortisone, prednisone, prednisolone and dexamethasone. Physiological cortisol secretion is 5–10 mg/m^2/day [52]. Dose equivalencies are for hydrocortisone 20–30 mg/day, prednisone/prednisolone 7.5–10 mg/day and dexamethasone 1–1.5 mg/day [52]. Prednisone has no substantial biological effects until activated by the liver into prednisolone. Hypothalamic-pituitary-adrenal (HPA) dysfunction is a common and under-diagnosed disorder in the critically ill child. Most importantly, administration of exogenous glucocorticoid can lead to adrenal insufficiency Suppression of the HPA axis is inevitable taking the equivalent of 15 mg/day or more of prednisolone for a long period [52]. Children who have been on long-term (>2 weeks) pharmacological doses of glucocorticoids should be considered to be at risk for adrenal insufficiency [53]. Also, short-term (<7 days), high-dose steroid therapy has suppressed adrenal function more regularly than has been appreciated [54].

Physicians should be aware that adrenal insufficiency may become longstanding and even permanent in exceptional cases [55]. Even minor degrees of adrenal insufficiency can be fatal in the stressed host [56]. It is necessary to evaluate the HPA axis function after hormonal treatment, and hydrocortisone substitution should be given until stimulated serum cortisol is >500 nmol/l in a standard ACTH test. In stressed individuals (such as those with a fever of >38 °C), doses of hydrocortisone 30–50 mg/m^2/day intravenously or orally (divided into three doses) should be administered [53]. Treatment with ACTH has been advocated as a preferable alternative to corticosteroid treatment because of its less suppressive effect on the HPA axis [57].

2.3.1 *Are Corticosteroids and Antiepileptic Drugs (AEDs) as Effective as ACTH for Short-Term Treatment of Infantile Spasms?*

In a Class I prospective randomised study ($N = 29$) [23] and a Class III prospective open-label study ($N = 49$) [47], high doses of ACTH (150 IU/m^2) had a better response on spasms than low-dose prednisone (2 mg/kg).

In a Class III prospective study from the UK [21], 107 patients were randomised to tetracosactide (synthetic ACTH) 0.5 mg/day (40 IU) on alternate days and prednisolone 40 mg/day. Prednisolone was increased to 60 mg/day if spasms continued. Cessation of the spasms were achieved in 76 % and 70 % of subjects, respectively. The difference was not significant on day 14 of treatment. TS was excluded in this study because vigabatrin was considered to be the drug of choice in TS [8]. It should be noted that large doses of prednisolone were used in the latter study. Large doses of prednisolone (40–60 mg/day) have recently been given with high response rates of 21/30 (70 %) [22], 51/72 (70 %) [58], 28/57 (49 %) [59] and 10/15 (66 %) [60]. The studies were not been evidence-based studies except for one [22]. However, oral

prednisolone is a promising and much less expensive alternative to intramuscular ACTH and that is why it is used in developing countries. However, it should be noted that large doses are associated with a high risk of HPA insufficiency.

In a small uncontrolled study of ten children (Class IV), Mytinger et al. [61] tested methylprednisolone pulse therapy: 20 mg/kg intravenously on each of three successive days followed by a 2-month prednisolone taper period in ten children. The response rate was 50 %.

In a study by Haberlandt [62] (Class IV) 7 of 14 children (50 %) with West syndrome exhibited 100 % response (total cessation of the spasms) when 20 mg/m^2/day dexamethasone was administered as pulse therapy for 3 days, with an interval of 4 weeks between each cycle. Every patient received at least five cycles. Prospective trials with larger numbers of patients would be needed to confirm these clinical observations. These two innovative approaches were partly motivated by cost, since the intravenous methylprednisolone/dexamethasone regimen had an estimated drug cost of US$200 compared with an estimated US$70,000 for treatment with ACTH in the US [62].

Ganaxolone is a synthetic neurosteroid analogue that modulates GABA(A) receptors. In an open-label, add-on trial, spasm frequency was reduced at least 50 % in 33 % of subjects (Class IV) [63–65]. The drug was well tolerated, but showed only modest and non-significant effectiveness. Its effect on hypsarrhythmia was not reported.

Go et al. [7] concluded that the evidence is insufficient to recommend the use of prednisolone, dexamethasone and methylprednisolone, or AEDs as being as effective as ACTH, which is preferred for the short-term treatment of infantile spasms (Level U).

3 Side Effects of Corticosteroids and Vigabatrin

The common side effects of both drugs are irritability, sleep disturbances and drowsiness [27, 39, 40, 48, 66]. Both drugs also have severe side effects. The side effects of ACTH are infections, arterial hypertension and adrenal hypofunction after therapy [61]. For infants with a history of frequent respiratory infections, prophylactic trimethoprim-sulfamethoxazole therapy might be recommended [18, 66].

Hypertension should be monitored and treated. In hypertensive patients the heart should be studied by ultrasound to recognise hypertrophic cardiomyopathy [18]. Hydrocortisone substitution should be given after ACTH therapy and continued until the adrenal function has normalised [18].

In Finland, ACTH therapy is given at a minimally effective dose and for the minimally effective time [18, 34]. With such treatment, no serious side effects were found [8, 34]. The potential side effects of ACTH might be severe but they are all treatable and reversible.

Large doses of ACTH (120 IU) gave more side effects than smaller doses (40 IU), but the difference was not significant, except infections were significantly more frequent with large doses compared with smaller doses ($p < 0.05$) [18].

Vigabatrin-specific side effects include peripheral visual field defects, and recently reported cerebral MRI structural abnormalities. The visual field defects caused by vigabatrin seem to be permanent [67]. Retinal damage, assessed by electroretinogram (ERG), can be seen as soon as 2–3 months following vigabatrin initiation [32]. In the US, vigabatrin is available only under a special restricted distribution programme (the Support, Help and Resources for Epilepsy (SHARE) programme [http://www.lundsbeckshare.com]; FDA, 2009). While taking vigabatrin, patients should have periodic ophthalmological evaluations beginning at the baseline evaluation at initiation of therapy as well as 3–6 months after cessation of treatment [http://www.lundsbeckshare.com]. The problem is that no reliable methods exist to detect whether or not visual field defects are developing ongoing vigabatrin therapy in infancy because they are not co-operative for perimetry assessment or measurements of the loss of retinal nerve fibre layer [32]. One recent systematic review showed that visual field defects occur in 40 % of adults and 34 % of older children receiving vigabatrin [68]. The earliest sustained onset of the vigabatrin-induced retinal defect studied by ERG is at 3 months [32]. Visual field defects are sufficient to prevent a person from driving. There are also concerns with children who might have a poor underlying function as a part of their overall neurological disabilities. There are only two small studies, including 16 patients, examining visual fields at school age after vigabatrin exposure in infancy. The risk for infants has been considered to be low [69, 70]. A larger recent multicentre study on visual field defects in school-age children treated with vigabatrin during infancy for infantile spasms [71] shows that vigabatrin causes visual field defects in children at rates comparable to adults.

To date, the most viable hypothesis for toxicity is not that it is accumulated GABA that affects the cone cells of the retina but rather a more direct effect of vigabatrin. One study in rodents showed that vigabatrin-associated retinopathy is associated with light exposure [72]. More recently, it has been suggested that a deficiency of taurine is implicated in the pathogenic process of vigabatrin-associated retinopathy [73, 74]. A pharmacogenetic exploration of vigabatrin-induced visual field constriction has also been undertaken, although no clear association has been identified [75]. However, genetic differences could explain why some children do not show any defects, even after long use of vigabatrin therapy [71].

New clinical trials should focus on the effect of taurine supplementation on vigabatrin therapy for infantile spasms. Limiting light exposure is also a simple and safe recommendation to limit the extent of vigabatrin-induced retinal lesions [74].

Drugs such as vigabatrin that increase synaptic concentrations of GABA in the brain can, in animals, cause apoptotic degeneration in the developing brain, but not after brain development has been completed [37, 38].

Hyperintensities in basal ganglia, thalamus, brainstem and dentate nucleus have, very recently, been shown in approximately one-third of those exposed to vigabatrin [76–79]. These MRI abnormalities may occur as early as 3 months after the initiation of therapy. They may be, in rare cases, accompanied by movement disorders [73]. Susceptibility seems to be restricted to infancy. They are reversible in most infants following discontinuation of therapy. Their clinical significance is still unknown. They might remain unnoticed in patients with psychomotor retardation and dyskinetic movements. Infants who display new neurological abnormalities, such as dyskinetic movements, during vigabatrin therapy might have a diagnostic MRI [79].

4 Is There a Role for AEDs other than Vigabatrin and for a Ketogenic Diet in Managing Infantile Spasms?

The evidence for other AEDs is extremely limited compared with vigabatrin. There are some Class IV studies of topiramate [80–82], valproic acid [83, 84], Class I of sulthiame [85] and Class IV of zonisamide [86–89], pyridoxine [90, 91], nitrazepam [92], levetiracetam [93], lamotrigine [94] and a ketogenic diet [95, 96].

Topiramate is a popular second-line treatment of infantile spasms and is often used as first-line treatment, especially where there is no access to vigabatrin [74] (Class IV). There is variable slow or fast titration up to 24 mg/kg/day [81], and the response is 40 % [80, 81]. Although there are studies of its use in intractable infantile spasms and as first-line treatment, there are no specific infantile spasm-related RCTs. Topiramate is generally considered to be tolerated at higher relative doses than in adults. The main concerns in infants relate to sleepiness, appetite suppression and weight loss, acid–base disturbance—particularly in the setting of concurrent ketogenic diet, reduced sweating, nephrocalcinosis, and potential impaired cognition and learning, which might only become apparent in the older child [80].

Valproic acid is often used as second-line treatment. It has been used as first-line treatment (30 mg/kg/day) in 100 children with a ‘complete or good’ response rate on spasms of 39 % [83] (Class IV). Adverse effects include hepatotoxicity, especially in multidrug treatment when large doses have been used [84].

Sulthiame remains an option when the first-line agents fail. In one small study of 34 infants with spasms and hypsarrhythmia, around one-third of subjects responded electroclinically to a sulthiame + B6 combination, compared with none of 17 taking B6 alone. Pyridoxine 150–300 mg/day was given before sulthiame. Sulthiame was started at 5 mg/kg/day and the dose was then doubled at day 7 (if no resolution of hypsarrhythmia). Spasm cessation with resolved hypsarrhythmia in sulthiame + B6 was 6/17 versus 0/16 for B6 alone. Adverse effects included hyperventilation, dyspnea, somnolence, paraesthesias, anorexia and psychiatric problems [85] (Class I).

Zonisamide has been studied in small open-label studies as an adjunct to high-dose pyridoxine. Spasm cessation was seen in 4/11 patients using doses up to 10 mg/kg/day [86] (Class IV) and in 9/27 patients with doses up to 20 mg/kg/day [87] (Class IV). Adverse effects are similar to topiramate and include drowsiness, ataxia, gastrointestinal symptoms, oligohydrosis and renal calculi [88, 89].

A ketogenic diet (high-fat, adequate protein, low carbohydrate) is an alternative to the other therapies for infantile spasms, especially for those children who have been resistant to AED treatments. A group in Baltimore reported its extensive experience with 104 consecutive infants treated with the diet, with 64 % having a reduction in spasm frequency 6 months after initiation of treatment [95, 96] (Class IV). A weakness of this study is that the main outcome measure was reduction in spasm frequency rather than a complete resolution of the spasms, which in general is considered to be the more important outcome relating to seizure control. However, there is no evidence that a ketogenic diet is better than the above-mentioned compounds following failure of hormone and vigabatrin therapy [7]. A specific indication for ketogenic diet may be identified in the future [88, 89]. Side effects include constipation, hyperlipidaemia, potential dehydration and renal calculi. It has been considered that the ketogenic diet has fewer side effects than ACTH therapy, and the frequency of side effects is lower [95].

In a small, single-centre RCT trial with 38 participants, complete cessation of spasms at 4 weeks occurred in 8/19 (42 %) patients treated with ACTH (25 IU/day) for 3 weeks compared with 12/19 (63 %) patients treated with ACTH + magnesium sulphate [97] (Class III).

There is often debate about whether infantile spasms should be treated with pyridoxine, pyridoxal phosphate and/or folinic acid. No RCTs comparing these therapies have been found. Pyridoxine therapy is considered first-line in some countries, including Japan [90, 91] (Class IV). Stockler et al. [98] have reviewed new developments

relating to pyridoxine-dependent epilepsy and deficiency of the enzyme antiquitin, also known as alfa-aminoadipic semialdehyde dehydrogenase. This condition is likely to present with neonatal seizures and not with infantile spasms. Apart from these clearly defined monogenic defects, pyridoxine may also have a non-specific therapeutic effect on spasms.

The above-mentioned agents have not been validated in large-scale studies, but remain options when first-line agents such as ACTH or vigabatrin fail or are contraindicated. There is no convincing evidence for the efficacy of these alternative therapies at this time.

5 Specific Aetiological Subtypes of Infantile Spasms

5.1 Cryptogenic Spasms

Better initial control of the spasms by hormonal treatment was associated with significantly better cognitive outcome at 14 months [50] and 4 years of age in patients with 'non-identified aetiology' [51] in the UK Study. Hormonal treatment may lead to improved developmental outcome in those with no identified aetiology [50, 51]. ACTH might be a drug of choice for cryptogenic infantile spasms [7].

5.2 Tuberous Sclerosis (TS)

TS represents an important cause of infantile spasms (10 %). The first small prospective study in children with infantile spasms and an underlying diagnosis of TS found vigabatrin to be more efficient than hydrocortisone at stopping the spasms [45]. In the study by Elterman et al. [40], which included subjects with TS, there were significantly more responders among children who had TS (13 of 15) compared with other aetiologies (19/117; $p < 0.001$). Vigabatrin has been considered the drug of first choice in TS [8].

However, in a Finnish study the response rate with ACTH was also high—73 % (16/22 infants) in the TS group [99]. The response rates with ACTH and vigabatrin are comparable in TS. Relapse rates are high after both drug trials. Because the use of ACTH is always given for a specified period, and vigabatrin for an indefinite period, vigabatrin is a better choice. TS has been attributed to mutations in the *TSC1* and *TSC2* genes. These genes, known as tumour suppressors, are responsible for the inhibition of the mammalian target of rapamycin (mTOR) signalling pathways [100]. Mutations in these genes cause hyperactivation of the mTOR system and result in excessive cell growth and hamartomatous tumours in multiple organs [100, 101]. Recently, novel treatment with mTOR inhibitors proved to be effective in the suppression of progressive proliferative growth of subependymal giant cell astrocytoma (SEGA) and renal angiomyolipomas [102]. Vigabatrin inhibits seizures and mTOR pathway activation in a mouse model of TS complex [103]. However, in the future, mTOR inhibitors (e.g. rapamycin) may challenge the role of vigabatrin as the preferred drug for infantile spasms caused by TS [104]. High-dose, pulse rapamycin treatment is also a promising, well-tolerated and disease-modifying new therapy for infantile spasms, including those not linked to TS [104, 105]. Clinical trials are ongoing to explore the benefits of this treatment to control other severe symptoms, such as epilepsy and skin lesions.

It has also been proposed that prophylactic antiepileptic treatment prior to the onset of infantile spasms might reduce epilepsy severity and risk of mental retardation in infants with TS [106] (Class IV); however, this statement needs an RCT to confirm the results.

5.3 'Other Symptomatic Infantile Spasms', Studies Excluding Patients with Cryptogenic Etiology and TS

New information has come to hand from summarising six published case series. Vigabatrin was effective (cessation of spasms) in 'other symptomatic spasms' in a total of 98/287 patients (29 %) receiving short-term treatment, as follows: 60/102 patients (59 %) [47]; 6/21 patients (28 %) [39]; 4/30 patients (13 %) [11]; 7/72 patients (10 %) [40]; 16/31 patients (51 %) [22]; and 5/31 patients (16 %) [107]. The high figures in the study by Aicardi et al. [47] could be explained by the lack of EEG evaluation. In the two studies where video telemetry was used [11, 40], the response rates were only 16–10 %. It should be noted that vigabatrin treatment may make spasms milder. Serial video EEG recordings have shown that during vigabatrin treatment there has been transition of motor spasms to subtle spasms that may remain unnoticed [26]. In contrast, ACTH was effective in 71/119 (59 %) patients [99] and ACTH or prednisolone in 21/30 (70 %) patients [22], for a total of 92/149 (62 %) patients. Hormonal therapy seems to be twice as effective as vigabatrin in the group of 'other symptomatic infantile spasms'.

6 Early Treatment

6.1 Does the Successful Early Treatment of Infantile Spasms Lead to Long-Term Improvement of Neurodevelopmental Outcomes or Decreased Incidence of Epilepsy?

In a retrospective study by Kivity et al. [10] (Class IV), long-term treatment with high-dose tetracosactide followed

by oral corticosteroids for about 9 months resulted in a normal cognitive outcome in all patients when treated within 1 month of the onset of infantile spasms, but only in 40 % when treated later. This study included only cryptogenic patients.

In a Class III study, early treatment initiation (<1 month following onset of symptoms) in 102 children with cryptogenic spasms, led to improved neurodevelopmental outcome [48]. Favourable cognitive outcome with shorter interval to treatment (<3 weeks [108], <4 weeks [109] and <4 weeks [42]) has also been seen in recent studies including patients with both cryptogenic and symptomatic spasms.

Furthermore, in the cryptogenic group ($N = 77$) of the UKISS study, Vineland Adaptive Behavioral Scores (VABS) at 4 years were 96 in the hormonal group versus 63 in the vigabatrin treatment group ($p = 0.033$) [51]. The UKISS Class II study showed that cognitive outcome was better after initial ACTH than vigabatrin in the cryptogenic subgroup but not in the identified aetiology subgroup [51]. The study showed a 3.9-point decrease in mean VABS was observed for each increase in category of time-to-initiation of treatment [110] (Class I).

The outlook was much improved for children who not only have a short treatment lag but who also responded to treatment. This was seen in Finnish patients with both cryptogenic and symptomatic spasms [111, 112].

A 2012 evidence-based review concluded "Hormonal therapy (ACTH or prednisolone) may be considered in preference to vigabatrin in children with cryptogenic spasms, to possibly improve developmental outcome (Level C)" and "A shorter lag time to treatment of infantile spasms with either hormonal therapy or vigabatrin may be considered to improve long-term cognitive outcomes (Level C)" [7].

Finally, because 25–30 % of patients continue to have spasms after intensive pharmacotherapy and express psychomotor retardation, they may be candidates for surgery. Many children previously classified as cryptogenic have been shown to have malformations.

7 Animal Models

Little is known about the pathogenesis of infantile spasms. For decades there were no good animal models for infantile spasms. However, a number of promising animal models have now been developed. Important pathophysiological insights can be gained if appropriate questions are posed. Current models are either on a specific cause of infantile spasms, such as loss of interneurons (aristaless-related homeobox ARX mouse), or propose a final common pathway underlying all causes of infantile spasms. Recently developed models are the ARX-linked aristaless-related knockout and knock-in mouse model, the multiple-hit model, corticotrophin-releasing hormone model, the *N*-methyl-D-Aspartate model and the tetradotoxin model [113]. No single model will replicate the human seizure exactly. CPP-115, a vigabatrin analogue with better tolerability than vigabatrin, has recently been shown to decrease spasms in the multiple-hit rat model of infantile spasms [114]. In a mouse model of TS, vigabatrin inhibits seizure activity and mTOR pathway activation [103]. Rapamycin, currently being evaluated within animal models for TS, is emerging therapy under investigation for infantile spasms [104, 105].

8 New Options

No current therapy is ideal, and novel agents are needed. Advanced molecular biology of the disease genetics and neuroimaging underlying this catastrophic epilepsy may facilitate more effective pharmacological interventions.

Flunarizine might have neuroprotective effects in patients with infantile spasms. In a Canadian study of 45 children treated with vigabatrin, ten flunarizine-treated children with no identified aetiology had better outcomes than eight controls treated with vigabatrin and placebo at 24 months on both the Vineland Scale and the Bayley Scale [115] (Class IV).

Pulse rapamycin is a promising treatment for ACTH-refractory infantile spasms. Rapamycin inhibits seizures and mTOR pathway activation in a mouse model of the TS complex [101, 103–105], And also improved cognitive outcome in a rat model of infantile spasms [104].

Other novel therapies include insulin-like growth factor (IGF)-1, which might increase synaptic development [116], melanocortin receptor agonists [117] and combination therapy with vigabatrin and corticosteroids [118] which is currently being tested in the ICISS (International Collaboration Infantile Spasms Study) study in the UK.

9 Conclusions

The most important goal of treatment is achievement of good cognitive outcome. Hormonal therapy and vigabatrin remain the first-line treatments of infantile spasms, with vigabatrin being the first-line therapy for TS. For other aetiologies, hormonal therapy seems to be more efficacious than vigabatrin. Evidence suggests resolution of spasms is faster and achieved in more infants with hormonal therapy than with vigabatrin. The optimal dosage and duration of ACTH therapy is still unknown, and low doses of ACTH are as effective as high doses. Shorter treatment lag

probably improves long-term cognitive outcome. ACTH is superior to vigabatrin for cognitive outcome in cryptogenic groups. Different corticosteroids and AEDs can be given as second-line drugs when first-line drugs are ineffective or are contraindicated.

The recently updated guidelines do not provide definitive answers to the five questions presented. Therefore, in the future (i) multicentre RCTs with multiple treatment arms should be conducted; (ii) long-term outcome in children treated with vigabatrin should be evaluated; (iii) management of relapses is also important to study; (iv) understanding and preventing visual field loss following vigabatrin treatment is important; and (v) recent experimental data emerging from animal models of infantile spasms are providing optimism that new and innovative treatments can be developed. Advances in our understanding of brain maturation, aetiologies, mechanisms and genetics underlying infantile spasms may facilitate more effective intervention.

Acknowledgments The author has no conflicts of interests that are directly relevant to the content of this review. No sources of funding were used to assist in the preparation of this review.

References

1. Benedek K, Juhasz C, Chugani D, et al. Longitudinal changes in cortical glucose hypometabolism in children with intractable epilepsy. J Child Neurol. 2006;21:26–31.
2. Berg A, Berkovic S, Brodie M, et al. Revised terminology and concepts for organization of seizures and epilepsies. Report of the ILEA Commission on Classification and Terminology, 2005–2009. Epilepsia. 2010;51:676–85.
3. Riikonen R. Favourable prognostic factors with infantile spasms. Eur J Ped Neurol. 2010;14:13–8.
4. Osborne J, Lux A, Edwards S et al. The underlying etiology of infantile spasms (West syndrome): information from the United Kingdom Infantile spasms Study (UKISS) on contemporary causes and their classification. Epilepsia 2010;51(10):2168-74
5. Yu J, Pearl P. Metabolic causes of epileptic encephalopathy. Epilepsy Res Treat. 2013;2013:124934. doi:10.1155/2013/124934.
6. Dunin-Wasowitcz D, Kasprzyk–Obara J, Jurkiewicz E, et al. Infantile spasms and cytomegalovirus infection: antiviral and antiepileptic treatment. Dev Med Child Neurol. 2007;49:884–92.
7. Go C, Mackay M, Weiss S, et al. Evidence-based guide line update: medical treatment of infantile spasms. Report of the Guideline Development Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. Neurology. 2012;78:1974–80.
8. Hancock E, Osborne J. Vigabatrin in the treatment of infantile spasms in tuberous sclerosis: literature review. J Child Neurol. 1999;14:71–4.
9. Paciorkowski A, Thio L, Dobyns W. Genetic and biologic classification of infantile spasms. Pediatr Neurol. 2011;20:197–202.
10. Kivity S, Lerman P, Ariel B, et al. Long-term cognitive outcomes of a cohort of children with cryptogenic infantile spasms treated with high-dose adrenocorticotropic hormone. Epilepsia. 2004;45:255–62.
11. Granström M-L, Gaily E, Liukkonen E. Treatment of infantile spasms: results of a population-based study with vigabatrin as the first drug for spasms. Epilepsia. 1999;40:950–7.
12. Hancock E, Osborne J, Edwards S. Treatment of infantile spasms. Cochrane Database Syst Rev. 2013;(6):CD001770
13. Riikonen R. Epilepsy: update to guidelines on treatment of infantile spasms. Nat Rev Neurol. 2012;8(9):480-2
14. Sorel L, Dusaucy-Bayloye H. A propos de 21 cas d'hypsarythmie de Gibbs. Son Traitement spectaculaire par lÀCTH. Acta Neurol Belg. 1958;58:130–41.
15. 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(10):1668–81.
16. Lux A, Osborne J. A proposal for case definitions and outcome measures in studies of infantile spasms and West syndrome: consensus statement of the West Delphi Group. Epilepsia. 2004;45:1416–28.
17. Treadwell B. Comparison of depot tetracosactrin and corticotrophin gel. BMJ. 1969;4:720–3.
18. Riikonen R. ACTH therapy of West syndrome: Finnish views. Brain Dev. 2001;23:642–6.
19. Gettig J, Cummings J, Matuszewski K. H.p. Acthar gel and cosyntropin review: clinical and financial implications. Pharm Ther. 2009;34(5):250–7.
20. Fukuyama Y. The Japanese scheme of ACTH therapy in West syndrome. Epilepsia. 2010;51:2216–8.
21. Riikonen R. A European perspective—comments on "Infantile spasms": a U.S. consensus report. Epilepsia. 2010;5:2215–6.
22. Lux A, Edwards S, Hancock E, et al. The United Kingdom infantile spasm study comparing vigabatrin with prednisolone or tetracosactide at 14 days: a multicentre, randomized controlled trial. Lancet. 2004;364:1773–8.
23. Pellock J, Hrachovy R, Shinnar S, et al. Infantile spasms: a U.S. consensus report. Epilepsia. 2010;51:2175–89. doi:10.1111/j.1528-1167.2010.02657.x.
24. Baram T, Michell W, Tourney A, et al. High-dose corticotrophin therapy for infantile spasms. Pediatrics. 1996;97:375–9.
25. Stafstrom C, Arnason B, Baram T, et al. Treatment of infantile spasms: emerging insights from clinical and basic science perspectives. J Child Neurol. 2011;26:1411–21.
26. Gaily E, Liukkonen E, Paetau R, et al. Infantile spasms: diagnosis and assessment of treatment response by video-EEG. Dev Med Child Neurol. 2001;43:658–67.
27. Hrachovy R, Frost J, Glaze D. High-dose, long-duration versus low-dose, short-duration corticotrophin therapy for infantile spasms. J Pediatr. 1994;124:803–6.
28. Yanagaki S, Oguni H, Hayashi K, et al. A comparative study of high-dose and low-dose ACTH therapy for West syndrome. Brain Dev. 1999;21:461–7.
29. Riikonen R. A long-term follow-up study of 214 children with earlier infantile spasms. Dev Med Child Neurol. 1981;23:747–60.
30. Riikonen R. Long-term outcome of patients with West syndrome. Brain Dev. 2001;23:683–7.
31. Appleton R, Peters A, Mumford J, et al. Randomized, placebo-controlled study of vigabatrin as first-line treatment of infantile spasms. Epilepsia. 1999;40:1627–33.
32. Willmore L, Abelson M, Ben-Menachem E, et al. Vigabatrin: update 2008. Epilepsia. 2009;50:163–73.
33. Vigabatrin Pediatric Advisory Group. Guideline for prescribing vigabatrin in children has been revised. BMJ. 2000;320:1404.
34. Heiskala H, Riikonen R, Santavuori P, et al. West syndrome: individualized ACTH therapy. Brain Dev. 1996;18:456–60.

35. Partikian A, Michell W. Neurodevelopmental and epilepsy outcomes in North American cohort of patients with infantile spasms. J Child Neurol. 2010;25:423–8.
36. Sapolsky G. Glucocorticoids, stress and exitotoxic neuron death. Semin Neurosci. 1994;6:323–31.
37. Bittigau P, Sifringer R, Ikonomidu C. Antiepileptic drugs and apoptosis in the developing brain. Ann NY Acad Sci. 2003;993:103–14.
38. Turski C, Ikonomidou C. Neuropathological sequelae of developmental exposure to antiepileptic and anesthetic drugs. Front Neurol. 2012;3:120.
39. Vigevano P, Cilio M. Vigabatrin versus ACTH as first-line treatment for infantile spasms: a randomized, prospective study. Epilepsia. 1997;38:1270–4.
40. Elterman R, Shields W, Mansfield K, Nakagawa J, the US Infantile Spasms Vigabatrin Group. Randomized trial of vigabatrin in patients with infantile spasms. Neurology. 2001;57:1416–21.
41. Elterman RD, Shields WD, Bittman RM. Vigabatrin for the treatment of infantile spasms: final report of a randomized trial. Child Neurol. 2010;25:1340–7.
42. Cohen-Sadan S, Kramer U, Ben-Zeev B, et al. Multicenter long-term follow-up of children with idiopathic West syndrome: ACTH versus vigabatrin. Eur J Neurol. 2009;16(4):482–7.
43. Ibrahim S, Gulab S, Ishaque S, et al. Clinical profile and treatment of infantile spasms using vigabatrin and ACTH: a developing country perspective. BMC Pediatr. 2010;10:1
44. Mohamed B, Scott R, Desai N, et al. Seizure outcome in infantile spasms: a retrospective study. Epilepsia. 2011;52:746–52.
45. Chiron C, Dumas C, Jambaque I, et al. Randomized trial comparing vigabatrin and hydrocortisone in infantile spasms due to tuberous sclerosis. Epilepsy Res. 1997;26:389–95.
46. Wohlrab G, Bolthauser E, Schmitt B. Vigabatrin as a first-line drug in West syndrome: clinical and electroencephalographic outcome. Neuropediatrics. 1998;29:133–6.
47. Aicardi J, Mumford JP, Dumas C, Wood S. Vigabatrin as initial therapy for infantile spasms: a European retrospective survey. Sabril IS Investigator and Peer Review Groups. Epilepsia. 1999;37:637-42.
48. Lombroso CT. A prospective study of infantile spasms: clinical and therapeutic correlations. Epilepsia. 1983;24:135–48.
49. Askalan R, Mavkay M, Brian J, et al. Prospective preliminary analysis of the development of autism and epilepsy in children with infantile spasms. J Child Neurol. 2003;18:165–70.
50. Lux A, Edwards S, Hancock E, et al. United Kingdom Infantile Spasms Study (UKISS) comparing hormone treatment with vigabatrin on developmental and epilepsy outcomes at age 14 months: a multicentre randomised trial. Lancet Neurol. 2005;4:712–7.
51. Darke K, Edwards SW, Hancock E, et al. Developmental and epilepsy outcomes at age 4 years in the UKISS trial comparing hormonal treatments to vigabatrin for infantile spasms: a multicentre randomised trial. Arch Dis Child. 2010;95:382–6.
52. Stewart P, Krone N. Therapeutic corticosteroids. Chapter 15 Adrenal cortex. In: Melmed S, Polonsky K, Larsen R, Kronenberg H, editors. Williams Textbook of Endocrinology, 12th edn. 2011.
53. Shulman D, Palmert M, Kemp S, et al. Adrenal insufficiency: still a cause of morbidity and death in childhood. Pediatrics. 2007;119:e484–94.
54. Axelrod L. Corticosteroid therapy. In: Becker K, editor. Principles and practice of endocrinology and metabolism. 3rd ed. Philadelphia: Lippincott Williams and Wilkins; 2001. p. 751–64.
55. Grossman A, Johannsson G, Quinker M, et al. Perspectives on the management of adrenal insufficiency: clinical insights from across Europe. Eur J Endocrinol. 2013;169:R165–75.
56. Marik P, Zaloga G. Adrenal insufficiency in the critically ill: a new look at an old problem. Chest. 2002;122:1784–96.
57. Perheentupa J, Riikonen R, Dunkel L, et al. Adrenocortical hyporesponsiveness after treatment with ACTH of infantile spasms. Arch Dis Child. 1986;6:750–3.
58. Azam M, Bhatti N, Krishin J. Use of ACTH and prednisolone in infantile spasms: experience from a developing company. Seizure. 2005;14(8):552–6.
59. Singhi P, Ray M. Profile of West syndrome in North Indian Children. Brain Dev. 2005;27:135–40.
60. Kossoff E, Hartman A, Rubenstein J, et al. High-dose oral prednisolone for infantile spasms: an effective and less expensive alternative to ACTH. Epilepsy Behav. 2009;14:674–6.
61. Mytinger JR, Quigg M, Taft W, et al. Outcomes in treatment of infantile spasms with pulse methylprednisolone. J Child Neurol. 2010;25:948–53.
62. Haberlandt E, Weger C, Baumgartner Sigl S, et al. Adrenocorticotropic hormone versus pulsatile dexamethasone in the treatment of infantile epilepsy syndromes. Pediatr Neurol. 2010;42:21–7.
63. Kerrigan J, Shields W, Nelson T, et al. Ganaxolone for treating intractable infantile spasms: a multicenter, open-label, add-on trial. Epilepsy Res. 2000;42:133–9.
64. Rogawski M, Reddy D. Neurosteroids and infantile spasms: the deoxycorticosterone hypothesis. Int Rev Neurobiol. 2002;49:199–219.
65. Tsai J, Pellock JM, von Hehn J, et al. A double-blind, placebo-controlled, dose ranging clinical study to evaluate the safety, tolerability, and antiepileptic activity of ganaxolone in treatment of patients with infantile spasms. Neurology. 2009;72(11 Suppl 3):A119.
66. Riikonen R, Donner M. ACTH therapy of infantile spasms: side effects. Arch Dis Child Neurol. 1980;55:664–72.
67. Nousiainen I, Mäntyjärvi M, Kälviäinen R. No revision in vigabatrin-associated visual field defects. Neurology. 2001;57:1916–7.
68. Marguire M, Hemming K, Wild J, et al. Prevalence of visual field loss following to vigabatrin therapy: a systematic review. Epilepsia. 2010;51:2423–31.
69. Gaily E, Jonsson H, Lappi M. Visual field defects at school-age in children treated with vigabatrin in infancy. Epilepsia. 2009;50:206–16.
70. Wohlrab G, Leiba H, Kästle R, et al. Vigabatrin therapy in infantile spasms: solving one problem and inducing another? Epilepsia. 2009;50:2006–8.
71. Riikonen R, Carmant L, Dorofeeva M, et al. Does vigabatrin treatment for infantile spasms cause visual field defects: an international, multicentre study. Eur J Ped Neurol. 2013;17(Suppl 1):S49.
72. Izumi Y, Ishikawa M, Benz A, et al. Acute vigabatrin retinotoxicity in albino rats depends on light but not GABA. Epilepsia. 2004;45:1043–8.
73. Jammoul F, Wang Q, Nabbout R, et al. Taurine deficiency is a cause of vigabatrin-induced retinal phototoxicity. Ann Neurol. 2009;65:98–107.
74. Jammoul F, Degardin J, Pain D, et al. Taurine deficiency damages photoreceptors and retinal ganglion cells in vigabatrin-treated neonatal rats. Mol Cell Neurosci. 2010;43:414–21.
75. Kinironis P, Cavalleri G, Singh R, et al. A pharmacogenetic exploration of vigabatrin-induced visual field constriction. Epilepsy Res. 2006;70:144–52.
76. Pearl PL, Vezina LG, Saneto RP, et al. Cerebral MRI abnormalities associated with vigabatrin therapy in patients with epilepsy. Epilepsia. 2009;50:184–94.
77. Wheless JW, Carmant L, Bebin M, et al. Magnetic resonance imaging abnormalities associated with vigabatrin in patients with epilepsy. Epilepsia. 2009;50:195–205.

78. Dracopoulos A, Widjaja E, Raubaud C, et al. Vigabatrin-associated reversible MRI signal changes in patients with infantile spasms. Epilepsia. 2010;51:1297–304.
79. Fong C, Osborne J, Edwards S, et al. An investigation into relationship between vigabatrin, movement disorders, and brain magnetic resonance imaging abnormalities in children with infantile spasms. Dev Med Child Neurol. 2013;55:862–7.
80. Glauser T, Clark P, Strawsburg R. A pilot study of topiramate in the treatment of infantile spasms. Epilepsia. 1998;39:1324–8.
81. Zou LP, Lin Q, Qin J, et al. Evaluation of open-label topiramate as primary or adjunctive therapy in infantile spasms. Topiramate Study Group. Clin Neuropharmacol. 2008;31:86–92.
82. Korinthenberg R, Schreiner A. Topiramate in children with West syndrome: a retrospective multicenter evaluation of 100 patients. J Child Neurol. 2007;22:302–6.
83. Chandra S, Bhave A, Bhargava R, et al. West syndrome: response to valproate. Front Neurol. 2012;3:166.
84. Dreifuss F, Langer D, Moline K, et al. Valproic and hepatic fatalities. II: US experience since 1984. Neurology. 1989;39:201–7.
85. Debus O, Kurlemann G. Sulthiame in the primary therapy of West syndrome: a randomised double blind placebo-controlled add-on trial on baseline pyridoxine medication. Epilepsia. 2004;45:103–8.
86. Glauser T, Pellock J. Zonisamide in pediatric epilepsy: review of the Japanese experience. J Child Neurol. 2002;17:87–96.
87. Suzuki Y, Nagai T, Ono J, et al. Zonisamide monotherapy in newly diagnosed infantile spasms. Epilepsia. 1997;38:1035–8.
88. Yanai S, Hanai T, Narazaki O. Treatment of infantile spasms with zonisamide. Brain Dev. 1999;21:157–61.
89. Yanagaki S, Oguni H, Yoshii K, et al. Zonisamide for West syndrome: a comparison of clinical responses among different titration rate. Brain Dev. 2005;27:286–90.
90. Ohtsuka Y, Ogino T, Asano T, et al. Long-term follow-up of vitamin B (6)-responsive West syndrome. Pediatr Neurol. 2000;23:202–6.
91. Pietz J, Benninger C, Schafer H, et al. Treatment of infantile spasms with high dosage vitamin B6. Epilepsia. 1993;34:757–63.
92. Dreifuss F, Farwell J, Holmes G, et al. Infantile spasms: comparative trial of nitrazepam and corticotropin. Arch Neurol. 1986;43:1107–10.
93. Mikati M, El Banna D, Sinno D, et al. Response of infantile spasms to levetiracetam. Neurology. 2008;70:574–5.
94. Veggiotti P, Cieuta C, Rey E, et al. Lamotrigine in infantile spasms. Lancet. 1994;344:1375–6.
95. Kossoff E, Hedderick E, Turner Z, et al. A case-control evaluation of ketogenic diet versus ACTH for new onset infantile spasms. Epilepsia. 2008;49:1504–8.
96. Hong A, Turner Z, Hamdy R, et al. Infantile spasms treated with the ketogenic diet: prospective single-centre experience in 104 consecutive infants. Epilepsia. 2010;51:1403–7. doi:10.1111/j.1528-1167.
97. Zou L, Wang X, Dong C, et al. Three-week combination treatment with ACTH + magnesium sulfate versus ACTH monotherapy for infantile spasms: a 24 week, randomised, open-label, follow-up study in China. Clin Ther. 2010;32:692–700.
98. Stockler S, Plecko B, Gospe S Jr, et al. Pyridoxine dependent epilepsy and antiquitin deficiency. Clinical and molecular characteristics and recommendations for diagnosis, treatment and follow-up. Mol Genet Metab. 2011;104:48–60.
99. Riikonen R, Simell O. Tuberous sclerosis and infantile spasms. Dev Med Child Neurol. 1990;32:203–9.
100. Crino P. Evolving neurobiology of tuberous sclerosis complex. Acta Neuropathol. 2013;125:317–32.
101. Zeng L, Xu L, Gutmann D, et al. Rapamycin prevents epilepsy in a mouse model of tuberous sclerosis complex. Ann Neurol. 2008;63:444–53.
102. Kotulska K, Chmielewki D, Borkowska J, et al. Long-term effect of everolimus on epilepsy and growth in children under 3 years of age treated for subependymal giant cell astrocytoma associated with tuberous sclerosis complex. Eur J Ped Neurol. 2013;17:479–85.
103. Zhang B, McDaniel S, Rensing N, et al. Vigabatrin inhibits seizures and mTOR pathway activation in a mouse model of tuberous sclerosis. PLOS one. 2013;8:e57445.
104. Raffo E, Coppola A, Ono T, et al. Pulse rapamycin therapy for infantile spasms and associated cognitive decline. Neurobiol Dis. 2011;43:322–9.
105. Galanopoulou A, Gorter J, Cepeda C. Finding a better drug for epilepsy: the mTor pathway as an antiepileptogenic target. Epilepsia. 2012;53:1119–30.
106. Jozwiack S, Kotsulska K, Domariska Pakiela D, et al. Antiepileptic treatment before the onset of seizures reduces epilepsy severity and risk of mental retardation in infants with tuberous sclerosis complex. Eur J Pediatr Neurol. 2011;15:424–31.
107. Lagae L, Velhest H, Ceulemans B, et al. Treatment and long-term outcome in West syndrome: the clinical reality. A multicentre follow-up study. Seizure. 2010;19(3):159–64.
108. Primec Z, Stare J, Neubauer D. The risk of lower outcome in infantile spasms increases after three weeks of hypsarrhythmia duration. Epilepsia. 2006;47:2202–5.
109. Camposano SE, Major P, Halpern E, et al. Vigabatrin in the treatment of childhood epilepsy: a retrospective chart review of efficacy and safety profile. Epilepsia. 2008;49:1186–91.
110. O'Callaghan F, Lux A, Darke K, et al. The effect of lead time to treatment and of age of onset on developmental outcome at 4 years in infantile spasms: evidence from the United Kingdom Infantile Spasms Study. Epilepsia. 2011;52:1359–64.
111. Riikonen R. Long-term outcome of West Syndrome: a study of adults with a history of infantile spasms. Epilepsia. 1996;37:367–72.
112. Riikonen R. Long-term outcome of patients with West syndrome. Brain Dev. 2001;23(7):683–7.
113. Stafstrom C. Infantile spasms: a critical review of emerging animal models. Epilepsy Curr. 2009;9:75–81.
114. Briggs S, Mowrey W, Hall C, et al. CPP-115, a vigabatrin analogue, decreases spasms in the multiple-hit rat model of infantile spasms. Epilepsia. Epub 28 Oct 2013. doi:10.1111/epi.12424.
115. Bitton J, Sauerwein H, Weiss S, et al. A randomized controlled trial of flunarizine as add-on therapy and effect on cognitive outcome in children with infantile spasms. Epilepsia. 2012;53:1570–6.
116. Riikonen R, Jääskeläinen J, Turpeinen U. Insulin-like growth factor-1 is associated with cognitive outcome in infantile spasms. Epilepsia. 2010;51:1283–9.
117. Catania A. Neuroprotective actions of melanocortins: a therapeutic opportunity. Trends Neurosci. 2008;31:353–60.
118. ICISS (unpublished data only) International Collaboration Infantile Spasms Study. Ongoing study. May 2007.