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A Risk-Benefit Assessment of Therapies for Lennox-Gastaut Syndrome

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Contents

Abstract

The treatment of Lennox-Gastaut syndrome has been improved for some patients by the introduction of adjunctive therapy with newer anticonvulsants such as lamotrigine and topiramate and the availability of vagal nerve stimulation and the re-emergence of the use of the ketogenic diet in recent years. The place of standard anticonvulsants and the role of callosotomy needs to be re-evaluated in view of the new developments.

Although recommendations for the treatment of patients with Lennox-Gastaut syndrome are difficult to make in the absence of direct head-on comparative trials, the following suggested treatment recommendations are based on the best evidence available. Medical treatment should start with valproic acid (sodium valproate) and be followed by adjunctive therapy with either lamotrigine or topiramate; clobazam can be added if necessary for better seizure control while trying to reduce the dose of the other anticonvulsants.

If standard treatment does not achieve sufficient seizure control or proves to be intolerable, vagal nerve stimulation, ketogenic diet, felbamate, benzodiazepines such as clonazepam, and phenobarbital (phenobarbitone) are recommended as third-line choices. Further considerations include ethosuximide, methsuximide, corticotropin (adrenocorticotropic hormone) or corticosteroids, pyridoxine (vitamin B6) and vigabatrin. If adequate drug treatment and vagal nerve stimulation provide insufficient seizure control, partial callosotomy may be an option

for the treatment of frequent, intractable and disabling drop attacks. These suggestions are based on the best evidence available and do not in any way exclude the use of other treatments if compelling individual risk-benefit considerations apply.

Lennox-Gastaut syndrome is an uncommon, age-related epileptogenic encephalopathy of childhood which comprises several types of brief, generalised seizures including tonic seizures, atypical absence seizures and frequent status epilepticus.[1] The electroencephalogram shows generalised slow spike waves of less than 2.5 cycles per second and, as the disease progresses, cognitive functions deteriorate.[2] Lennox-Gastaut syndrome is certainly one of the most difficult epilepsies to treat. A recent long term follow-up study disclosed the persistent occurrence of seizures in 68 of 88 patients (76.4%) and severe mental defect in 48 (53.9%).[3] Dose-related drug toxicity is common.[4]

Any risk-benefit assessment of therapies of Lennox-Gastaut syndrome has to address several specific problems. Diagnostic ascertainment in patients with Lennox-Gastaut syndrome is notoriously difficult. Other epileptic encephalopathies of infancy and childhood including West syndrome, severe myoclonic epilepsy of early childhood and related syndromes may be difficult to exclude. The erroneous inclusion of patients with other epilepsy syndromes such as frontal partial epilepsy and other epileptic encephalopathies into clinical trials may be a problem. Standard anticonvulsants that are often used for first-line treatment such as valproic acid (sodium valproate) have never been evaluated rigorously in controlled clinical trials, which were not required when these drugs entered the market many years ago. The seizure outcome of drug trials is very difficult to quantify in patients with Lennox-Gastaut syndrome. Typically, the syndrome is characterised by tonic-axial seizures, drop attacks, atypical absence seizures and severe and progressive mental retardation. Drop attacks, characterised by a sudden loss of posture control causing the patient to fall to the ground, may be attributable to tonic and atonic seizures. During electroencephalographic examination, diffuse slow spike and wave discharges and bursts of fast rhythms at around 10Hz during sleep are noted. Absence seizures can be assessed only for a very short time span by video-monitoring, while eye-witness accounts of associated tonic-clonic seizures or falls attributable to drop attacks may be more reliable. Slow disease fluctuations in seizure frequency may be seen over several months independent of drug treatment, making evaluation of drug trials with only 3 month's of drug exposure difficult, although long term seizure outcome data have become available recently, e.g. for felbamate and topiramate. Risk assessment is notoriously difficult for the occurrence of uncommon but serious adverse effects and for cognitive changes in a patient who is handicapped.

Despite all of these difficulties, several new anticonvulsants which help where standard drugs have failed, and the introduction of vagal nerve stimulation in instances where both new and older drugs have failed, offer new hope and prompt a risk-benefit assessment of therapies for Lennox-Gastaut syndrome. Adequate risk-benefit assessment will allow to practitioners to choose a stepwise approach to treating patients with Lennox-Gastaut syndrome, while optimising treatment.

1. Valproic Acid (Sodium Valproate) and Other First Generation Anticonvulsants

Although valproic acid is often recommended as first-line treatment and may be effective in reducing the number of atypical absence seizures and associated myoclonic seizures, the effect of valproic acid and other standard anticonvulsants on tonic-axial seizures, drop attacks and tonic-clonic seizures is often unimpressive.[5] Also because of the risk of life-threatening hepatic toxicity, valproic acid should be used with great caution in young children, especially those under 3 years of

age who are receiving or are likely to receive several anticonvulsants and those patients who are suspected of having an underlying metabolic abnormality.[6] In a larger series of patients studied by Covanis et al.,[7] who were treated with valproic acid, 38 had myoclonic astatic epilepsy, a term used by the authors synonymously with Lennox-Gastaut syndrome. Of these patients, 7 became and remained seizure-free while taking valproic acid. In addition, a 50 to 80% improvement was achieved after the addition of valproic acid in one-third of these patients, and other anticonvulsants were withdrawn or reduced.[7]

The addition of clobazam, a benzodiazepine that is widely available in Europe and Canada but not in the USA, was shown to reduce seizure frequency by 50% in 16 of 25 patients.[8] Many children showed improvement in behaviour as well. In fact, clobazam may be better tolerated than other benzodiazepines such as clonazepam or nitrazepam[9] although head-on comparisons are not available. Adverse effects of clonazepam and nitrazepam include increased oral secretion and sedation which have been claimed to occur less often during treatment with clobazam.

The long term use of carbamazepine, phenytoin and barbiturates, such as phenobarbitone (phenobarbital) has in general been disappointing. In addition, carbamazepine and phenytoin may aggravate Lennox-Gastaut syndrome in some patients and barbiturates may exacerbate behaviour problems which are common in many children with Lennox-Gastaut syndrome. Ethosuximide may be useful in reducing absence seizures in some patients and some may respond on a short term basis to treatment with corticosteroids or corticotrophin (adrenocorticotropic hormone). It should be noted, however, that the adverse effects of corticosteroid or corticotrophin exposure may be serious and include Cushing's syndrome, arterial hypertension and renal calcification.

In summary, the potential benefit of treatment with first generation anticonvulsants has not been convincingly demonstrated by controlled trials. Long term clinical observations suggest benefits for some patients; however, for most the drugs seem to produce little benefit. In addition, serious organ toxicity has been associated in high risk groups with the use of valproic acid and with corticosteroids. Behavioural problems and seizure exacerbation may occur with phenobarbital and carbamazepine, respectively.[4] It is therefore not surprising that many physicians eagerly awaited the introduction of newer, second generation anticonvulsants for the treatment of Lennox-Gastaut syndrome such as felbamate, lamotrigine and topiramate.

2. Felbamate

Felbamate was the first compound shown to be effective in a controlled study in patients with Lennox-Gastaut syndrome The efficacy of felbamate was assessed in 73 patients ranging in age from 4 to 36 years who had the Lennox-Gastaut syndrome.[10] Following a 28-day baseline phase, felbamate or placebo was administered for 70 days in addition to the patient's current anticonvulsant medications. The dosage of felbamate was titrated during the first 14 days of the treatment phase to a maximum of 45 mg/kg of bodyweight per day or 3600 mg/day, whichever was less. The primary efficacy variables were the total number of seizures counted during a 4 hour period of video recording, parents' or guardians' global evaluations of the patients' quality of life, and the total number of atonic seizures, as reported by parents or guardians. The patients treated with felbamate had a 34% decrease in the frequency of atonic seizures, as compared with a 9% decrease in the patients who received placebo ($p = 0.01$). The patients treated with felbamate had a 19% decrease in the total frequency of seizures, as compared with a 4% increase in the placebo group ($p = 0.002$). The global-evaluation scores were significantly higher in the felbamate group than in the placebo group from day 49 to the end of the study. There were no significant differences in the frequency of seizures occurring during video monitoring, but there was a significant reduction ($p = 0.017$) in the number of tonic-clonic seizures during the maintenance period in the felbamate group. Approximately 50% of patients

randomised to felbamate obtained at least a 50% reduction in seizure frequency compared with about 15% receiving placebo. In general, felbamate was well tolerated, with only gastrointestinal symptoms and somnolence seen more often with felbamate compared with placebo.

In addition, 12-month follow-up data in patients who completed the controlled part of the study confirmed the long term efficacy of felbamate.[11] The types and frequency of adverse effects were similar in the 2 treatment groups. In the first month of felbamate treatment, 62% of the patients who had previously received placebo had a reduction in total seizure frequency of >50%. By the 12-month follow-up point, approximately half of the patients had a 50% reduction in total seizure count. Astatic seizures responded even better, with two-thirds of patients having a reduction of >50% in astatic seizure frequency after 12 months of treatment. Although few patients became seizure-free, the frequency of the most severe seizure types decreased and the patients' global functioning improved.

The behavioural effects of felbamate were assessed in 20 patients (aged 2 to 19 years) who were participating in a compassionate plea protocol for children with Lennox-Gastaut syndrome.[12] Parents completed a questionnaire concerning aspects of behavioural change once all medications were in a constant regimen. Significant improvements were suggested in social functioning, intellectual functioning, motor functioning, attention and concentration, alertness, initiative, variability in performance, and memory. There was a tendency for these effects to reverse when the drug was discontinued.[12] In clinical observations, 60% (48 out of 80 patients) achieved a seizure reduction of 50% or more, including 6% (5 out of 80 patients) who became seizure-free.[13] The results of this uncontrolled study suggest that felbamate could be useful in patients with epilepsies which are refractory to other anticonvulsants after careful risk-benefit assessment and consideration of all circumstances involved.

It became evident during the first year of postmarketing use that felbamate was associated with a relatively high incidence of life-threatening adverse effects. Almost exactly 1 year after its release, the number of cases of aplastic anaemia that had accumulated was such that the drug became close to being withdrawn from the market.[14,15] Several cases of severe and occasionally fatal hepatotoxicity were also reported.[16] At the present time, 31 patients were reported to have aplastic anaemia and 13 of these patients have died; after careful review, felbamate was considered the likely cause of aplastic anaemia in 23 patients, of whom 7 have died; 23 patients with hepatotoxicity were reported, and felbamate was considered the likely cause in 10, of whom 5 have died.

With an estimated denominator of 110 000 patients treated with felbamate, the calculated combined risk for both of these complications is about 1 : 4600, with a risk of death of about 1 : 9300.[15] Many patients in the paediatric age range have been treated with felbamate, but aplastic anaemia was not reported in anyone under the age of 13 years and only 2 patients were under of the age of 20 years. Discounting the risk of aplastic anaemia, the risk of death from hepatotoxicity in prepubertal children would be about 1 : 22 000.[15] This is slightly lower than the risk of hepatic fatality associated with valproic acid monotherapy in children above the age of 2 years, and clearly lower than the rate of hepatic fatalities associated with valproic acid polytherapy in children under the age of 10 years.[6]

Possible risk factors for felbamate-induced aplastic anaemia have been identified, which include a history of allergy or cytopenia with other anticonvulsants, polytherapy, and evidence of a concomitant immune disorder. The hypothesis of the abnormal accumulation of an felbamate metabolite, atropaldehyde, is currently being explored as a means of identifying patients at risk of a severe reaction to felbamate.[17]

A careful risk-benefit assessment would include the following consensus recommendations.[18,19] Felbamate should only be used as add-on treatment for children age 4 and above and adults with severe epilepsies, especially in patients with Lennox-Gastaut syndrome, who cannot be treated satisfac-

torily with other relevant anticonvulsants. Prior to prescribing felbamate a careful history should be taken concerning haematological disorders including leuco- and thrombocytopenia, hepatic disorders, autoimmune disease and drug-induced exanthema. In addition, a blood count and liver function tests (ALT AST, bilirubin) should be performed. Felbamate should be given only after a very careful risk-benefit assessment in patients with clearly abnormal laboratory tests and a history of above mentioned disorders. Patients and relatives must be informed about the risk of aplastic anaemia and acute hepatic failure and their early clinical signs and symptoms because laboratory monitoring will not reliably detect the early stages of clinical disease. As about one-third of patients with aplastic anaemia will have abnormal blood tests in the early course of the disease, blood count monitoring should be done based on individual considerations, especially during the first year of treatment. Frequent presentations (e.g. every 4 to 6 weeks) are recommended for assessing the tolerability. Felbamate should be slowly discontinued in patients without significant improvement after treatment for several months. At the present time, the main indication for felbamate is in children with Lennox-Gastaut syndrome who have failed to respond to other medications such as valproic acid, clonazepam, lamotrigine and topiramate.

3. Lamotrigine

A double-blind, placebo-controlled trial of the anticonvulsant lamotrigine was conducted in patients with Lennox-Gastaut syndrome.[20] Eligible patients had more than 1 type of predominantly generalised seizure, including tonic-clonic, atonic, tonic, and major myoclonic, and had seizures on average at least every other day. After a 4-week baseline period in which all participants received placebo, 169 patients (age range, 3 to 25 years) were randomly assigned to 16 weeks of lamotrigine (n = 79) or placebo (n = 90) therapy in addition to their other anticonvulsants. The median frequency of all major seizures changed from baseline levels of 16.4 and 13.5 per week in the lamotrigine and placebo groups, respectively, to 9.9 and 14.2 per week after 16 weeks of treatment ($p = 0.002$). 33% of the patients in the lamotrigine group and 16% of those in the placebo group had a reduction of at least 50% in the frequency of seizures ($p = 0.01$). There were no significant differences between groups in the incidence of adverse events, except for colds or viral illnesses, which were more common in the lamotrigine group ($p = 0.05$). Lamotrigine was shown to be an effective and well tolerated treatment for seizures associated with Lennox-Gastaut syndrome.[20]

Another double-blind, placebo-controlled crossover study of lamotrigine as add-on treatment in therapy-resistant, generalised epilepsy in 30 children and adolescents including 20 patients with Lennox-Gastaut syndrome had a similar outcome,[21] providing further evidence that lamotrigine is a well tolerated and effective treatment in children with intractable generalised epilepsies, including those with Lennox-Gastaut syndrome.[21]

Although lamotrigine is well tolerated in patients with Lennox-Gastaut syndrome, rash can occur in 5 to 10% of patients receiving the drug. In rare cases, fatal and life-threatening cases of Stevens-Johnson syndrome and toxic epidermal necrolysis have been noted[4,22] with an incidence of approximately 1 : 1000 cases. In addition, there has been concern that the incidence of rash may be higher in children.[23,24] Rash usually begins within the first 8 to 10 weeks of exposure. The risk of rash is increased with the concomitant use of valproic acid which inhibits the metabolism of lamotrigine, and with a rapid dose titration. To minimise the risk of rash, lamotrigine should be titrated slowly. The effective dose should be achieved by 1 to 2 week increments over a period of 6 to 8 weeks. Parents and guardians should be advised to stop lamotrigine and seek immediate attention at the earliest sign of rash following the introduction of lamotrigine.

Apart from the development of rash, lamotrigine is well tolerated and effective for children with Lennox-Gastaut syndrome. Quality of life improvements were especially striking in patients with seizures secondary to brain damage and in the Lennox-

Gastaut syndrome[25]. In a report on 120 children aged 10 months to 16 years from several studies, concomitant treatment could be reduced to monotherapy with lamotrigine in 12 patients.[26] 25% of patients receiving concomitant valproic acid exhibited skin rash, appearing 3 to 18 days after starting lamotrigine. For 4 of these patients, lamotrigine could be reintroduced safely after valproic acid was withdrawn. Ten patients had ataxia and/or drowsiness and 2 had vomiting. For all other patients, tolerance was excellent.

4. Topiramate

The efficacy of topiramate as adjunctive therapy in children Lennox-Gastaut syndrome was evaluated in 2 randomised, double-blind, placebo-controlled trials.[27,28] Sachdeo et al.[27] found that adjunctive therapy with topiramate resulted in a significant reduction in drop attacks (tonic or atonic seizures). The median percentage reduction from baseline in drop attacks was 14.5%, while a 5% increase was noted for the placebo group ($p = 0.04$). Parents or guardians felt that the severity of seizures was improved in 53% of patients, compared with in only 28% of placebo recipients ($p = 0.004$).

During an open-label extension of their trial, Sachdeo at al.[29] found that the efficacy of topiramate improved as the dose was increased. 11 of 16 patients (69%) receiving topiramate 10 mg/kg/day of experienced a 50% reduction in their overall seizure frequency compared with the baseline of the controlled phase. The minimally effective topiramate dosage for adjunctive therapy in children with refractory epilepsy was found to be 6 mg/kg/day.

Topiramate was well tolerated with only mild or moderate adverse effects being noted that were predominantly related to the CNS.[27-29] The most common adverse events associated with adjunctive treatment with topiramate were somnolence, bodyweight loss, mental slowing, fatigue, ataxia and irritability.[27,28] Most of these events were reversible, but withdrawal of treatment was required in 6 out of 15 patients as a result of ataxia in 2 patients, somnolence, metabolic acidosis, irritability or psychotic symptoms in 1 patient each.[28] The most important strategy for minimising the risk of CNS adverse events is a 'start low, go slow' approach. An initial topiramate dosage of 0.5 to 1 mg/kg/day followed by weekly increments of 0.5 to 1 mg/kg is usually well tolerated.[29]

Based on the results of these studies,[27-29] topiramate has been shown to be an important addition to the treatment of refractory Lennox-Gastaut syndrome. Topiramate appears to be one of the safest anticonvulsants for Lennox-Gastaut syndrome. To date, topiramate has not been associated with life-threatening adverse events.

5. Potential Anticonvulsants for Lennox-Gastaut Syndrome

Although controlled trials are not available, zonisamide, bromide therapy and the xanthine oxidase inhibitor allopurinol have been used as adjunctive antiepileptic drug therapy with limited success for patients with Lennox-Gastaut syndrome whose seizures are unresponsive to other drugs.[30-32] Exacerbation of seizures in Lennox-Gastaut syndrome by gabapentin has been noted.[33] Flunarizine was studied in a placebo-controlled, crossover trial of 20 patients aged 6 to 18 years, 10 of whom had Lennox-Gastaut syndrome.[34] A 30 to 60% reduction in seizure frequency was found in 5 out of the 13 patients who completed the trial. Adverse effects were rare. Unfortunately, the slow clearance of the metabolite of flunarizine renders the interpretation of crossover trials such as this one very difficult. Repeated intravenous immunoglobulin treatment at a high dose was found to reduce seizure activity by 70% in a small pilot investigation in which no control group was available.[35] A placebo-controlled trial using a lower dose showed less impressive results.[36]

The antiepileptic effect of vigabatrin in children has been demonstrated in controlled and open studies.[37] In patients with myoclonic epilepsies of early childhood and especially those with Lennox-Gastaut syndrome, the effect of vigabatrin has been investigated only to a limited extent and the pattern of response was variable. According to the literature, results were good to excellent in partial sei-

zures and in infantile spasms.[37] In patients with myoclonic epilepsies of early childhood and especially those with Lennox-Gastaut syndrome, the effect of vigabatrin has been investigated only to a limited extent and the pattern of response was variable and exacerbation of myoclonic seizures may occur.[37] Reacting to recent reports of concentric, vigabatrin-associated visual field loss in approximately 33% of adult and adolescent patients,[38] the European Commission has recently revised the indication for vigabatrin to include monotherapy for West syndrome plus adjunctive therapy for partial seizures refractory to all adequate combinations of anticonvulsants. Ophthalmoscopic examination including perimetry is required before vigabatrin treatment and at a minimum of every 3 months afterwards. Perimetry cannot be reliably performed in those with a developmental age of less than approximately 8 years and it is therefore difficult to assess the risk of visual field defects in this age group. Alternative testing methods are currently under investigation. Gradual withdrawal is recommended in all patients with an equivocal clinical response, and patients and guardians are encouraged to enquire about any new or unusual visual problems during treatment with vigabatrin.

6. Ketogenic Diet

The ketogenic diet requiring a high degree of compliance with a high fat, low carbohydrate, low protein regimen has been found to be effective in many children with refractory severe epilepsy, including Lennox-Gastaut syndrome.[39] Although controlled trials are not yet available, a recent publication shows efficacy in a double-blind fashion in the treatment of Lennox-Gastaut syndrome[40] and mentions an upcoming large trial. Adverse effects include renal stones, hyperuricaemia, acidosis and other metabolic derangements. In patients with cognitive or behavioural problems implementation may be difficult.

7. Vagus Nerve Stimulation

The long term efficacy of the vagus nerve stimulator was assessed in 64 patients with refractory epilepsy including 8 patients with Lennox-Gastaut syndrome. After implantation, intermittent stimulation was delivered and seizure frequency and severity were counted. Average treatment time was 20 months. Five of 8 patients with Lennox-Gastaut syndrome had >50% seizure reduction. Adverse effects were mild. Vagus nerve stimulator appears to be a well tolerated and effective treatment for refractory epilepsy including Lennox-Gastaut syndrome.[41] 16 children, 10 boys and 6 girls aged 4 to 19 years, were treated with vagus nerve stimulator for 12 to 24 months. Seizure frequency, seizure severity, changes in quality of life (measured using a visual analogue scale), and adverse effects were recorded. Eight children had partial and 8 had generalised seizures; 4 of the latter had Lennox-Gastaut syndrome. During the tenth to twelfth month of vagus nerve stimulator, 6 of 16 children experienced 50% or greater reduction in seizure frequency. One girl became seizure-free. Seizure severity showed an average decrease in the score from 15 to 11. After 10 months of treatment, quality of life was estimated to have improved by 50% or more in 6 of 16 children. Six children experienced hoarseness, 1 had neck pain, 2 had hypersalivation, 2 experienced tiredness, 2 (with pre-existing dysphagia) had aspiration episodes during liquid intake, and 6 had electrical transmission problems; in 4 of these children the problem has been surgically corrected. Five stimulators were turned off because of lack of efficacy.[42] In fairness, it should be noted that the number of technical problems seen in this trial is atypical and may be related to the relative inexperience during early days of implanting vagus nerve stimulator in children.

In another report regarding the tolerance and efficacy of the vagus nerve stimulator in a group of 19 children with medically and surgically intractable epilepsy, follow-up continued from 2 months to 30 months, with the study period ending in October 1995. All 3 children with unsuccessful corpus callosotomy had improvement after implantation of the stimulator, and 5 of 6 children with Lennox-Gastaut syndrome had a 90% reduction of

seizures. Five patients required fewer antiepileptic medications, and 1 patient had an increase in medication requirement. Adverse effects included 2 possible wound infections, 1 instance of generator failure, and hoarseness during stimulation in all patients. Changing stimulation parameters to increase the rate of stimulation and reduce the interval between stimulations resulted in improved seizure control in 4 of 5 patients. Periodic vagus nerve stimulator was well tolerated by these children and may have a role in the management of refractory epilepsy.[43] Most recently, the results of vagus nerve stimulator use in 16 children with Lennox-Gastaut syndrome and related epilepsies were reported.[44] Four had >50% seizure reduction and 1 became seizure-free. Interestingly, 6 children had significantly improved verbal performance. In a recent report on the seizure outcome following vagus nerve stimulator in a group of 46 patients with Lennox-Gastaut syndrome ranging in age from 5 to 27 years, the mean reduction in drop seizures was 71% at 6 months of vagus nerve stimulator, and 2 of 15 patients had no more drop seizures at follow-up.[45] In the view of the authors these results appeared comparable to corpus callosotomy. Vagus nerve stimulator appears to be – together with topiramate – among the safest therapeutic interventions available for the treatment of Lennox-Gastaut syndrome. To date, neither has been associated with serious adverse events or death.

In contrast to vagus nerve stimulation, chronic electrical stimulation of the centromedian thalamic nuclei was not found to be effective in 6 patients with refractory Lennox-Gastaut syndrome.[46]

8. Callosotomy

Occasionally, surgery may be useful in the management of refractory Lennox-Gastaut syndrome. Resective surgery may be considered if there is a possibly causal, structural surgically amenable focal lesion. However, most patients have multiple structural or functional lesions as seen by positron emission tomography and thus are not candidates for resective surgery. Corpus callosotomy is effective in reducing the number of tonic-clonic seizures by preventing their generalisation from partial seizures and in preventing drop attacks including atonic seizures in as many as 60 to 80% of patients.[47] Axial tonic seizures which may be a cause of drop attacks or other seizure types seem to respond less well to callosotomy,[48] although improvement may be seen in individual patients. Poor outcomes for drop attacks have been found to be more likely if there was associated severe intellectual handicap or bilateral independent spikes on interictal electroencephalogram.[49] A two-thirds anterior callosotomy is usually performed as a first step and may be followed by completion of callosal division as a second stage in those patients in whom a significant improvement has not been observed. In patients who are severely retarded and who have multiple seizure types, one-stage complete section may be performed. The procedure is relatively safe, with a low incidence of morbidity and clinically significant long term neuro-psychological deficits.[50,51] Anterior corpus callosum section should be considered as a therapeutic option in appropriately defined medically refractory patients who do not qualify for excisional surgery.[47]

9. Algorithm for the Treatment Sequence of Lennox-Gastaut Syndrome and Related Syndromes

Although recommendations for the treatment of children and adults with Lennox-Gastaut syndrome are difficult to make in the absence of direct head-on comparative trials, the following algorithm is suggested based on the best evidence available for assessing risks versus benefits. As discussed above, the risk-benefit ratio of a given compound may be depend on the age of the patient. We therefore propose an algorithm which differentiates treatment for children below age 5 and for patients above age 5 (fig. 1). Proposal of this algorithm is not intended to exclude the use of the other treatment measures that have been discussed in this brief overview, if individual risk-benefit considerations apply. A trial of pyridoxine may be useful to exclude the possibility of a child below age 5 having vitamin B6 dependency seizures presenting as Lennox-

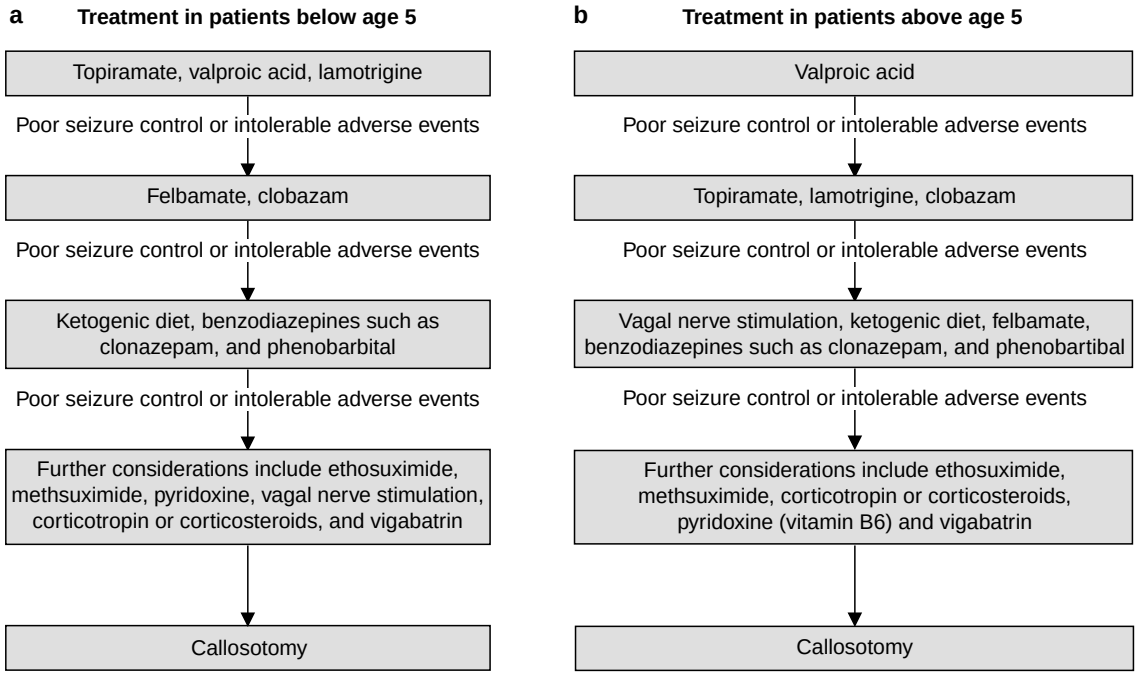

Fig. 1 Algorithm for the treatment sequence of Lennox-Gastaut syndrome and related syndromes. (**a**) In the absence of controlled comparative trials, the algorithm is based on the best available evidence on the risk-benefit of the therapeutic interventions. For children below age 5 years, topiramate would appear to be the safest anticonvulsant available to initiate treatment. If it cannot be initiated quickly enough because of tolerability problems encountered during fast titration then valproic acid (sodium valproate) could be used first despite its higher risk of hepatotoxicity in patients in this age range. The tolerability of lamotrigine is improved when treatment is initiated with a slow titration, especially in the presence of valproic acid. (**b**) In adults, adolescents and children of age 5 years and older, who have a lower risk of hepatotoxicity, valproic acid (sodium valproate) could be used first because it can be titrated more rapidly than topiramate. The addition of topiramate avoids the possibility of drug-induced rash if valproic acid is added to lamotrigine. If a patient does not benefit from the addition of topiramate to valproic acid then a decision can be made about introducing lamotrigine at a slow titration rate.

Gastaut syndrome. With very low risk, a large benefit is can be derived if such a child can be identified. Furthermore, and of relevance for all patients with Lennox-Gastaut syndrome, use of a helmet is an option for patients experiencing frequent falls while control of drop attacks with other treatments is improved.

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