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REVIEW ARTICLE

Improving Outcomes in Infantile Spasms: Role of Pharmacotherapy

Anand Iyer[1] · **Richard Appleton**[1]

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Abstract Infantile spasms, and specifically within the context of West syndrome, is one of the most common epileptic encephalopathies to occur in early infancy. Early recognition and treatment can improve neurodevelopmental outcome in some cases, although the underlying aetiology is probably the most important prognostic factor in both spasm suppression and developmental outcome. Corticosteroids, either adrenocorticotrophic hormone (ACTH) or prednisolone, and vigabatrin are currently the preferred first-line treatment options. Vigabatrin is the treatment of choice when the underlying cause is tuberous sclerosis complex (TSC). Emerging evidence suggests that a combination of steroid and vigabatrin may be more effective in the suppression of spasms and resolution of hypsarrhythmia, the electro-encephalographic signal of spasms. Several other anti-epileptic drugs (AEDs) (levetiracetam, nitrazepam, sodium valproate, topiramate, zonisamide) are usually used as add-on or adjunctive treatment in refractory cases. Pyridoxine (or pyridoxal phosphate) and the ketogenic diet are established treatment options in refractory cases. There is some evidence that neuro-active steroids, including ganaxolone, may be effective; however, clinical trials undertaken intermittently for over a decade have yet to prove their efficacy, not only for the suppression of infantile spasms but also for the resolution of hypsarrhythmia, which may be as important as seizure control in developmental outcome in these children. Insights into developing novel treatment options have emerged from rodent models of infantile spasms, and research is continuing into the efficacy of rapamycin in improving outcomes in infantile spasms. This review provides a brief overview of the existing scientific literature around treatment options and outlines emerging newer treatment options in infantile spasms.

Key Points

Vigabatrin and steroids remain the drugs of first choice in the treatment of infantile spasms.

Other anti-epileptic medications have proven to be effective; however, any decision to use them depends on individual practice and the specific aetiology of the infantile spasms.

Further research into novel treatments in infantile spasms is important and is in progress.

1 Introduction

Infantile spasms are characterised as an early infantile epileptic encephalopathy (EIEE) and associated with neurocognitive plateau or regression. Although predominantly occurring during infancy, they can persist beyond infancy or, rarely, recur or develop for the first time in early childhood. Consequently, the terminology 'epileptic spasms' has been adopted as a more appropriate term [1]. Traditionally, the triad of infantile spasms, hypsarrhythmia and onset of developmental plateau is defined as West syndrome (WS), named after Dr. West, who described these unique seizures in his own son. However,

✉ Anand Iyer
anand.iyer@alderhey.nhs.uk

[1] The Roald Dahl Department of Neurophysiology, Alder Hey in the Park Children's NHS Foundation Trust, Eaton Road, Liverpool L12 2AP, UK

developmental plateau or regression is not essential for a diagnosis of WS and may be absent if the diagnosis of the spasms and hypsarrhythmia is made soon after their onset. Infantile spasms have a distinct pharmaco-sensitivity and frequently demonstrate no response or only a limited response to conventional anti-epileptic drugs (AEDs). There is some evidence that early recognition and treatment may lead to cessation of spasms in select cases and may improve neuro-developmental and later cognitive outcome [2–5]. However, the longer-term prognosis is more likely related to the underlying aetiology. The International League Against Epilepsy (ILAE) has proposed a revised classification for aetiology in the epilepsies, with the previous terms (idiopathic, symptomatic and cryptogenic) being replaced by genetic, structural, metabolic or unknown. Clearly, each of these categories is not mutually exclusive, as a number of causes will have both a structural or metabolic and genetic basis [e.g. tuberous sclerosis complex (TSC), non-ketotic hyperglycinaemia]. Advances in genetic research have identified, and will continue to identify, several new genetic causes of the EIEEs. Early surgery (e.g. lesionectomy or lobectomy) may suppress the spasms and significantly improve neuro-developmental/cognitive outcomes in a significant minority of infants and young children with an obvious structural cause for their epilepsy, such as in focal cortical dysplasia, hypothalamic hamartoma, and TSC.

Vigabatrin and steroids, used either alone or in combination, are generally used as first-line drugs in the treatment of infantile spasms [5, 6]. Several other treatment options [nitrazepam, pyridoxine (and pyridoxal phosphate), sodium valproate, topiramate, zonisamide] are frequently used in resistant cases and in infants and children who experience a relapse in spasms following an initial period of control. The ketogenic diet is an important treatment option and, ideally, should be considered early in the course of drug-resistant infantile spasms. What defines 'early' will depend on a number of factors but probably indicates no later than the failure of two, certainly three, AEDs, as well as a trial of pyridoxine/pyridoxal phosphate. Further discussion of the ketogenic diet is outside the remit of this review. Newer treatment options are under evaluation, including ganaxolone (although this drug has been linked with the treatment of infantile spasms for almost 2 decades, and its efficacy has yet to be proven), flunarizine, pulsed rapamycin [an inhibitor of mammalian target of rapamycin (m-TOR)], melanocortin receptor agonists and medical cannabinoids. Clearly, these latter drugs will require robust and large-scale trials to determine whether or not they offer viable, appropriate and safe treatment options in this epileptic encephalopathy.

One of the long-standing and ongoing (and controversial) issues in the evaluation of the efficacy of the different therapies in the management of infantile spasms is that the vast majority of studies, including UKISS (UK Infantile Spasms Study) [5] and ICISS (International Collaborative Infantile Spasms Study) [6], have failed to address the heterogeneity of their cause; there are at least 60 different causes of infantile spasms. This is important, if not crucial, because the different responses to a specific treatment may be primarily dependent on the underlying cause and not the treatment. This is exemplified in TSC, where vigabatrin is clearly the most effective therapy and is now acknowledged as the drug of first choice in the treatment of infantile spasms caused by this disorder. Another recurring issue is that many studies have been anecdotal and/or without robust statistical methodology and have involved only small numbers of patients.

This review focuses on available information about common drug treatments as well as recent advances in the pharmacotherapy of infantile spasms.

To identify appropriate articles, we searched Cochrane Epilepsy and the Cochrane Library as well as the online databases MEDLINE, Embase and Ovid using the following medical subject heading (MeSH) terms: 'infantile spasms', 'epileptic spasms', 'hypsarrhythmia', 'West syndrome', 'epileptic encephalopathy', 'vigabatrin' and 'corticosteroids'. Selected articles were also manually searched. Searches were not limited to randomised controlled trials (RCTs) or publication in the English language. Search dates were from 1950 to February 2016. Identified articles were included based on a range of criteria to allow a comprehensive review of all reported treatment options. Consequently, this included prospective RCTs and small retrospective studies. This methodology was considered appropriate as the remit of this paper was not to provide a systematic or Cochrane review of the treatment of infantile spasms.

2 First-Choice Drugs

2.1 Corticosteroids

The mechanism by which corticosteroids (steroids) act in infantile spasms is unclear. Modification of corticotrophin-releasing hormone expression has been hypothesised, but further detailed discussion is outside the remit of this review.

Different types, regimens and doses of steroids have been used in the treatment of infantile spasms for almost 60 years [7]. These include intramuscular preparations, adrenocorticotrophic hormone (ACTH)—also called 'corticotrophin'—and its synthetic equivalent, tetracosactide, and oral preparations, dexamethasone, hydrocortisone and prednisolone. Pulsed intravenous methylprednisolone has been rarely used in the treatment of infantile spasms and is

usually followed by a course of oral prednisolone [8]. Corticosteroids have been extensively studied in RCTs and open clinical trials. ACTH is available in a 'natural' form derived from bovine or porcine sources in the USA or as a synthetic product, tetracosactide, in the UK. Tetracosactide (synacthen depot) is predominantly available in Europe, is considerably less expensive than the natural ACTH and has a longer duration of action of 24–48 h, allowing it to be administered in an alternate-day regimen. ACTH 80–100 IU is equivalent to tetracosactide 1 mg. No formal head-to-head open or blinded studies have compared these two preparations in the treatment of newly diagnosed infantile spasms.

Table 1 summarises prospective studies that have compared different clinical trials of corticosteroids in infantile spasms. A Class I study compared low-dose (20 IU/day) with high-dose (150 IU/day) natural ACTH for 3–6 weeks in 50 infants with newly diagnosed infantile spasms. Spasm reduction was similar in both groups [9]. A Class II study showed similar spasm suppression results between low-dose ACTH (20 IU/m^2) and high-dose ACTH (150 IU/m^2) in 25 infants [10]. The combined responder rates from both these studies was 76–79 %. The American Academy of Neurology guideline development sub-committee concluded that low-dose natural ACTH should be considered in the short-term treatment of infantile spasms. However, the adverse effect profile associated with ACTH (or tetracosactide, more commonly available in UK) makes it less favourable as a first-line treatment (personal opinion). Data comparing oral prednisolone 2 mg/kg/day and ACTH are minimal. A Class II study compared low-dose ACTH (20 IU/day) with oral prednisolone (2 mg/kg/day), both administered for 2 weeks, and showed responder rates of 42 % with ACTH and 33 % with oral prednisolone [11]. A Class III study evaluated high-dose ACTH (150 IU/m^2/day) compared with oral prednisolone (2 mg/kg/day); responder rates were 87 % (ACTH) and 29 % (prednisolone) [12]. UKISS was a large Class III study that compared high-dose oral prednisolone (40–60 mg/day) with synthetic ACTH and showed similar responder rates of 70–76 % [5]. Go et al. [13] summarised other studies that used pulsed intravenous methylprednisolone followed by oral prednisolone or dexamethasone and other formulations of steroids and concluded that evidence was insufficient to recommend the use of any steroid preparation other than ACTH. A recent Class III study assessed the effect of ACTH (intramuscular tetracosactide 0.5 mg every 48 h) with daily oral prednisolone (40–60 mg/day) on hypsarrhythmia improvement in infants with newly diagnosed infantile spasms (excluding TSC); patients treated with prednisolone experienced 'significant' improvement [14]. A prospective study found that responder rates were better with ACTH than with oral prednisolone (55 vs. 39 %, respectively) [15].

Opinions on the role, preparation, dose and treatment regimen of corticosteroids in the management of infantile spasms continues to vary widely. Practice varies between centres and even between clinicians (paediatric neurologists) within a centre. Decisions will be based on published evidence, clinicians' prejudice and the opinions of the family over the potential risks and benefits of corticosteroids. High doses of corticosteroids can lead to suppression of the hypothalamic-pituitary-adrenal axis and significant immunosuppression, increasing the risk of serious and potentially fatal infections. They often cause irritability, sleep disturbances, hypertension and hyperglycaemia. Steroids may also cause radiological evidence of global cerebral atrophy of unknown clinical significance; although usually transient, it may persist for months following withdrawal of the steroid.

2.2 Vigabatrin

Vigabatrin is an inhibitor of 4-aminobutyrate aminotransferase and leads to elevated levels of γ-aminobutyric acid

Table 1 Prospective studies of corticosteroids in infantile spasms

Study	Patients (*n*)	Steroid dose	Treatment duration (weeks)	Spasm resolution (%)	EEG resolution (%)
Baram et al. [12]	15	ACTH 150 IU/m^2/day	2	87	87
	12	Prednisolone 2 mg/kg/day	2	33	33
Hrachovy et al. [9]	26	ACTH 150 IU/m^2/day	3	50	23
	24	ACTH 20–30 IU/day	3	58	21
Vigevano and Cilio [17]	19	ACTH depot 10 IU/day	3	74	78
Lux et al. [5]	25	Tetracosactide 0.5 mg every 48 h	2	76	70
	30	Prednisolone 40–60 mg/day	2	70	70
Knupp et al. [15]	97	ACTH 75 IU/m^2/day	2	53	53
	54	Prednisolone 40 mg/day	2	21	21

ACTH adrenocorticotrophic hormone, *EEG* electroencephalogram

(GABA)—a cerebral inhibitory neurotransmitter with potent anti-epileptic properties—in the brain. Its efficacy in clinically suspected or confirmed cases of TSC justifies its position as the treatment of choice in the infantile spasms that occur in this neuro-cutaneous disorder. The largest randomised trial to provide Class III evidence, UKISS, which excluded children with known TSC, randomised 107 patients to either corticosteroids or vigabatrin; responder rates after 14 days of treatment were 76 % (corticosteroids) and 52 % (vigabatrin) [5]. Although the initial responder rates were higher with steroids, long-term follow-up after 14 months demonstrated no difference in relapse rates between the two treatments [16]. Neurodevelopmental outcome at 14 months was almost identical in the two treatment groups; however, developmental outcome in infants with no identified aetiology (the 'cryptogenic' or 'idiopathic' group) was slightly better in those treated with corticosteroids. The minimum dose of vigabatrin used in UKISS was 100 mg/kg/day [5].

Table 2 provides a summary of prospective studies of vigabatrin in infantile spasms. In another Class III study, 42 infants received either vigabatrin (100–150 mg/kg/day) or ACTH (10 IU/day) for 20 days [17]. Electro-clinical resolution of spasms was better with ACTH (74 %) than with vigabatrin (48 %). Other Class IV studies have investigated ACTH or prednisolone compared with vigabatrin or vigabatrin compared with placebo and have reported similar responder rates (60–80 %) [18–20]. Similar to findings in UKISS, infantile spasms with no identified cause responded better to corticosteroids than to vigabatrin.

Numerous open retrospective case studies have also reported on short- and long-term outcomes of infants treated with vigabatrin. One of the largest, which studied 180 infants in a single centre in Serbia, defined the primary outcome as seizure cessation with resolution of hypsarrhythmia on electroencephalogram (EEG) at 14 days [21]. Vigabatrin was introduced and titrated rapidly: 50 mg/kg on day 1, 100 mg/kg on days 2 and 3 and 150 mg/kg/day from day 4 and until at least day 14. A total of 101 (56.1 %) patients became and remained spasm free at day 14, 83 % of these within 7 days of starting treatment. The most important prognostic factors were the underlying aetiology and pre-existing developmental profile; those with no identified cause and normal developmental outcome at the diagnosis of infantile spasms demonstrated the best response and best long-term outcome. The authors considered that the long-term outcome in their patients was similar to the outcome in patients treated with ACTH or corticosteroids, as reported in earlier studies [16, 21].

The predominant adverse side effects associated with vigabatrin include hypotonia and irritability, which are usually mild and transient, and peripheral visual constriction, which may be severe and potentially irreversible. This complication has let to its use being severely restricted in the UK, the rest of Europe and the USA; consequently, its prescription is now limited to the treatment of infantile spasms. The prevalence of the visual deficit is reported to occur in approximately 40–45 % of adults treated with the drug. Its prevalence in children is generally accepted to be lower, at approximately 25–35 %. However, this figure is only an estimate in view of the difficulty in reliably assessing peripheral visual fields in children, particularly if the child has significant attention or learning difficulties. It is also important to understand that development of the visual field deficit is not an 'all or nothing' phenomenon and primarily depends on the duration of exposure to the drug and cumulative dose taken. Current information suggests that, in adults, the minimum exposure to vigabatrin necessary to cause the deficit is 12 months, and the minimum daily dose during this time is 1000 mg. Visual field deficits have not been reported in children after <15 months of exposure [22]. Numerous hypotheses have attempted to explain the pathophysiology of the retinal toxicity that may lead to the visual field deficit. It may involve accumulation of GABA in the cone cells or a deficiency of taurine. Vigabatrin-induced retinal damage can be monitored via electroretinogram, although the practicalities of doing this in infants may be challenging. Reliable results from formal perimetry (e.g. Goldmann) are impossible in children with a cognitive age <9 years. Field deficits are generally regarded as irreversible in adults;

Table 2 Prospective studies of vigabatrin in infantile spasms

Study	Patients (*n*)	Dose (mg/kg/day)	Duration at maximal dose (weeks)	Spasm resolution (%)	EEG resolution (%)
Appleton et al. [20]	20	150	0.8	25	23
Elterman et al. [18, 19]	75	18–32	12	23	–
	67	100–150	12	11	–
Vigevano and Cilio [17]	23	150	–	48	36
Lux et al. [5]	52	100–150	14	54	50
Knupp et al. [15]	47	150	14	17	17

EEG electroencephalogram

however, although this was previously thought to be the same in children, some evidence indicates that the retinal toxicity may not be permanent [23]. Magnetic resonance imaging (MRI) has shown symmetric or asymmetric hyperintensities in the basal ganglia, thalamus, brainstem and dentate nucleus in one-third of infants exposed to vigabatrin, and these may be seen as early as 3 months after therapy initiation. In some cases, they can be accompanied by movement disorder [24, 25]. However, both the radiological abnormalities and movement disorder are reported to resolve following discontinuation of the drug.

Early results from ICISS indicate that, in all aetiologies of infantile spasms except TSC (as the study excluded infants with infantile spasms due to this disorder), combined treatment with steroids and vigabatrin may be more effective in spasm cessation than steroids only [6]. If confirmed, this would represent an example where 'rational polytherapy' rather than the traditional monotherapy becomes the preferred approach to the treatment of a newly diagnosed specific epilepsy syndrome.

3 Other Anti-Epileptic Drugs

3.1 Sodium Valproate

Sodium valproate is an effective AED in a number of early onset (infantile) and childhood epileptic encephalopathies. Most reports on its use in the treatment of infantile spasms are old, with no data from the past 20 years. Prats et al. [26] used very high doses of sodium valproate (200 mg/kg/day) in 42 infants with infantile spasms; 33 demonstrated complete cessation of spasms between 4 and 21 days after initiation of the drug. A total of 25 % of patients experienced somnolence, vomiting and thrombocytopenia, and eight patients experienced a relapse. Earlier studies also demonstrated varying efficacy with higher doses of valproate [27, 28].

One retrospective report suggested a synergistic effect of a benzodiazepine (nitrazepam) with valproate, with a 45 % responder rate [29].

In a significant minority of children, WS subsequently evolves into Lennox–Gastaut syndrome (LGS), characterised by multiple seizure types. Sodium valproate is generally considered the most appropriate AED in the treatment of LGS because of its broad spectrum of action.

3.2 Topiramate

Topiramate has several mechanisms of action—sodium channel blockage, GABA agonist, carbonic anhydrase and potent glutamate antagonist. Glauser et al. [30] undertook a pilot study on the effectiveness of topiramate in refractory infantile spasms. Children ($n = 11$; median age 3.6 months, range 3–25) received an initial dose of topiramate 25 mg/day, and the dose was escalated (to a maximum of 24 mg/kg/day) until spasms were completely controlled or to maximum tolerated dose. Five patients experienced full electro-clinical control, and another four achieved >50 % reduction in spasms. The mean dose in the 11 children was 15 ± 5.7 mg/kg/day, and the most common adverse effect was irritability. Of the five who achieved full control, two showed complete cessation of spasms within 14 days of starting treatment; the remaining three within 3 months of starting treatment. All five patients remained seizure free for a median follow-up of 134 days.

A number of other retrospective studies, but with small patient numbers, have reported spasm-free rates of 20–30 % [31–34]. A large multicentre, open-label clinical trial in China evaluated the efficacy of topiramate as first-line or adjunctive therapy in the treatment of infantile spasms in 544 patients [35]. Following 20 weeks of treatment, 43.9 % of patients were seizure free and continued to remain well controlled without relapses; many of these were receiving monotherapy. The most commonly reported adverse effects were anorexia and somnolence.

A prospective study that evaluated topiramate as first-line therapy followed by low-dose ACTH showed complete cessation of spasms in 67.5 % of patients; however, 60 % of patients who were spasm free required a combination of ACTH and topiramate [36]. The maximum dose of topiramate used was 8 mg/kg/day, less than that used in previous studies. Some Class IV studies do not support sustained electro-clinical remission or prevention of relapses with topiramate [31, 37].

In clinical practice, topiramate is an effective option in patients who are refractory to treatment with steroids or vigabatrin. Although topiramate is an effective AED, the tolerability of this medication may limit its use in infants, particularly because of its appetite-suppressant and behavioural side effects. Finally, the lack of a readily available flavoured solution or syrup limits its usefulness in this age group.

3.3 Zonisamide

Zonisamide is a broad-spectrum AED that shares some of the mechanisms of action of topiramate. The drug has been used in Japan since 1989, predominantly for focal epilepsies and refractory infantile spasms.

Suzuki [38] evaluated the short-term efficacy of zonisamide monotherapy in 54 infants with a mean age at onset of spasms of 6.9 months who were intractable to pyridoxine (vitamin B_6), a commonly used first-line medication for the treatment of infantile spasms in Japan.

Zonisamide was started at 3–4 mg/kg/day and increased every 4th day until either spasms stopped or the maximum dose of 10–13 mg/kg/day was reached. Overall, 20.3 % of infants (11 of 54) experienced a response, defined as cessation of spasms and resolution of hypsarrhythmia. Spasms ceased in responders within 2 weeks of commencing treatment and with a mean dose of zonisamide 7.2 mg/kg/day. The 11 responders were maintained on zonisamide and followed-up for between 24 and 79 months; 64 % of patients (7 of 11) remained spasm free at the end of follow-up on zonisamide monotherapy.

Lotze and Wilfong [39] studied the effect of zonisamide in 23 infants with symptomatic intractable spasms; they introduced zonisamide as a first-line single AED in ten of these patients. Cessation of spasms and resolution of hypsarrhythmia occurred in six of the 23 (26 %) infants; three of these six children received zonisamide monotherapy. Two children had no clinical spasms even though the EEG continued to show hypsarrhythmia. The mean latency from starting zonisamide to cessation of spasms was 19 days. Zonisamide was well tolerated, with no child discontinuing medication because of adverse effects.

Numerous other open-label studies, undertaken in small numbers of patients and for limited periods (often <3 months), have reported similar response rates (20–30 %) with adjunctive zonisamide therapy [40–43]. The outcome measures in these studies were not uniform, and only two evaluated the dual effect of zonisamide on both cessation of epileptic spasms and resolution of hypsarrhythmia. Its similarity to topiramate, its better tolerability and the availability of an aqueous preparation would render it a preferred option over topiramate in the treatment of refractory infantile spasms, initially as adjunctive therapy and potentially subsequently as monotherapy.

3.4 Levetiracetam

Levetiracetam has a novel mechanism of action, binding to the SVA2 protein that modulates inhibitory neurotransmission. It also inhibits the N-type calcium channel and causes modulation of GABA and glycine receptors.

Several small case series and individual case reports have shown some efficacy in infantile spasms. This includes two separate case reports, one using a low dose of levetiracetam 15 mg/kg/day as add-on therapy with clobazam in an infant with infantile spasms of a structural cause [44, 45]. Gümüş et al. [46] used levetiracetam as initial monotherapy in five patients with newly diagnosed cryptogenic infantile spasms [46]. Two became spasm free, two demonstrated a >50 % reduction in seizure frequency, and one experienced no change. Doses started at 30 mg/kg/day, increasing to 50 mg/kg/day. No patient who became spasm free had relapsed at a 9-month follow-up. Mikati et al. [47] used levetiracetam in seven infants with refractory infantile spasms. One became spasm free at a high dose of 117 mg/kg/day, and the frequency of spasms reduced by >75 % in one and by >50 % in five infants. Mahmoud et al. [48] randomised 20 infants who had not responded to prednisolone to receive either topiramate or levetiracetam and found that only one infant with cryptogenic spasms responded to either treatment.

Levetiracetam is not used as frequently as other medications for refractory infantile spasms in clinical practice. Its superior tolerability profile, its increasingly established use in non-convulsive (electrical) status epilepticus [49], and its availability in intravenous and oral formulations would justify a more formal evaluation of its efficacy in the treatment of infantile spasms and hypsarrhythmia.

3.5 Nitrazepam

Nitrazepam is one of the benzodiazepine group of anticonvulsants and—unlike clobazam and clonazepam—is rarely used in the management of the epilepsies. Its use is generally restricted to the treatment of infantile spasms, generally when the spasms have been refractory to corticosteroids and vigabatrin. Its efficacy in observational studies has been reported to be as high as 35 % [34, 50], although spasm cessation, the ideal outcome of the treatment of infantile spasms, was low: only 4 of 25 infants or 16 % [34] and 25 % [50]. The most frequently used starting dose is 0.2 mg/kg/day, increasing to 1–1.5 mg/kg/day. Commonly reported adverse side effects include excessive drooling, sedation and hypotonia, all of which may limit its use to a few weeks or months.

A single study compared the benefits of nitrazepam versus those of ACTH (corticotrophin) in 52 patients in a 4-week multicentre RCT in newly diagnosed infantile spasms [51]. The efficacy of the drugs was evaluated in 48 patients, all aged <2 years. Both treatments resulted in a statistically significant reduction in spasm frequency compared with baseline, but the difference between treatments was not significant. Side effects were similar in the two treatment groups, but the adverse effects encountered in the ACTH-treated group were qualitatively more severe and required the discontinuation of treatment in six patients.

Nitrazepam is used in some centres as the treatment of first choice pending results of investigations to identify a cause. It is then substituted with steroids in cases with no identified aetiology or with vigabatrin in cases with an identified cause, and specifically in those with a structural or genetic cause. This practice exemplifies the often idiosyncratic and even prejudicial approach different paediatric neurologists take in the treatment of infantile spasms.

4 Anti-Epileptic Drugs Rarely Used

4.1 Sulthiame

Sulthiame is an old AED that has emerged as a treatment option in severe and drug-resistant epilepsies, particularly involving focal and myoclonic seizures. Debus et al. [52] conducted a double-blinded study in which infants with a new diagnosis of WS were randomised to receive sulthiame ($n = 20$) or placebo ($n = 17$). For the sulthiame-treated group, the responder rate (spasm cessation) was 30 %. The most commonly reported side effects included restlessness, vomiting, somnolence and loss of appetite. In clinical practice, the drug may be an option in the adjunctive treatment of late-onset (not specifically infantile) epileptic spasms, particularly those that occur in LGS.

4.2 Lamotrigine

Lamotrigine has been used with some success in some infants with steroid-resistant spasms at low doses of 0.12–0.5 mg/kg/day [53, 54]. In a study of 30 infants with drug-resistant epileptic spasms already receiving sodium valproate, adjunctive lamotrigine was helpful in completely terminating the spasms in five patients [53]. Patients remained spasm free for a mean duration of 24 months after starting treatment. A further four patients demonstrated a >50 % reduction in seizure frequency. Most patients who responded had epileptic spasms that were considered secondary to 'brain injury'. Although the drug is generally very well tolerated, the lack of an aqueous preparation and the long titration time to achieve a potential therapeutic effect preclude its use in infants with infantile spasms. However, it probably remains an option in the management of late-onset (non-infantile) and drug-resistant epileptic spasms in LGS.

4.3 Ganaxolone

Ganaxolone (3-hydroxy-3-methyl-5-pregnan20-one) is the 3-methylated synthetic analogue of allopregnanolone. It is classified as a neurosteroid and is known to modulate the GABAergic inhibitory system by acting through the $GABA_A$ receptors without hormonal adverse effects [55].

A multicentre open-label add-on trial investigated treatment with ganaxolone in 20 children aged 7 months to 7 years with refractory epileptic spasms [56]. Treatment was initiated with ganaxolone 4.5 mg/kg/day, and the dose was gradually escalated to 36 mg/kg/day or to the maximum tolerated dose over a 4-week period. This dose was maintained for 8 weeks and then gradually discontinued. Of the 16 recruited patients who completed the study, 33 % demonstrated >50 % reduction in the frequency of spasms and an additional 33 % experienced a 25–50 % reduction. Somnolence and diarrhoea were the most commonly reported adverse effects.

Other trials have evaluated the efficacy of similar doses of ganaxolone in older children with a refractory epilepsy. In one study, 4 of 15 patients showed a >50 % reduction in seizure frequency [57]. Somnolence was the most frequently reported adverse event.

Theoretically, ganaxolone should be associated with fewer adverse side effects than ACTH (or tetracosactide) or prednisolone, and this might indicate it could become the preferred steroid in the treatment of newly diagnosed infantile spasms. However, if this drug does not actually completely terminate the spasms (as commonly seen with ACTH, tetracosactide and prednisolone) but only reduces their frequency, it is highly unlikely that ganaxalone would become the preferred steroid in the treatment of infantile spasms. Well-designed RCTs will be needed to demonstrate an efficacy similar or superior to that of ACTH/prednisolone before it could secure this role. Currently, ganaxolone is neither widely used in nor available for routine clinical use.

5 Newer Insights into Novel Treatment Options

The catastrophic onset of infantile spasms and associated neurodevelopmental stagnation or regression necessitate clinical trials to address not only spasm cessation but also resolution of the hypsarrhythmia, as 'normalisation' of the EEG will rarely be possible. However, most spasms relapse or evolve into other electro-clinical syndromes, typically LGS. The focus should be more on epileptogenesis and an attempt to reduce or prevent the development of a chronic and medically refractory epilepsy rather than on simply controlling seizures (infantile spasms). A number of rodent models of infantile spasms have been created that will hopefully increase our understanding of both the pathogenesis of infantile spasms and the development of novel therapies, and how chronic epilepsy might then develop. While not all of these rodent models respond to ACTH or vigabatrin, identification of a neuroprotective or rescue effect of treatment would at least suggest the model is feasible and allow the testing of newer treatments. All these models are at an early developmental stage, and further research is clearly required to develop potentially 'multiple-hit' models that could be used in clinical trials [58].

It is believed that ACTH exerts its anticonvulsant action through suppression of the expression of corticotrophin-releasing hormone, which is considered to have a role in

the pathophysiology of infantile spasms. ACTH belongs to the family of endogenous peptides called melanocortins, derived from pro-opiomelanocortin. Melanocortins are critical for a variety of physiological processes, and possess anti-inflammatory, neuro-protective and blood pressure regulatory properties. ACTH acts on different melanocortin receptors in the brain, which has led to several hypotheses regarding its established efficacy in infantile spasms. Further research into other melanocortin receptor agonists in the treatment of infantile spasms may help in the development of novel treatments for this refractory epilepsy that have similar (or greater) efficacy but fewer adverse side effects [59].

6 Newer Treatment Options

6.1 Flunarizine

Flunarizine is a calcium channel blocker that is believed to prevent or reduce neurotoxic effects by blocking the glutamate receptors and L-type voltage-gated channels. A randomised, multicentre, placebo-controlled trial of flunarizine as an add-on therapy to standard treatment (vigabatrin, steroids or topiramate) failed to demonstrate any beneficial effect on cognitive outcome 2 years from the onset of spasms [60]. Ten children with no identified aetiology for the infantile spasms were treated with flunarizine and demonstrated improved outcomes on the Vineland Scale at 24 months [59]. There is no other evidence that any other calcium channel blocker, such as nifedipine or nimodipine, has been efficacious in the treatment of any epilepsy, including infantile spasms [61].

6.2 Mammalian Target of Rapamycin Inhibitors

m-TOR is a critical protein kinase that functions to integrate multiple intra and extracellular signals to regulate cell survival through a complex pathway that includes alterations in gene expression and protein translation. The discovery that hamartin and tuberin, proteins of TSC, limit activation of the m-TOR pathway led to several theories about the role of m-TOR pathways in epileptogenesis and potentially the identification of a novel targeted treatment. The m-TOR pathway plays a role in not only these genetic epilepsies but also in animal models of acquired epilepsies [62].

One study evaluated the effect of rapamycin, an inhibitor of the TORC1 complex, on a multiple-hit rat model of ACTH-refractory symptomatic infantile spasms [63]. It evaluated the effect on spasms and other seizures, performance in cognitive tests and expression of the phosphorylated S6 ribosomal protein (a TORC1 target) in the cortex using immunofluorescence. A 3-day pulsed rapamycin treatment at different doses (1–6 mg/kg/day) was administered as an intra-peritoneal injection. The response was monitored through clinical parameters (spasms and behavioural tests) and epidural EEG. Dose-dependent spasm suppression was observed, with an improvement in cognitive outcome that was correlated with normalisation of the pS6 activity in the cortical EEG. Other studies have demonstrated the benefits of rapamycin in different animal modes of temporal lobe epilepsies [64–66]. Translation of these findings into human studies may begin to address whether these treatments could alter epileptogenesis. Some support for this hypothesis has emerged from recent clinical studies in TSC. The EXIST 1 (Examining everolimus in a study of TSC) RCT evaluated the effect of everolimus (an mTOR-inhibitor) on the size of sub-ependymal giant cell astrocytomas in patients with TSC. Follow-up data at 5 years indicated that the frequency of focal and tonic–clonic seizures reduced as a secondary outcome measure [67]. These observational data led to EXIST 3, a placebo-controlled study of efficacy and safety of two trough ranges of everolimus as adjunctive therapy in patients with TSC and refractory partial-onset seizures. Preliminary results of this study were presented at the Annual Meeting of the American Academy of Neurology (AAN) in Canada in 2016; full results will be published in late 2016. It is almost certain that studies will now be designed to assess the efficacy and safety of everolimus in the treatment of infantile spasms caused by TSC.

7 Conclusion

Corticosteroids and vigabatrin generally remain the preferred first-choice drugs for the treatment of infantile spasms; they have maintained this position for almost a decade and are specifically cited as such in the 2012 UK National Institute for Health and Care Excellence (NICE) clinical guideline on epilepsy (CG137) [68]. A corticosteroid is generally the drug of choice in ‘idiopathic’ or ‘cryptogenic’ cases and vigabatrin is the first choice in cases caused by TSC [68]. Alternative drugs for drug-resistant cases include nitrazepam, sodium valproate, topiramate and zonisamide. Most clinicians will base their management decisions on published evidence but may be influenced by a number of factors, including the opinion of the family (following open and honest discussion about the risks and benefits of the different treatments) and their own personal experience and prejudice. Ongoing and future research will hopefully identify more effective and safer therapies, particularly in the area of epileptogenesis and the prevention of a chronic epilepsy. However, in view of the marked heterogeneity of aetiologies of infantile spasms, it

is highly unlikely that an individual drug that will be effective in all cases will be found.

Compliance with ethical standards

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