The medical management of the epilepsies in children: conceptual and practical considerations

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Epilepsy in children encompasses several syndromes. The cardinal feature of these syndromes is a predisposition to epileptic seizures but each is associated with different prognoses. The goals of treatment will clearly differ between children who become seizure-free on antiepileptic drug (AED) treatment and those children with refractory epilepsy. Treatment should be tailored to the needs of the patient, with a comprehensive approach that addresses the common additional morbidities in children with epilepsy. In this Review, we present an overview of the medical management of epilepsy in children and discuss the dilemmas of everyday practice, such as selection of AED, assessment of outcome, monitoring of treatment, and the decision to withdraw medication when the child is free from seizures. Furthermore, we emphasise the need to establish rational goals for treatment, such as aiming for the best possible quality of life rather than freedom from seizures at all costs.

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Introduction

Epilepsy in children encompasses several syndromes that are characterised by a predisposition to recurrent epileptic seizures and have different prognoses, additional morbidities, and differ in their response to treatment.[1] The treatment of seizures is only one aspect of the management of children with epilepsy, and the treatment of the associated morbidities might be as important as the treatment of seizures when determining outcome.

This Review is a clinically oriented overview of the principles of the medical management of epilepsy in children. Current dilemmas in the selection of antiepileptic drugs (AEDs), the use of appropriate outcome measures, treatment monitoring, the use of polytherapy, and withdrawal of medications are reviewed. We highlight quality of life as the ultimate outcome measure and acknowledge the limitations in the accuracy of the definition and assessment of quality of life in current clinical practice. Some medical treatments can seriously impair quality of life without an appreciable benefit, whereas others greatly enhance quality of life. Both situations are possible with the use of AEDs; thus, the necessity to establish rational goals for treatment and minimise adverse seizure, cognitive, and psychiatric outcomes are emphasised.

Principles of treatment

The causes and prognoses of epilepsies in children are varied and, therefore, each child with epilepsy needs an individualised, multiaxial assessment of their epilepsy syndrome, the potential underlying brain disorders, and any additional morbidities.[2–4] Children with epilepsy can be divided into two groups. The first group comprises those children with idiopathic focal or generalised epilepsies, who are more likely to respond rapidly to AEDs; their associated cognitive and behavioural impairments are unlikely to be severe. The second group comprises children with epilepsies that have an identifiable cause (symptomatic), epilepsies that behave as if they have a cause, although the cause has not been identified (probable symptomatic), and a group of severe epilepsies characterised as epileptic encephalopathies. The epilepsy syndromes in the second group are less likely to respond to AEDs, and the children are more likely to have additional morbidities that result from the complex interaction of the underlying cause, the epileptogenic process, the seizures, and the presence of subclinical epileptic discharges. However, this dichotomy is not absolute, and it would not be reasonable to rely solely on aetiology to predict the existence of additional morbidities or response to AED therapy.[5,6] Considerable evidence is available about the occurrence of cognitive dysfunction in several idiopathic, benign, epilepsy syndromes (eg, benign childhood epilepsy with centrotemporal spikes), which might not necessarily occur in children with ominous symptomatic epilepsies (eg, children with tuberous sclerosis, who might respond well to AEDs and who lack notable cognitive effects).[7,8] Nevertheless, for direct patient management, the dichotomy is important for the prediction of outcome at diagnosis, which gives the doctors and family a benchmark from which to audit progress. Such an approach means that there will be outcomes that are not as predicted, which would, therefore, trigger clinical re-evaluation; for example, unfavourable outcome of seizures associated with fever, which suggests a diagnosis of Dravet syndrome.

Targets of AED therapy

60–70% of children with newly diagnosed epilepsy will become seizure-free with no treatment or a low-to-moderate dose of the first or second choice AED as monotherapy.[5] The remaining 30–40% include children who have epilepsies that are either initially difficult to control but have a favourable outcome and those children with long-term intractable epilepsies, who are likely to continue to have seizures despite multiple AEDs.[5,9–12] The goals of treatment with AEDs will differ accordingly. Seizure control with one AED and without adverse events is a reasonable target for children in the first group, and for some no treatment is appropriate. For epilepsies that are refractory, the main goal should not be complete

seizure control at all costs but an equilibrium between maximum seizure control with minimum adverse effects, to ensure the best quality of life.[13] Accordingly, the evaluation of outcome in children who have epilepsies that are refractory should clearly extend beyond seizure counting.[14,15]

The evaluation of whether an epilepsy is likely to be refractory might be possible at presentation owing to the presence of additional impairments (particularly cognitive), multiple seizure types, structural brain abnormalities, and a known history of a specific epilepsy syndrome.[16–18] Thus, making a particular diagnosis is helpful in management not only to guide the selection of AED but also to discuss possible outcomes and to set realistic goals for seizure control. However, an early diagnosis of epilepsy syndrome might not be possible; therefore, diagnosis, prognosis, and treatment goals will need periodic review.[2]

Initiation of and modifications to AED therapy

AED therapy should only be started once the diagnosis of epilepsy is confirmed. The prescription of an AED as a clinical test to confirm the diagnosis of epilepsy is not advisable.[3] Treatment is commonly started after two unprovoked seizures because the risk of further seizures increases thereafter.[19] However, other variables need to be taken into account before the decision to start AED therapy is made. AED therapy might be postponed if the seizures are infrequent or if a benign epilepsy syndrome is suspected (eg, Panayiotopoulos syndrome or benign childhood epilepsy with centrotemporal spikes). By contrast, there are situations where treatment should be started after the first unprovoked seizure, such as when there is a higher risk of either seizure recurrence (eg, severe epileptiform abnormalities on EEG or cortical dysplasia) or the prospect of harm from subsequent seizures (eg, severe osteoporosis or anticoagulant therapy). Treatment could be started before the first seizure in children with epileptic encephalopathies, in whom the regression of cognitive and developmental skills may be due to the epilepsy.[20]

Monotherapy is the gold standard in epilepsy treatment, and the dose of an AED is usually titrated to the maximum dose that can be tolerated before another AED is tried if seizures persist. The dose of the current drug should be tapered only after an adequate dose of the new AED has been reached.[21] If the pre-existing AED is reduced and the new AED titrated simultaneously, any deterioration due to the reduction of a partly active AED or to AED-induced deterioration might be impossible to ascertain. Increasing the dose of an AED to near-toxic doses assumes an appropriate dose–response relationship. However, increasing the dose to the maximum that can be tolerated by patients who report seizures at average dose is beneficial in only about 13–15% of patients. Therefore, if the benefit does not outweigh the adverse effects of treatment with the maximum dose, the average dose should be reinstated and another AED tried (table 1).[22] Accordingly, the effectiveness of treatment, which includes both efficacy (ie, seizure control) and tolerability (ie, absence of side-effects), is the appropriate outcome measure.[23]

The outcome in patients who fail the first monotherapy is strongly associated with the reason for treatment discontinuation: four to five times more patients are seizure-free after treatment with another AED if the failure of the first treatment was due to adverse events rather than lack of efficacy.[24] The failure of the first monotherapy is a risk factor for poor outcome, and the chances of long-term freedom from seizures after the failure of the second AED drops to less than 10%.[5,10,24] When two or three appropriate monotherapies fail to control seizures, many patients are offered polytherapy. Polytherapy might be started earlier if specific epilepsy syndromes, such as Dravet syndrome or Lennox-Gastaut syndrome, are suspected, although the evidence that favours early polytherapy in these drug-resistant epilepsy syndromes is scarce.[2] Furthermore, for some epilepsy syndromes, such as myoclonic–astatic epilepsy or epilepsy with myoclonic absences, polytherapy might be preferable to monotherapy, even in untreated patients.[25] In each case, the clinical features that predict the success

	Starting dose (mg/kg/day)	Maintenance dose (mg/kg/day)*	Number of daily doses
Carbamazepine	4	20–30	2–3
Clobazam	0·25–1·00	0·5–1·0	1–3
Clonazepam	0·05	0·1–0·2	2–3
Ethosuximide	10	20–30	1–2
Felbamate	15	30–45	2
Gabapentin	5–10	20–100	2–3
Lamotrigine monotherapy	0·50	2–10	2
Lamotrigine with valproate	0·15	1–5	2
Lamotrigine with enzyme inducers	0·50	5–15	2
Levetiracetam	5	20–60	2
Nitrazepam	0·10–0·25	0·5–1·0	2
Oxcarbazepine	5–10	30–50	2–3
Phenobarbital	3	3–5	1–2
Phenytoin	5	4–10	2
Prednisolone	2	..	1
Primidone	10	20	2–3
Sodium valproate	10	15–40	2–3
Stiripentol	50	50–100	2–3
Sulthiame	5	5–15	2–3
Tiagabine	0·25	0·5–2·0	2
Topiramate	0·5–1	2–10	2
Vigabatrin	50	100 (≤150 for infantile spasms)	2
Zonisamide	2	4–12	2

*The upper limit of the maintenance dose is the usually accepted maximum dose, although this should be tailored to each patient on the basis of age, efficacy, tolerability, and coadministration of other drugs that might interact.

Table 1: **Usual dosage and frequency of administration of currently available AEDs**

of polytherapy (eg, freedom from seizures, the ability to concentrate at school, and improvements in quality of life) should be clearly defined when polytherapy is started. Unsuccessful treatments can then be reversed early and the potential adverse effects of polytherapy can be avoided. Therefore, when combination therapies fail to achieve meaningful benefits, the most effective monotherapy should be restarted.[3]

Identification and management of additional morbidities

Additional morbidities are common in children with epilepsy but frequently go unrecognised and undertreated. When additional morbidities are recognised, they are often deemed secondary to the epilepsy and to require no treatment other than AEDs. However, the association between additional morbidity and quality of life implies that the treatment of the additional morbidities in patients with epilepsy might considerably improve the overall quality of life.[26] Thus, autism spectrum disorder, attention-deficit hyperactivity disorder, and sleep disturbances should be identified and treated appropriately. The search for autism spectrum disorder in children with epilepsy is more compelling because of data that suggest that the early detection of autism spectrum disorder and initiation of behavioural interventions in the first few years of life can improve cognitive and behavioural outcomes.[27] Estimates of the prevalence of attention-deficit hyperactivity disorder in children with epilepsy range from 14–40%, compared with about 5% in normal school-aged children; attention-deficit hyperactivity disorder in children with epilepsy can independently contribute to academic underachievement.[28,29] Methylphenidate commonly improves the symptoms of attention-deficit hyperactivity disorder with no exacerbation of seizures in children with either well controlled or active epilepsy.[30] Epilepsy can also disrupt sleep and contribute to daytime sleepiness. In turn, disordered sleep can increase seizure activity and aggravate the impaired behaviours seen in children with autism spectrum disorders and epilepsy or attention-deficit hyperactivity disorder and epilepsy. Therapeutic interventions to improve sleep in children with behavioural comorbidity and epilepsy might, therefore, have beneficial effects on seizure control and daytime behaviours.[31] Additional morbidities that are also more prevalent in children with epilepsy than in the general population include cerebral palsy, migraine, learning disabilities, and behavioural and psychiatric disorders apart from autism or attention-deficit hyperactivity disorder (eg, depression or anxiety). The appropriate management of these might also positively influence the psychosocial and educational outcome of children with epilepsy.[14]

Thus, management strategies for children with epilepsy should have broader aims than just the prevention of seizures, which should never be the only outcome; fewer seizures can be accompanied by intolerable side-effects.[32,33] The identification and management of additional morbidities requires the same vigour that is applied to the identification and management of seizures to accomplish the main goal of treatment—the best quality of life.

Pharmacological properties of AEDs

By understanding the basic pharmacokinetic and pharmacodynamic properties of AEDs, appropriate decisions can be made on the dosing strategy (dose, frequency of dose, and route of administration). Pharmacokinetically, the ideal AED should have good bioavailability, rapidly achieve steady-state concentrations, have linear-invariant and time-invariant kinetics, minimum protein binding, minimum metabolism, and a long elimination half-life.[34] However, none of the currently available AEDs has all these properties, although most of the new AEDs have a better pharmacokinetic profile than older AEDs. Most AEDs have multiple mechanisms of action, and how much of each mechanism contributes to the overall anticonvulsant effect is unknown. Theoretically, the mechanism of action should be an important criterion when selecting an AED, but the incomplete understanding of the mechanisms of action limits their clinical use in the prediction of therapeutic success and, thus, in the selection of AEDs for individual patients.[35]

AED selection

The selection of the most suitable AED needs careful assessment of the characteristics of the epilepsy, the patient, and the effectiveness of the AEDs available.[36]

The decision not to treat with AEDs

On occassions, although a child might have had more than one epileptic seizure it is not reasonable to use AEDs because treatment might not modify the outcome. Children with febrile seizures or benign epilepsies (eg, benign childhood epilepsy with centrotemporal spikes or Panayiotopoulos syndrome) are mostly untreated, although if the attacks are frequent or prolonged prophylactic treatment with AEDs might be warranted.[37–39] Children with severe developmental delay and mild epilepsy can also be left untreated if drug treatment does not bring any clinical benefits.[1]

The choice of first AED

The choice of first AED is probably the most important single therapeutic decision because most children will enter remission shortly after the start of therapy and will potentially remain on this drug for many years.[40] Treatment-responsive patients will probably respond to low doses of all AEDs; thus, for this population, the emphasis should be on selection of the AED that is the best tolerated and is least likely to have a negative effect on quality of life.[41]

The number of randomised controlled trials that have investigated the efficacy and tolerability of AEDs

can complicate this decision. Most randomised controlled trials are designed for regulatory purposes and might not help in clinical practice.[42] Published guidelines are an attempt to create available information to guide practice. Despite reports that new AEDs are better tolerated than classic AEDs, sodium valproate is usually recommended as the first choice for generalised-onset seizures and carbamazepine for focal-onset seizures, although the evidence to support this recommendation is sparse.[43] There is no unequivocal evidence that carbamazepine has any advantage compared with valproate for the treatment of focal seizures, and the results of the recent SANAD study suggest, not without controversy, that lamotrigine and possibly oxcarbazepine might be preferable as the initial monotherapy for adults and children with focal epilepsy because they are better tolerated.[44] The heterogeneity of the population studied, the random assignment to valproate or carbamazepine on the basis of the clinician's choice of what is best for that individual (rather than assignment by epilepsy syndrome or seizure type), and the recommended rapid titration scheme of carbamazepine might all limit the validity of the conclusions from the SANAD trial.[45–47]

The International League Against Epilepsy guidelines were developed through a systematic review of the evidence for the efficacy or effectiveness of AEDs for patients with newly diagnosed or untreated epilepsy. The findings in the guidelines were that no randomised controlled trials support a particular AED as initial monotherapy for most children with epilepsy.[48] Only oxcarbazepine for children with focal seizures was supported by level A evidence of efficacy and effectiveness. Neither common seizure types (generalised tonic–clonic and absence seizures) nor epilepsy syndromes (benign childhood epilepsy with centrotemporal spikes and juvenile myoclonic epilepsy) responded to any AED with evidence of level A or level B efficacy or effectiveness as an initial monotherapy (table 2). This poor evidence base is the probable explanation for the discrepancies among guidelines for the first-line treatment in many situations, which extend from newly diagnosed patients with benign epilepsy syndromes to patients with refractory epilepsy.[49] A consensus guideline for appropriate AED treatment in accord with the epilepsy syndrome is shown (table 3), which, in view of the above, is open to debate. However, the consensus guideline is adequate for clinicians faced with a child who has epilepsy, if the broader issues are taken into consideration.

Despite the limited specificity of the available AEDs, some therapies might be considered syndrome-specific. Giving these therapies might be appropriate for children with certain epileptic encephalopathies, such as administration of stiripentol to children with Dravet syndrome, hormone therapy (eg, corticosteroids or adrenocorticotrophic hormone) and vigabatrin to children with infantile spasms, and benzodiazepines and hormone therapy to children with Landau-Kleffner and other syndromes with continuous spike-wave of sleep.[20,50,51] Although these treatments can be used in other circumstances, they should be thought of as syndrome-specific and regarded early in the above circumstances.

In daily practice, AED selection should be matched to age, sex, weight, concomitant medication, and additional morbidities. The practical problems for the treatment of children with AEDs include the calculation of dose per kilogram, which should be checked against the recommended adult dose in older children; the selection of AEDs with longer half-lives or those with slow-release preparations; the availability of preparations that can be broken into smaller doses that can be adapted to weight or of liquid and dissolvable granule preparations that are palatable.

	Class I studies	Class II studies	Class III studies	Level of efficacy and effectiveness evidence
Focal seizures	1	0	17	Level A: OXC Level B: None Level C: CBZ, PB, PHT, TPM, VPA
Generalised-onset tonic–clonic seizures	0	0	14	Level A: None Level B: None Level C: CBZ, PB, PHT, TPM, VPA
Absence seizures	0	0	6	Level A: None Level B: None Level C: ESM, LTG, VPA
Benign childhood epilepsy with centrotemporal spikes	0	0	2	Level A: None Level B: None Level C: CBZ, PB, PHT, TPM, VPA
Juvenile myoclonic epilepsy	0	0	0	Level A: None Level B: None Level C: None

CBZ=carbamazepine. ESM=ethosuximide. LTG=lamotrigine. OXC=oxcarbazepine. PB=phenobarbitone. PHT=phenytoin. TPM=topiramate. VPA=valproate. The class of evidence for efficacy or effectiveness studies was assessed in accordance with several study characteristics, such as randomisation, double-blinding, detectable non-inferiority boundary, exit criterion, and treatment duration. Specific combinations of clinical trials ratings were used to classify the level of evidence to support the indication of a particular AED according to seizure type and epilepsy syndrome. AEDs with level A evidence had the highest supporting level of clinical trial evidence followed sequentially by levels B, C, and D. On the basis of efficacy and effectiveness data, a recommendation was established that those AEDs that met the criteria of level A or B evidence for a specific seizure or epilepsy type should be used as initial monotherapy, whereas AEDs that met the criteria of level C evidence might be considered for initial monotherapy. Reproduced with permission from Blackwell Publishing.[48]

Table 2: **Studies and level of evidence for each seizure type and epilepsy syndrome in children**

Use of polytherapy after monotherapy has failed

The goal of polytherapy should be to improve effectiveness of treatment by improving efficacy, tolerability, or both.[52] Several criteria to select the constituents of combination regimens have been proposed, including the lack of pharmacokinetic interactions and the lack of toxicity. However, our incomplete understanding of the pharmacodynamic mechanisms that determine the combined efficacy of AEDs prevents the rational use of drug combinations. Clear-cut evidence of the superiority of one combination over another is not available, and the evidence from studies of epilepsy in animals is inconclusive.[53,54] Furthermore, there is controversy about whether the effectiveness of AEDs might be improved by

a combination that works on the same neurotransmitter system or ion channel or whether this is better accomplished by a combination of AEDs that have different mechanisms of action.[52]

There is, however, some evidence, gathered mainly from non-randomised controlled trials, that certain regimens might have additive or even synergistic effects (eg, valproate and ethosuximide for absence seizures, valproate and lamotrigine for absence and myoclonic seizures), and such combinations might be more effective in some patients than increasing the dose of any of the constituents in monotherapy.[55] Additionally, the combination of AEDs with prominent sedative effects should be avoided, and at least one broad-spectrum AED should be used in children with multiple seizure types.

Children with refractory epilepsy might benefit from alternative interventions that can limit the use of polytherapy. A short course (2–3 days) of benzodiazepines, such as clobazam or diazepam, after the first seizure might be useful in children with seizure clusters.[2] Also, the management of prolonged seizures requires treatment with transmucosal benzodiazepines (ie, buccal, rectal, or intranasal administration) as rescue medication for carers to use in those patients who are at high risk. Because most prolonged seizures start in the community, care pathways have been developed to incorporate prehospital and hospital treatments.

Refractory epilepsy and polytherapy

The prevalence of refractory epilepsy is variably reported as 9–24% of children with epilepsy.[5,10,16,56] The variability can be explained by differences between studies in terms of the definition of intractability (ie, number of AED failures, number or frequency of seizures, and the time interval during which seizures are counted) or the time of assessment of such intractability.[57] Indeed, fluctuations during the treatment course do occur, and fulfilling the criteria for intractability might be temporary: several studies have shown that up to a quarter of children with early intractability (within the first 2 years of follow-up) have a remission of at least 1 year at 5 years.[5,16,58] Less commonly, intractability can be delayed for many years and can be preceded by a period of relative calm or even complete remission, particularly in children with focal epilepsies.[5,59]

However, several epilepsy syndromes have a predictable high-risk of being refractory in the long term. These include, among others, Ohtahara syndrome, infantile spasms, Dravet syndrome, myoclonic–astatic epilepsy, Lennox-Gastaut syndrome, and symptomatic focal epilepsies due to malformations in cortical development.

A common approach to deal with refractory epilepsy is to maximise AED therapy to achieve full seizure control because continuing seizures or subclinical discharges can worsen the outcome. However, fewer than 5–10% of children with refractory epilepsy will be seizure-free after taking any subsequent AED as monotherapy or

	First-line drugs	Second-line drugs	Other drugs	Drugs to avoid (might worsen seizures)
Childhood absence epilepsy	Ethosuximide Lamotrigine Valproate	Levetiracetam Topiramate		Carbamazepine Oxcarbazepine Phenytoin Tiagabine Vigabatrin
Juvenile absence epilepsy	Lamotrigine Valproate	Levetiracetam Topiramate		Carbamazepine Oxcarbazepine Phenytoin Tiagabine Vigabatrin
Juvenile myoclonic epilepsy	Lamotrigine Valproate	Clobazam Clonazepam Levetiracetam Topiramate	Acetazolamide	Carbamazepine Oxcarbazepine Phenytoin Tiagabine Vigabatrin
Epilepsy with generalised tonic–clonic seizures	Carbamazepine Lamotrigine Topiramate Valproate	Levetiracetam	Acetazolamide Clobazam Clonazepam Oxcarbazepine Phenobarbital Phenytoin Primidone	Tiagabine Vigabatrin
Focal epilepsies: cryptogenic or symptomatic	Carbamazepine Lamotrigine Oxcarbazepine Valproate Topiramate	Clobazam Gabapentin Levetiracetam Phenytoin Tiagabine	Acetazolamide Clonazepam Phenobarbital Primidone	
Infantile spasms	Hormone therapy* Vigabatrin	Clobazam Clonazepam Valproate Topiramate	Nitrazepam	Carbamazepine Oxcarbazepine
Benign epilepsy with centrotemporal spikes	Carbamazepine Lamotrigine Oxcarbazepine Valproate	Levetiracetam Topiramate	Sulthiame	
Benign epilepsy with occipital paroxysms	Carbamazepine Lamotrigine Oxcarbazepine Valproate	Levetiracetam Topiramate		
Dravet syndrome (severe myoclonic epilepsy of infancy)	Clobazam Clonazepam Valproate Topiramate	Levetiracetam Stiripentol	Phenobarbital	Carbamazepine Lamotrigine Oxcarbazepine Vigabatrin
Continuous spike wave of slow sleep	Clobazam Clonazepam Ethosuximide Hormone therapy* Lamotrigine Valproate	Levetiracetam Topiramate		Carbamazepine Oxcarbazepine Vigabatrin
Lennox-Gastaut syndrome	Lamotrigine Valproate Topiramate	Clobazam Clonazepam Ethosuximide Levetiracetam	Felbamate	Carbamazepine Oxcarbazepine
Landau-Kleffner syndrome	Hormone therapy* Lamotrigine Valproate	Levetiracetam Topiramate	Sulthiame	Carbamazepine Oxcarbazepine
Myoclonic astatic epilepsy	Clobazam Clonazepam Valproate Topiramate	Lamotrigine Levetiracetam		Carbamazepine Oxcarbazepine

*Hormone therapy (eg, corticosteroids or adrenocorticotrophic hormone). Table reproduced with permission from the National Institute for Health and Clinical Excellence.[3]

Table 3: **Recommended drug options according to epilepsy syndrome**

polytherapy when two or three AEDs as monotherapy have failed to achieve full seizure control.[5,24] Additionally, this approach can lead to unacceptable side-effects, which can be worse than the seizures.[60] During the early stages of identifying seizure resistance to AEDs, the combination of clinical, MRI, and EEG evidence should be reviewed to assess the possibility of surgery[61] or alternative medical treatments, such as immunoglobulins, hormone therapy, or a ketogenic diet, which are extensively discussed elsewhere and will not be covered in this Review.[62,63]

Randomised controlled trials usually report on the short-term efficacy and safety of AEDs as add-on therapies; they do not report the overall effectiveness of polytherapy or its effect on quality of life. Furthermore, they are usually too small to give meaningful data on safety, particularly for children, who are included in controlled trials less commonly.[64] Improvements reported by families and carers after frequent AED trials or polytherapy can be biased because parents want their children to improve and, therefore, may place major importance on relatively subtle and recent changes. Severe epilepsies are fluctuating disorders, and changes in AEDs tend to be started during periods of poor seizure control; therefore, it is possible that improvements attributed to the new AED are just an observation of an individual child's fluctuation. Therefore, objective assessments of seizure fluctuations in association with quality of life scales should be used in children with refractory epilepsies to assess drug effectiveness.[65,66]

Goals to balance seizure control with overall quality of life

Most randomised controlled trials of AEDs report a 50% reduction in seizure frequency as the primary outcome measure, although the effect of this magnitude of seizure reduction on quality of life is controversial. Surgical series and studies of AEDs show that notable improvement in quality of life is mainly seen in patients who are free from seizures.[67–69] However, studies of adults have also found seizure reduction to be associated with an improvement in quality of life, which suggests that freedom from seizures might not be a prerequisite for psychosocial improvement.[70–72] In addition, a simple seizure count might not register improvements in seizure severity or pattern, such as conversion from diurnal to nocturnal, which might be important for quality of life assessment. Thus, it is unclear whether patients who are not seizure-free can benefit from fewer seizures, and for many patients the risk–benefit balance favours risk with higher doses or numbers of AEDs given.[23] Finally, seizure control might not be a relevant outcome measure for some epileptic encephalopathies with continuous spikes and waves during slow sleep, where seizure freedom might not be associated with improved outcome.[73]

Prevention of overtreatment

Overtreatment in epilepsy is defined as an "unnecessary or excessive AED load in the management of epilepsy leading to a suboptimal risk-to-benefit balance".[23,32,74,75] A precise evaluation of the frequency of overtreatment is not easy because a dose that is insufficient for one patient might be excessive for another patient.[76]

One of the commonest forms of overtreatment is the failure to reduce unsuccessful polytherapy and to start an alternative monotherapy.[23] The potential benefits of a reduction in overtreatment include decreased severity of side-effects and their easier attribution to a given drug, improved compliance by simplifying the medication schedule, reduced costs, and, sometimes, seizure reduction if the patient had overtreatment-associated seizure aggravation.[74]

Several authors report that reduced use of AEDs can effectively maintain seizure control with fewer adverse effects in individuals with refractory epilepsy.[77–84] These studies were done mainly in adults, used non-standardised or generic measures of quality of life, and most have reported the effect of the reduction of AEDs only in isolated aspects of quality of life. No epilepsy-specific, standardised questionnaire-based studies have been published on the effect on quality of life of reducing the AED load in children with refractory epilepsy; however, drug reduction might be associated with improved cognitive and behavioural outcomes and with little effect on seizure control.

There is little evidence that increasing AED load improves the likelihood of seizure control in children with refractory epilepsies, and there is considerable evidence that a greater AED load increases the likelihood of side-effects, with further impairment of quality of life. An appraisal of the potential risks and benefits associated with increases in the AED load in children with refractory epilepsy suggests that the best tolerated and the most effective AED should be chosen, preferably as monotherapy, and quality of life should be the most important outcome. Schmidt states that it might well be concluded that "in AED treatment of refractory epilepsy, less may be more".[23] Furthermore, for a minority of children with refractory epilepsies and frequent seizures, despite multiple AED trials, the requirement for regular AED therapy should be addressed.

Side-effects

AED toxicity is possibly the most important preventable aspect of disability and poor health associated with epilepsy.[85,86] AED toxicity is particularly relevant in children with refractory epilepsy, who are frequently given high AED loads that might worsen pre-existing impairments, such as feeding problems caused by benzodiazepines in children with spastic tetraplegia and behavioural problems due to taking several AEDs.[87]

There are several types of adverse effects related to AED therapy. Most adverse reactions fall in the broad category of neurotoxicity, which includes drowsiness, dizziness, cognitive impairment, ataxia, or diplopia. The neurotoxic adverse effects are predictable, dose-dependent, and

might be explained by the known pharmacological properties of the AED. All AEDs may have a detrimental effect on cognition or behaviour and this might be particularly worrying with classic AEDs (eg, the association between phenobarbital and lower IQ) and newer AEDs (the associations between topiramate and attention and verbal dysfunction, and zonisamide and psychosis). However, the newer AEDs are generally deemed to be safer at the cognitive level than the older AEDs.[88,89] By contrast, idiosyncratic reactions are unpredictable in susceptible individuals and can include rash, Stevens–Johnson syndrome, serum sickness reaction, agranulocytosis, aplastic anaemia, and hepatic failure.[90] Younger age is a major risk factor for valproate-induced severe hepatotoxicity, particularly in infants below 2 years old who are on polytherapy.[91] The risk of serious and non-serious skin rashes due to lamotrigine is also increased in young children, particularly in those with a history of AED-associated rash, rapid titration schedules, and concomitant treatment with valproate.[92]

In children, there are also concerns about the long-term consequences of chronic AED therapy. Even modest cognitive side-effects in young children can have substantial consequences if they restrict the acquisition of academic skills.[88] The earlier in life that epilepsy begins, the lower the patient's subsequent mental abilities tend to be,[93] which could be a consequence of aetiology, greater seizure-induced damage, or diminished educational attainment. However, it is also possible that the tendency for these patients to have been treated with more AEDs with harmful cognitive and behavioural effects than patients with better mental performance could have also played a role.[94]

Adverse effects are particularly prominent in patients who receive polytherapy and are often the result of undesirable drug–drug pharmacokinetic or pharmacodynamic interactions; whether the increased toxicity is additive or supra-additive is unclear.[95] Furthermore, the association of toxicity with only the number of AEDs might be simplistic because it is the total AED load of a multiple regimen that is regarded as the main determinant of toxicity. A study in adults found no differences in the effectiveness of equal loads of carbamazepine monotherapy or a combination of valproate and carbamazepine.[96] Whether these results are applicable to children with refractory epilepsy who are on more than two AEDs has not been adequately tested.

The possibility of AED-induced aggravation of seizures is commonly unrecognised. Some AEDs aggravate seizures in a fairly predictable way when used against specific seizure types or syndromes—seizure aggravation is not paradoxical or idiosyncratic. Examples include the aggravation of absence and myoclonic seizures with carbamazepine, phenytoin, and vigabatrin, or worsening of seizures with lamotrigine in patients with Dravet syndrome. However, many examples of AED-induced seizure aggravation are paradoxical; for example, when a drug that is normally expected to reduce the frequency of seizures has the opposite effect. The converse is also seen; a drug that often aggravates seizures can, unexpectedly, prove effective. Therefore, until these mechanisms are better understood it is important not to be too rigid about when to avoid an AED.[97]

Monitoring of treatment

Children should be assessed soon after the start of treatment (4–6 weeks) and then on a regular basis, regardless of seizure control. A lifetime record of all AEDs taken should be kept by the patient and their medical advisers.[3]

Clinical follow-up: quality of life and adverse-effects questionnaires

Neurotoxicity is often overlooked and should be investigated soon after the start of treatment.[98] Children with refractory epilepsy and mental impairment are at particular risk of neurotoxicity but they might not be able to describe the side-effects, which might be interpreted as a lack of side-effects.[99] In addition, adverse effects on behaviour, cognition, memory, and motor ability can be similar to effects that are directly attributed to the epilepsy. Thus, it might be impossible to determine just by taking a history whether a symptom is due to epilepsy or an adverse effect to an AED. Systematic screening for the side-effects of AEDs can improve the identification of toxicity and guide changes to medication to reduce adverse effects and possibly improve quality of life.[100]

Measurement of quality of life is conceptualised as a broad assessment of well-being in various categories.[101] Screening of quality of life is hampered by the lack of validated questionnaires that can be used in routine clinical care, and it has been argued that most questionnaires just assess health and physical or social and psychological function, which are predictors of quality of life but not quality of life itself.[101,102] Current epilepsy-specific quality of life questionnaires are also criticised because they lack the sensitivity to detect the within-patient changes over time that occur either naturally or as a result of treatment changes.[102] Furthermore, the interpretation of quality of life scores requires a notion of what constitutes clinically important changes in instrument scores in individual patients.[103] Therefore, new scales that better assess improvements beyond the reduction in seizures need to be developed and applied to assess the effect of therapeutic interventions on actual quality of life.[102–105]

Blood tests

Routine blood screening is discouraged and might actually interfere with treatment. There is no evidence that systematic blood screening reduces the rate of idiosyncratic reactions, which are, by definition, unpredictable. Misinterpretation of minor abnormal results, which might not be necessarily attributable to

AEDs, might lead to unnecessary changes in AEDs in an asymptomatic patient.[3,106] However, blood tests should always be done in patients in whom toxicity is suspected and there are circumstances in which they are recommended even in asymptomatic patients. For example, haemostatic dysfunction can be found in

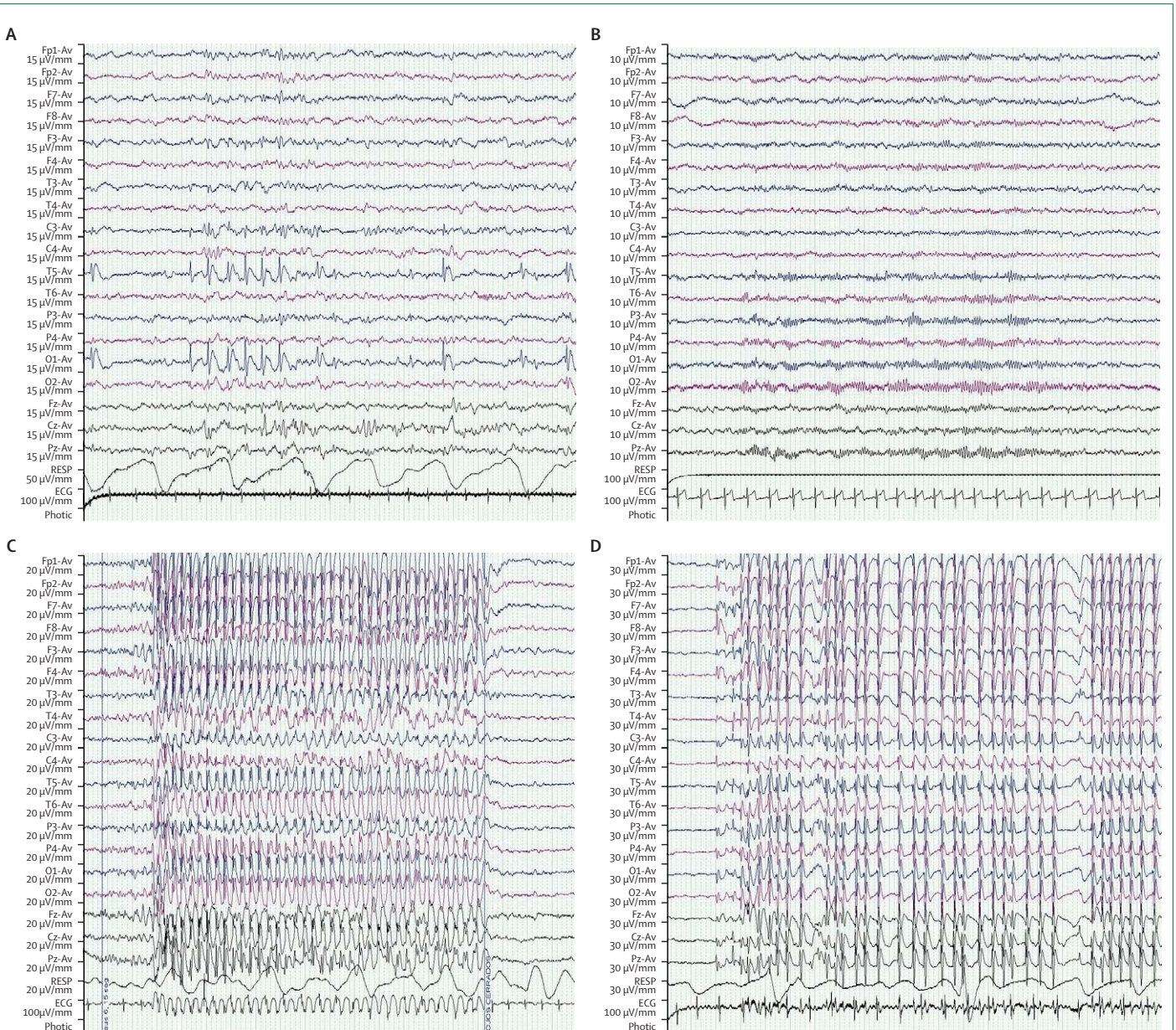

Figure: **Samples of conventional video-EEG in children with different epilepsy syndromes**

(A) Interictal EEG of a child with Panayiotopoulos syndrome. This previously normal 3-year-old girl had a single nocturnal seizure with prominent autonomic signs in September 2005. She has been monitored up to the present date, when this follow-up EEG was done. Despite the persistence of prominent subclinical epileptiform discharges over the left temporal-occipital region, no recurrence or other concerns have been raised. (B) Interictal EEG of a child with refractory temporal lobe epilepsy. Despite multiple AED trials, this 10-year-old boy had weekly focal seizures with impaired consciousness, pronounced oral automatisms, and frequent tonic–clonic generalisation. Brain MRI scans showed right mesial temporal sclerosis but interictal EEGs were repeatedly normal. He underwent right anterior temporal resection in 2006 and is currently seizure-free. (C) EEG sample of typical absence seizures. This 6-year-old girl was diagnosed with childhood absence epilepsy and was started on valproate. Her parents reported seizure cessation within the first few days of starting AED treatment. One month later, however, the video-EEG showed persistence of absence seizures, although they had become clinically less evident. The dose of valproate was increased, and she is now seizure-free and has a normal EEG. (D) Sleep EEG sample of continuous spike and wave syndrome. This 8-year-old boy was diagnosed with benign childhood epilepsy with centrotemporal spikes after three brief nocturnal rolandic seizures and an EEG that showed prominent spikes, predominantly over the left centrotemporal region. He was started on carbamazepine and, although no further seizures were noted, he was admitted to hospital 4 months later to evaluate his severe cognitive and behavioural deterioration. The EEG was compatible with continuous spike and wave syndrome, and his condition dramatically improved after substitution of carbamazepine with valproate.These traces show how the degree of EEG abnormalities might only be weakly related to the severity of epilepsy and add little in the case of clinical stability (A,B); conversely, the merit of EEG is highlighted in other cases, where it might have unquestionable value (C,D).

children who receive sodium valproate, and these parameters should be checked in every child who undergoes surgery.[107] Because of the risk of potentially serious haematopoietic and hepatic side-effects with felbamate use, regular monitoring of blood count and liver function is advised, although there is no clear evidence that this can prevent adverse outcomes.[108]

AED serum concentrations

Many clinicians routinely measure AED serum concentrations and modify the dose to achieve therapeutic concentrations under the assumption that seizures are more likely to be controlled and side-effects minimised.[98] However, no randomised controlled trials addressing the utility of regular monitoring of AED serum concentrations and subsequent serum concentration-guided dose modification have found them to be of any use.[109–111] By contrast, this approach might not only reduce the efficacy of AEDs by decreasing a well tolerated and effective dose in asymptomatic patients who have supratherapeutic concentrations but might also lead to more toxicity by increasing an effective dose in asymptomatic patients with infratherapeutic concentrations. Thus, the routine monitoring of plasma concentrations is costly and does not add valuable information if clinical stability has been achieved; however, routine monitoring might be useful to assess compliance and to explain recent changes in seizure frequency or tolerability, particularly in children on polytherapy where the problematic AED is unclear.[98]

EEG

EEG is essential for the correct diagnosis of an epilepsy syndrome and has an important role in the selection of an appropriate AED. However, in the absence of subsequent clinical changes (eg, a change in seizure pattern or cognitive regression) or a high risk of paradoxical aggravation (eg, in children on carbamazepine therapy who have extensive cortical dysplasias) EEG is of little use for monitoring treatment. Indeed, epileptiform discharges are weakly related to the severity of epilepsy, and it is commonly accepted that epileptiform discharges that are not accompanied by obvious clinical events are subclinical or interictal. Notable exceptions are epileptic encephalopathies, in which seizures might not be obvious but where subclinical seizures might influence outcome. In these cases, EEG monitoring is mandatory to guide the management and assess the response to therapy (figure).[20] However, if normalisation of the EEG requires polytherapy but the normalisation is not associated with an improvement in quality of life, then it is valid to ask whether polytherapy is appropriate.

Finally, EEG might help to evaluate the risk of seizure relapse after withdrawal of an AED. Despite some reports to the contrary, most studies report that an abnormal EEG before withdrawal of the AED is associated with an increased risk of relapse.[6,112–114] However, the significance of an abnormal EEG has to be qualified and should not preclude AED withdrawal in children with, for instance, benign childhood epilepsy with centrotemporal spikes, in whom normalisation of EEG is usually seen after clinical remission.[2]

Discontinuation of drug treatment

Commonly, AED therapy is maintained for at least 2 years of seizure-freedom, although the optimum time to discontinue an AED is not known.[115] This decision to stop an AED has to weigh the risk of recurrence against the potential side-effects of chronic and potentially unnecessary treatment;[116] when possible, the criteria on which this decision will be taken should be established soon to avoid the widespread treatment for life misconception, which does not apply for most children with epilepsy.

Overall, about 70% of children with epilepsy will be seizure-free 2 years after the withdrawal of an AED, and 80–90% of seizure recurrences occur within the first year after AED discontinuation.[117] Epilepsy syndrome seems to be the main determinant of the duration of therapy and the risk of seizure recurrence after discontinuation of an AED. For example, AED withdrawal could be done earlier in patients with clearly age-dependent syndromes and a low risk of recurrence, such as benign infantile convulsions,[118] whereas AED withdrawal should be deferred for several years or even indefinitely in patients with juvenile myoclonic epilepsy, in whom the recurrence after AED withdrawal is greater than 50%.[1,119] Unfortunately, most studies of AED withdrawal do not provide separate figures for recurrence on the basis of epilepsy syndromes, and other factors are inconsistently reported to modify the risk of seizure recurrence after withdrawal of an AED, such as the presence of multiple seizure types, age at onset, long duration of epilepsy, a known structural lesion, neurological abnormalities, and abnormal EEG, although the accurate prediction of individual outcome before withdrawal is problematic.[112,120,121] Reinstatement of AED treatment does not guarantee a complete nor an immediate return to complete seizure control. The reported risk of developing uncontrollable epilepsy ranges from 1% to greater than 20%, with the latter figure leading some authors to discourage AED withdrawal in patients with a higher-than-average risk of recurrence.[59,121,122] AED withdrawal is clearly another controversial issue in paediatric epileptology that must be mentioned in discussions about the risks of discontinuing AEDs in children with previously well controlled seizures.[121] The evaluation of such risks should, again, take into consideration the characteristics of the individual. For example, risk is negligible in children with childhood absence epilepsy but might be notable in some children with symptomatic focal epilepsies. A trial period off treatment might be important for seizure-free adolescents owing to concerns about seizure provocation at a later age when they are away from home or want to drive.

***Panel:* Summary of recommendations for the appropriate medical therapy of children with epilepsy**

1 Make a clinical diagnosis of seizure type, epilepsy syndrome, and additional impairments
2 Adopt a holistic approach for the best possible quality of life. Additional morbidity should be identified early and managed appropriately (eg, behavioural or psychiatric problems)
3 Consider possible outcomes according to the underlying aetiology or epilepsy syndrome
4 Set realistic goals with respect to seizure control
5 Select an AED not only on the basis of seizure type or epilepsy syndrome but also on the patient's characteristics, such as age, comorbidities, and concomitant treatments
6 Individualise the dose of AEDs on the basis of response and tolerability
7 Use one or two AEDs in monotherapy, with structured time frames to assess whether the AED is effective. If a seizure-free state is not reached, avoid maintaining an ineffective AED regimen because, in theory, it is the appropriate one, and consider whether the child has refractory epilepsy
8 Systematically screen for AED side-effects
9 Avoid systematic blood testing, blood concentrations, and EEG as "per protocol", ie, avoid putting more emphasis on "visiting the complementary exams" rather than exploring the well-being of the child
10 Weigh the reduction of frequency or severity of seizures against the side-effects of AEDs (ie, use effectiveness rather than efficacy as an outcome measure)
11 Avoid overtreatment—when an AED is ineffective at the maximum tolerated dose reduce the dose until further dose reductions are precluded by unacceptable increases in seizure frequency or severity
12 Rule out causes of pseudoresistance (ie, pseudoseizures, accuracy of seizure or syndrome classification, compliance with medication, ensure that the maximum well tolerated dose has been used, presence of negative lifestyle factors) and consider the possibility of AED-induced aggravation
13 In the case of definite refractory epilepsy, consider monotherapy with the best tolerated and the most effective AED and non-drug treatments, such as surgery
14 Avoid the paternalistic approach (ie, not allowing children and carers to take part in the decision-making process)

There is little evidence with regard to the optimum rate of AED tapering, although the recommendations state that the AED should be withdrawn slowly—over a period of at least 6 weeks—to reduce the risk of withdrawal-associated seizures,[123] and reduction should be particularly slow for benzodiazepines and barbiturates.[3]

Conclusions

In this Review, we have summarised the principles of medical management for children with epilepsy and we have highlighted several areas that remain problematic (panel). Problems of quality of life remain at the clinical level because the currently available quality of life scales are inadequate. Therefore, clinicians should not only investigate problems of seizure frequency but also the well-being of the child and their family, whether appropriate social and educational support are available (eg, respite care and government allowances), and assess whether there are interventions that could improve well-being. In the era of evidence-based medicine, it is noteworthy that the management of epilepsy in children is still largely guided by personal experience and expert opinion rather than by high-quality evidence. Owing to the size of the problem, there is a need for further comparative, pragmatic, and long-term clinical trials in which the actual effect of AEDs on quality of life is assessed, ideally on specific populations of children with more precise selection criteria and clear-cut epilepsy syndrome diagnoses. Data provided by such studies should not only fulfil the needs of the regulatory bodies but also provide clinically relevant information that might ultimately lead to improved quality of life for children with epilepsy.

Search strategy and selection criteria

References for this Review were identified by searches of MEDLINE up to October, 2007, with the search terms "adverse effect", "antiepileptic drug", "children", "cognition", "epilepsy", "guidelines", "management", "monitoring", "neuropsychological", "side-effect" and "treatment". References were also identified from relevant review articles and through searches of the authors' files. Only papers published in English were reviewed. The final reference list was generated on the basis of the relevance to the topics covered in the Review.

Contributors
All authors contributed equally to the preparation of the Review.

Conflicts of interest
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