Assessing risk to benefit ratio in antiepileptic drug therapy

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Abstract

Assessment of risk to benefit ratio in patients with epilepsy is crucial in determining the need for treatment, the choice of drugs and the use of monitoring tools such as laboratory tests and other investigations. Active epilepsy per se carries significant risks in terms of increased mortality, susceptibility to psychopathology and physical injury, and reduced quality of life as a result of restricted lifestyle, stigma and prejudice. By preventing the occurrence of seizures, antiepileptic drugs (AEDs) attenuate or eliminate altogether seizure-related risks, but other risks may arise due to the side effects of the drugs, all of which have a relatively narrow therapeutic index. While there are no major differences in the degree of efficacy between AEDs which are effective in any given seizure type, side effect profiles differ considerably from one agent to another and represent a major factor in determining choice of treatment. Assessment of risk to benefit ratio should also take into consideration patient-specific factors such as type and severity of the epilepsy, age, sex, childbearing potential, medical and drug history, associated disease, use of concomitant medication (including the contraceptive pill) and the prospected patient's compliance. In some benign epilepsy syndromes, such as idiopathic partial epilepsy with centro-temporal spikes, the risk of side effects from AEDs may outweigh potential benefits in terms of seizure control, and treatment is generally not indicated. At the opposite end of the spectrum, the serious morbidity and mortality associated with severe epileptic encephalopathies, such as the Lennox–Gastaut syndrome, justifies aggressive treatment even with drugs associated with a relatively high risk of life threatening side effects such as felbamate. The present article will provide an overview of specific risks associated with epilepsy and with the various drugs used for its treatment, and will attempt to evaluate the complex balance between these risks and therapeutic benefits in different categories of patients. © 2000 Elsevier Science B.V. All rights reserved.

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1. Introduction

Most life decisions are governed by an assessment (conscious or unconscious) of the consequential risk and benefit, and treatment decisions in epilepsy are no exception. In this, as in other fields, assessment of the risk to benefit ratio is difficult. It has to be made on the basis of information which is often incomplete and it must account for disease, personal and treatment factors which are themselves often neither quantified nor predictable. It is furthermore a subject that has seldom been addressed in any synoptical fashion in the epilepsy literature.

The purpose of this article is to consider and weigh those factors that have a major impact on the risk to benefit equation when deciding whether to treat and which drug to offer as treatment. By reviewing the relevant literature and highlighting those areas where this is deficient, we hope to illuminate and clarify a topic of self-evident importance but one that has been previously largely ignored.

The risk to benefit equation is influenced by the stage of the epilepsy, its severity and its type; the age of the sufferer; associated medical factors; nature of the drug being proposed for treatment; the patient's individual aspirations, and what aspects of morbidity are being encompassed. Some conclusions will be firm, and some tentative, but we hope that this paper will allow the physician and the patient to understand better the basis for rational prescribing.

2. Risks associated with uncontrolled epilepsy

2.1. Mortality

Epilepsy is a potentially life-threatening condition, a fact which is often overlooked. The risk of death, which is obviously an important element in the risk–benefit assessment, varies with factors such as the etiology of the epilepsy and the frequency and type of seizures. Severe childhood epilepsy syndromes often have a high mortality that is usually related to the underlying cause. By contrast, in absence epilepsy or partial epilepsies, overall mortality rates in small studies did not differ from those found in the general population (Hauser et al., 1980).

2.1.1. Incidence of death associated with epilepsy

2.1.1.1. Newly diagnosed epilepsy. Mortality rates in 564 patients with newly diagnosed epilepsy were investigated by Cockerell et al. (1997). Overall, 161 (29%) patients died after a follow-up of at least 6 years. The standardized mortality ratio (SMR), defined as the ratio between the number of deaths observed in the test group compared with that found in an age- and gender-matched general population, was 3.0. SMR was highest in the first year after diagnosis (6.6) and fell to 1.3 after 6 years. Because the excess mortality in the early years is due almost entirely to the underlying disease and not the epilepsy itself, AED treatment is unlikely to have much impact on mortality rates at this stage.

2.1.1.2. Chronic active epilepsy. In contrast to new-onset epilepsy, much of the excess mortality in patients with chronic active epilepsy is seizure- or epilepsy-related. Because risk is much greater in convulsive seizures, and in patients with frequent seizures (Nashef and Shorvon, 1997), successful AED therapy could have an important preventive role.

Several studies provide a framework for establishing risk in different populations. In a mixed population of 9061 patients with epilepsy identified by the fact that they had at one time been admitted to hospital, with a retrospective follow-up of 53 520 patient-years, overall SMR was 3.6 (95% C.I. 3.5–3.7) (Nilsson et al., 1997). Among 601 adult outpatients attending tertiary referral clinics during calendar year 1990, and followed for over 3 years, SMR was 5.1 (95% C.I. 2.9–3.1), with 24 deaths being recorded in 1849 patient-years of follow-up (Nashef et al., 1995a). Most patients in this population had long-standing intractable partial or secondarily generalized seizures. Of the 24 deaths, 14 were seizure-related, and 11 of these were classified as sudden unexpected death in epilepsy (SUDEP). The incidence of SUDEP was approximately 1:200/year, and

1:100/year in patients aged between 15 and 34 years. At a rough approximation, one can estimate that in an outpatient adult population one in every 2139–5000 convulsive seizures will result in SUDEP (Shorvon, personal communication).

Information on death rates in children with epilepsy is limited. In a community-based study in Nova Scotia, mortality rates among 693 children who developed epilepsy between 1977 and 1985 were determined after a follow-up of 14–22 years (Camfield and Camfield, 1999). Death rates over this period were 0/97 for absence epilepsy, 12/511 (2%) for partial and primarily generalized seizures, and 9/36 (25%) or 4/49 (8%) for secondarily generalized seizures with onset before or after 1 year of age respectively. Only one patient died from probable SUDED, and did so at 21 years of age, suggesting that SUDEP is rare in an unselected population of children with epilepsy. All other deaths were from comorbidity, homicide or suicide. In another pediatric community-based study, Harvey et al. (1993) found that mortality rates associated with symptomatic epilepsy were 50-fold higher than in the general population, but there was no increased mortality in idiopathic epilepsy. Mortality rates are particularly high in severe myoclonic epilepsy in infancy (Dulac and Arthuis, 1982) and, more generally, in severe childhood epilepsies associated with learning disability. In a study which surveyed 310 children in a residential school over a 23-year period, with a mean follow-up of 13.3 years (equal to 4135 person-years), SMR was 15.9 (Nashef et al., 1995b). Most of these children had very severe epilepsy and additional mental and neurological handicaps. Of 28 deaths recorded during the follow-up, 20 were seizure-related and, of these, 14 were classified as SUDEP. The SUDEP rate was 1 in 295 person-years. Therefore, seizure type and syndrome are important factors in assessing death risk.

Two recent studies compared mortality rates in patients who underwent epilepsy surgery. Sperling et al. (1999) found that patients with recurrent seizures postoperatively had a SMR of 4.69, with a risk of death of 1.37 in 100 person years, whereas mortality rate among patients who became seizure free was comparable to that seen in age- and sex-matched non-epileptic controls. It was concluded that the long-term risks of continuing unsuccessful AED treatment are higher than the risk of epilepsy surgery in suitable candidates. Hennessy et al. (1999) found a SMR of 4.5 in patients after temporal lobe epilepsy surgery, suggesting that surgery lowers, but does not normalize the overall mortality associated with chronic epilepsy. This study found a less clear relationship between postoperative seizure control and mortality rate.

2.1.2. Causes of death in epilepsy

Based on underlying etiology, deaths associated with epilepsy can be classified into three categories: (1) those caused directly by the seizures, such as accidental death and, probably, SUDEP; (2) those related indirectly, or only partly, to epilepsy, e.g. suicide; and (3) those due to other factors, including the underlying causes of the epilepsy. Successful AED therapy should prevent deaths belonging to the first category, it could reduce the incidence of the second category, but it will have no preventive effect in the third category.

2.1.2.1. Seizure- and epilepsy-related deaths. Although its precise pathophysiological mechanisms remain unclear, SUDEP is likely to be seizure-related, and it is by far the most common cause of death in this category (see Section 2.1.1). Risk factors for SUDEP include high seizure frequency, symptomatic epilepsy, convulsive seizures, learning disability, seizures during sleep and unwitnessed seizures, young age (Nashef and Shorvon, 1997), AED polytherapy (Nilsson et al., 1999) and preexisting cardiac pathology (Natelson et al., 1998). SUDEP is rare in partial seizures without secondary generalisation, and it does not occur in absence seizures. By reducing seizure rate, AEDs should also reduce the frequency of SUDEP, but this assumption has not been formally tested.

Death rate in status epilepticus depends on the definition of status. Mortality rates of over 20% are expected for cases admitted to an intensive care unit, but death is usually due to the underlying cause (Shorvon, 1994). Status accounts for

less than 2% of deaths among people with epilepsy, and it is comparatively more common in children, especially those with learning disability.

The risk of traumatic death is greatly increased in epilepsy. Among the 9061 patients with epilepsy surveyed by Nilsson et al. (1997) and identified by the fact that they had at one time been admitted to hospital, SMR for accidental death and poisoning was 5.6 (95% C.I., 5.0–6.3). Death is usually the result of an accident during a seizure, with drowning being one of the leading causes (Hauser et al., 1980; Spitz, 1998). Drowning accounted for 11 of 14 accidental deaths over a 10 year period in one study (Krohn, 1963), and for 17 (19%) of 90 deaths in which epilepsy was mentioned on the death certificate in another study (Blisard and McFeeley, 1988). In Florida, 58 of 2381 drowning deaths recorded in a 5-year period were seizure-related: these affected especially adults between 25 and 34 years of age and occurred most frequently in bathtubs and swimming pools (Ladd and Pryor, 1999).

Because epilepsy is associated with an increased risk of depression, suicide may be considered partly epilepsy-related. Indeed, suicide rate is increased in certain subgroups of people with epilepsy, and this is partly due to overdose with AEDs. Suicide is said to account for between 2 and 10% of all deaths in epilepsy (Nashef et al., 1995c). SMR from suicide was 3.5 (95% C.I., 2.6–4.6) in the study by Nilsson et al. (1997), whereas Barraclough (1987) found a 25-fold excess risk in temporal lobe epilepsy. The literature, however, is rather contradictory, and two population-based studies did not find an increased suicide rate among people with epilepsy (Hauser et al., 1980; Cockerell et al., 1995). Some AEDs, including phenobarbital, appear to be implicated as a potential cause of severe depression, and may therefore contribute to an increased incidence of suicide (Brent et al., 1987).

2.1.2.2. Non-seizure related deaths. As mentioned above, there is no reason to predict that non-seizure related deaths can be prevented by AED therapy. Indeed, the reverse may be true in two regards. First, there is a theoretical possibility that AED-induced cardiac conduction defects can result in sudden death, including death in the immediate post-ictal period, although this has not been systematically studied. Although there are case reports of AED-induced cardiac arrhythmia, these are rare and they are not likely to be a major factor in the risk to benefit analysis for most patients. Secondly, there is a possibility that AED therapy predisposes to neoplastic disease (White et al., 1979; Shirt et al., 1986; Olsen et al., 1989; Klenerman et al., 1993). Several studies, including some population-based, have reported increased SMR, 1.5–3.4, for neoplasms also when CNS tumors have been excluded (Hauser et al., 1980; Cockerell et al., 1995; Nilsson et al., 1997; Shackleton et al., 1999). These observations point to an association between epilepsy, and possibly AED therapy, and increased mortality in neoplasms, however, without evidence for a causal relationship.

2.2. Morbidity

That epilepsy should result in higher rates of morbidity is unsurprising. Studies have concentrated on accidents and injury, psychiatric and social morbidity and quality of life. Most data refer to selected patient cohorts, and most show higher rates in patients with epilepsy, although in one major clinic-based study the overall risk of accidental injury among 833 epileptic adults and children was not much greater than that found in matched healthy controls (Beghi and Cornaggia, 1997). In studies showing increased risk, factors leading to a higher incidence of accidents, fractures, head injury and burns were a high seizure frequency, seizures with falls or loss of consciousness, and severe seizures. This is important because treatment, by reducing seizure frequency or severity, may lower morbidity rates. It has to be emphasized, however, that there are no sound data on these potential benefits, except for a metanalysis of double-blind placebo-controlled add-on studies of levetiracetam in refractory partial epilepsy, whereby patients on active treatment had significantly lower rates of accidental injuries (Shorvon, S.D., personal communication). Other aspects of epilepsy, including the underlying neurological disease, stigma, and developmental

status, are also likely to influence morbidity rates but these may not be alleviated by AEDs. A final issue of relevance to the risk to benefit equation is that taking simple precautions without recourse to AED therapy could reduce many of the risks discussed below (e.g. accidents, burns, driving).

2.2.1. Spinal injury

Fractures of the vertebral bodies are common in convulsive seizures (crush fracture (Polatin et al., 1939)), occurring in 15–16% of patients in two series (Vasconcelos, 1973; Pederson et al., 1976). These fractures induce pain but no other disability.

Neurological deficit due to cervical cord injury in a convulsive seizure is a rarer but much more serious event. Seven cases were observed in about 3500 patient-years of follow-up in a residential centre for patients with severe epilepsy, which corresponds to an incidence of about one case per 500 patient-years (Allen et al., 1982). Cord injury can result in paraparesis or quadriparesis of varying degree, on occasions causing complete and permanent paralysis. Marked cervical spinal changes are found on radiology in many patients with severe epilepsy, presumably caused by repeated falls, and these predispose to the risk of spinal cord injury.

2.2.2. Head injury

Head injury is common in severe epilepsy and is usually relatively minor (Spitz, 1998). Most injuries result from falls during seizures, although there is also an excess of non-seizure related falls due to ataxia (sometimes drug-induced) and impaired balance which are also common neurological findings in patients with chronic epilepsy. In a 12-month survey of 255 patients with severe epilepsy in residential care, 27 934 seizures were recorded of which 12 626 (45.2%) were associated with falls (Russell-Jones and Shorvon, 1989). There were 766 significant head injuries, 422 requiring simple dressing and 341 sutures. There was one recorded skull fracture, and two post-traumatic hematoma, one extradural and one subdural. Thus, one in 37 falls resulted in the need for sutures and about one in 6139 falls in a potentially life-threatening intracranial hemor-

rhage. Fractures of facial bones are also common, although there are no authoritative estimates of frequency or severity. In a population-based survey of patients with at least one seizure per year, 24% reported a head injury and 10% a dental injury due to seizures in the previous 12 months (Buck et al., 1997).

2.2.3. Other accidental injuries

It has been estimated that in epilepsy fractures occur at a frequency of about one per person every 14 years, compared to a population risk of one per person every 50 years (De Silva et al., 1996). In the population-based survey referred to above, a fracture was sustained by 5% of the respondents in the previous 12 months (Buck et al., 1997).

In a study of childhood and juvenile absence epilepsy in Canada, the risk of accidental injury during an absence was 9% per person per year. Amongst these children, bicycle accidents were a particular problem (Wirrell et al., 1996).

Scalding or burning are also relatively common amongst people with epilepsy in all societies (Spitz, 1992; Spitz et al., 1994; Spitz, 1998). The risk depends upon social habits: in some African villages, epilepsy is known as the 'burn disease' because of the frequency of seizure-related burns incurred by falling into open fires. In Western societies, burns due to falls against radiators, eating or drinking hot fluids, during showering or during cooking are amongst the most common of all injuries. In a survey of 244 outpatients, 25 (12%) reported having been burned seriously enough to warrant medical attention and 12 (5%) required hospitalization (Spitz et al., 1994). In the population-based survey carried out by Buck et al. (1997), 16% of patients reported a burn in the prior 12 months.

The risk of accidents amongst motor vehicle drivers with a history of epilepsy has been extensively investigated. In an early study, the risk of accidents was about twice that amongst drivers without a history of epilepsy. Motor vehicle accidents causing injury occurred 1.6 times as often in patients with epilepsy in a study from Wisconsin (Hansotia and Broste, 1993). Up to 50% of blackouts or collapses at the wheel resulting in acci-

dents are due to epileptic seizures. This risk needs to be placed in perspective however, and in the study of Hansotia and Broste (1993) the excess risk associated with epilepsy accounted for only 13 of 5665 accidents over the four years of the study.

2.2.4. Psychiatric disorders

There is a huge and contradictory literature on the psychiatric risks of epilepsy. In summary, most studies suggest, at a rough approximation, that about one third to one half of people with epilepsy have psychiatric difficulties, in a broad and vaguely defined sense. The precise incidence depends on what conditions are included and what definitions are applied.

Psychiatric disturbances include depression, anxiety, psychosis, and personality disorders. In an older study, 28% of 245 patients with epilepsy in a general population reported psychosocial difficulties and overall psychiatric morbidity in epilepsy was estimated to range from 20 to 50% (Pond and Bidwell, 1959). In a reliable population-based study, the rate of psychiatric disorders among children with epilepsy was as high as 27% compared with 7% in the general population (Rutter et al., 1979). By contrast, in an adult referral population the prevalence of psychiatric disturbances was only mildly increased in patients with epilepsy (19 vs. 15%) compared with sex- and age-matched controls (Fiordelli et al., 1993). In a study of 512 persons with epilepsy in Iceland, 7% had been psychotic at some point in time (Gudmundsson, 1966). The more chronic or more severe the epilepsy, the higher the rate of psychiatric disorders. The causation of psychiatric disturbances in epilepsy is probably multifactorial and includes the biological effects of seizures, the genetic and neurological context of the epilepsy, the effects of drugs and social factors. Because some psychiatric morbidity will be alleviated and some caused by AED therapy, assessing risk and benefit is difficult in this situation.

2.3. Quality of life

People with epilepsy usually score lower on quality of life scales than do healthy controls.

Although a comprehensive review of the literature is beyond the scope of this article, studies have consistently shown that epilepsy results in decreased psychological adjustment, reduced social adjustment, reduced rates of marriage and fertility, higher rates of unemployment and underemployment, and educational underachievement (Hunt and McKenna, 1995). Comparative findings from different European countries support the concept that epilepsy has a considerable impact on driving and, to a lesser extent, on education, occupation, leisure activities and insurance. Social implications are partly related to the severity and to the clinical manifestations of epilepsy (Beghi and RESt-1 Group, 2000).

The effects of epilepsy on quality of life measures are considerably less in population-based surveys than in hospital-based studies. Of importance is the universal finding that seizure frequency is the most important single factor reducing quality of life. By reducing seizure frequency, AED therapy has the potential for improving quality of life and some short-term studies have indeed shown this. A recent study of 975 adults without learning disabilities found that scores in scales of depression, anxiety and eight quality of life domains were all significantly worse in patients with more than one seizure a month compared to those who were seizure free (Baker et al., 1997). Compared with seizure-free patients, patients with uncontrolled seizures had a higher prevalence of anxiety (44 vs. 13%) and depression (21 vs. 4%). There was a difference of 30% or more between the two groups in six of the quality of life domains.

2.4. Implications for long-term prognosis

In some animal models of epilepsy, with special reference to kindling (Goddard et al., 1969) and secondary epileptogenesis (Goldensohn, 1984), there is evidence that uncontrolled seizure activity leads, with time, to the establishment of a chronic, self-sustained epileptic condition. There is also evidence that this process may be associated with structural alterations, such as neuronal loss, rearrangement of neuronal circuitries, axon sprouting, proliferation of mossy fibers and sclerotic changes

in the hippocampus (Morrell, 1991; Cavazos et al., 1994; Leite et al., 1996; Bengzon et al., 1997). If either kindling or secondary epileptogenesis do occur in humans, it would make sense to start treatment as early as possible in order to prevent the progression and chronicization of the epilepsy. Moreover, there could be implications for drug choice, because in animal models some AEDs exert a putative anti-epileptogenic effect while others have a purely symptomatic action on the already established epileptic condition (Stasheff et al., 1989; Silver et al., 1991).

Whether repeated seizures can alter the long-term prognosis of epilepsy in humans has been hotly debated (Chadwick, 1995; Reynolds, 1995). Evidence has been presented that, in patients with temporal lobe epilepsy, the severity of hippocampal damage correlates with the duration of epilepsy (Salmenpera et al., 1998; Theodore et al., 1999; Tasch et al., 1999), with the estimated number of partial or generalized seizures experienced by the patient (Kalviainen et al., 1998; Salmenpera et al., 1998), and with a history of febrile seizures (Theodore et al., 1999). However, these changes may not be caused necessarily by repeated seizures (Sidodiya et al., 1998; Jefferys, 1999), and there are also findings suggesting that some underlying progressive disorder unrelated to seizures may itself be responsible for hippocampal sclerosis (Fernandez et al., 1998). The observation that patients with frequent seizures prior to treatment have a lower probability of achieving remission compared to patients with a pre-treatment history of fewer seizures has been interpreted as supporting evidence that repeated seizures lead to pharmacological intractability (Reynolds et al., 1983). However, it could also be argued that frequent seizures simply reflect a more severe epilepsy at the onset of the disorder, and that seizure recurrence has no effect on the ultimate prognosis (Chadwick, 1995). Indeed, population-based studies seem to suggest that in many patients epilepsy is a self-limiting condition. In a survey from Finland that included patients with at least two untreated unprovoked seizures (Keranen and Riekkinen, 1993; Shinnar, 1998), the probability of spontaneous remission was 42% at 10 years and 52% at 20 years. Spontaneous remis-

sion was reported in 30% of patients with untreated epilepsy in Poland (Zielinski, 1974). Community-based studies in developing countries also have documented relatively high remission rates in largely untreated patients (Osuntokun et al., 1987; Placencia et al., 1992; Watts, 1992), even though difficulties in patient tracing, an insufficient diagnostic ascertainment, and higher mortality rates may have biased estimates of the prognosis of untreated epilepsy in these populations.

More recent evidence does not support the view that early AED therapy prevents the development of chronic epilepsy (Shinnar and Berg, 1996). In two studies from Italy, no differences in prognosis was found between patients who had one versus two seizures (Musicco et al., 1997) or between those who had two–five versus six or more seizures (Collaborative Group, 1992) prior to initiation of AED therapy. In a Canadian pediatric study, having ten seizures or less prior to treatment had no influence on ease of control or ultimate remission rates (Camfield et al., 1996). In developing countries, administration of AEDs to patients whose epilepsy had not beed treated for many years produced response rates comparable to those achieved in newly diagnosed patients in more economically developed countries (Feksi et al., 1991). Finally, studies looking at the long-term consequences of early prevention of acute post-traumatic seizures, acute postcraniotomy seizures and febrile seizures failed to demonstrate any protective effect on the subsequent risk of developing epilepsy (see Section 4.1).

Based on these data, the currently predominant view is that the outcome of most forms of epilepsy is determined primarily by etiology and syndromic classification, irrespective of time at which AED treatment is initiated (Sander, 1993; Shinnar and Berg, 1996). According to Sander (1993), epileptic syndromes can be divided into four main groups depending on ultimate outcome. The first group, that includes benign partial epilepsies and epilepsies with seizures precipitated by specific modes of activation, is characterized by excellent prognosis, to the extent that treatment may not be required. The second group includes epilepsies with good prognosis (childhood absence epilepsy,

epilepsy with nonspecific generalized tonic-clonic seizures, some localization-related epilepsies), which can be easily controlled by treatment and tend to remit spontaneously. The third group, that includes juvenile myoclonic epilepsy and most localization-related epilepsies, is characterized by an uncertain prognosis and the associated seizures, which may be controlled by AEDs, tend to relapse when treatment is stopped. The fourth group encompasses epileptic conditions with bad prognosis (epilepsies associated with congenital neurological deficits, progressive neurological disorders and some symptomatic or cryptogenic partial epilepsies), in which seizures tend to recur despite intensive treatment. The above classification could be complemented by including an additional group represented by epilepsies that are easily controlled and disappear around the end of the first decade, but are associated with persisting cognitive impairment of variable degree: these comprise syndromes with major spike and wave activity during sleep, Landau–Kleffner and epileptic encephalopathy with continuous spike waves in slow sleep.

While the evidence discussed above argues against a major impact of available treatments on the natural course of epileptic disorders, some specific conditions exist in which early effective treatment probably does improve the ultimate prognosis. The best examples may be provided by West syndrome and other early childhood myoclonic encephalopathies associated with progressive cognitive decline. In these conditions, achievement of early seizure control seems to be important, even though it has been suggested that its ultimate benefits may relate to cognitive outcome rather than long-term seizure control (Shinnar and Berg, 1996).

3. Risks associated with AED therapy

3.1. Life-threatening side effects

Life-threatening adverse effects are rare with all major AEDs. In the vast majority of cases, fatal outcome results from idiosyncratic or hypersensitivity reactions affecting the bone marrow, the liver, the skin or other organs.

Serious manifestations of bone marrow toxicity such as agranulocytosis or aplastic anemia have been described with most AEDs but, if exception is made for felbamate, they are exceedingly rare. The package inserts of some drugs, most notably carbamazepine, contain prominent warnings about bone marrow suppression and many physicians feel disoriented when confronted with this information. Several studies, however, indicate that hematological toxicity has been overemphasized for most of these drugs and the risk of serious reactions is actually low. For carbamazepine, this has been set at about 1:200 139 for aplastic anemia, 1:700 000 for agranulocytosis and 1:450 000 for death associated with these events (Pellock, 1987). Among major AEDs, felbamate is the only agent for which the risk of bone marrow suppression is so high as to restrict severely its clinical use. The incidence of aplastic anemia with felbamate may be as high as 1:2000 or 1 in 5000 (Pennell et al., 1995), though a more recent estimate considered more likely a risk of 1:4800 to 1:37 000 (Kaufman et al., 1997). Regular hematological checks are mandatory after starting felbamate, but to date the number of patients who underwent intensive monitoring is insufficient to determine whether these checks can reduce the risk of fatal outcome from aplastic anemia.

The drugs most commonly implicated in fatal hepatotoxicity are valproic acid and felbamate. At least 132 patients have died of valproate-induced liver failure and/or pancreatitis, the highest risk (1:600) being found in children under 2 years of age with complex neurological disorders receiving polytherapy (König et al., 1994; Bryant and Dreifuss, 1996). In older patients the incidence is no more than 1:37 000 for monotherapy and 1:12 000 for polytherapy, and fatalities beyond 20 years of age are exceedingly rare. For felbamate, the overall incidence of fatal liver toxicity has been estimated at 1:26 000 to 1:34 000 (Pellock and Brodie, 1997). Serious hepatotoxicity has been reported occasionally with other AEDs. With phenytoin, carbamazepine, phenobarbital, primidone and lamotrigine, this usually occurs as part of a hypersensitivity reaction accompanied by skin rashes and fever in the early weeks of

treatment. Once hepatotoxicity develops, mortality rates are 10–38% with phenytoin and about 25% for carbamazepine (Battino et al., 2139). Repeated indiscriminate monitoring of liver function tests is not indicated in patients taking most AEDs, and greater attention should be focused on recognition of high risk groups (Section 5.3) and supply of information about symptoms of incipient hepatic failure (Schmidt and Siemes, 1998).

The anticonvulsant hypersensitivity syndrome is a potentially fatal reaction to arene oxide producing anticonvulsants such as phenytoin, carbamazepine and phenobarbital (Vittorio and Muglia, 1995; Schlienger and Shear, 1998). It occurs in one out of 1000–10 000 exposures and its main manifestations include fever, rash and lymphadenopathy accompanied by multiorgan system abnormalities. Cross-reactivity among drugs is as high as 70–80%. The reaction may be genetically determined and siblings of affected patients may be at increased risk. Outcome depends on rapid discontinuation of the offending agent and care of conjuntival and skin lesions.

Stevens–Johnson syndrome and Lyell's syndrome are the main serious cutaneous reactions to AEDs. Lamotrigine, phenytoin, carbamazepine and barbiturates are most commonly involved. For Stevens–Johnson syndrome, the highest incidence (1:50 to 1:300) is observed in association with use of lamotrigine in pediatric patients, particularly when a high starting dosage is used or the child is comedicated with valproate, but this incidence seems to be decreasing following introduction of a slower rate of dose escalation. In adults, the incidence of lamotrigine-induced Stevens–Johnson syndrome is in the order of 1–1000 (Battino et al., 2000; Ruble and Matsuo, 1999).

Many other organs and systems may be affected by serious hypersensitivity reactions, but these are fortunately rare. Examples of life-threatening reactions not mediated by hypersensitivity include neonatal hemorrhage in the offspring of mothers treated with certain AEDs during pregnancy (a reaction prevented by vitamin K administration to the mother or to the newborn)(Zahn et al., 1998), severe bradyarrhythmias after intravenous phenytoin (Tomson et al., 1997), aspira-

tion pneumonia with nitrazepam treatment in young children (Rintahaka et al., 1999), and respiratory arrest following high-dose intravenous benzodiazepines (Battino et al., 2000). Fatal outcome has been observed as a result of drug–drug interactions: for example, deaths have resulted from hemorrhage in warfarin-treated patients when concomitant enzyme inducing AEDs were discontinued without adjusting the dosage of the anticoagulant (MacDonald and Robinson, 1968). Most of these adverse reactions can be prevented or minimized through knowledge of the underlying mechanisms and risk factors, and competent clinical management.

3.2. Other irreversible side effects

The best known example of an irreversible effect of AEDs is the production of fetal malformations following maternal exposure. Overall, the risk of major birth defects among babies born to drug-treated epileptic women is about 6–8% compared to 2–4% in the general population, and the difference is related, to a large extent, to the effects of AEDs (Lindhout and Omtzight, 1994; Steegers-Theunissen et al., 1994; Waters et al., 1994; Samren et al., 1997; Canger et al., 1999; Kaneko et al., 1999). Minor anomalies such as hypertelorism, epicanthal folds and hypoplasia of distal digital phalangia also occur more frequently in children of mothers with epilepsy, although the incidence varies markedly between studies. A delay in intrauterine growth has also been observed, but the available data are partly conflicting (Teramo and Hiilesmaa, 1982; Bertollini et al., 1987; Battino et al., 1999). None of the major anticonvulsants (phenytoin, carbamazepine, valproate and phenobarbital) is free from teratogenic potential, and there is no pattern of malformations that is specific for a given drug. However, facial clefts and congenital heart defects are somewhat more common with phenytoin and barbiturates, whereas neural tube defects such as spina biphida are more common with valproic acid (2–3% risk) and carbamazepine (0.5–1% risk). Some studies suggest that the incidence of fetal malformations increases with increasing dosages, number of drugs and, at least for valproic acid, increasing

peak serum drug concentrations (Kaneko et al., 1999; Lindhout and Omtzight, 1994; Samren et al., 1997; Canger et al., 1999; Kaneko et al., 1999).

Although some of the newer AEDs have little or no teratogenic potential in animal models, the predictive value of these studies with respect to human safety is uncertain and clinical data are insufficient to assess the effects of newer drugs on the development of the human fetus (Lindhout and Omtzight, 1994; Tomson et al., 1997). Apart from teratogenesis, the suggestion has been made that a child seemingly normal at birth may later show impaired physical or mental development as a result of prenatal exposure to certain AEDs, especially phenytoin and barbiturates (Scolnik et al., 1994; Reinisch et al., 1995; Koch et al., 1999). Available information, however, is inconclusive, mainly due to the small number of studies with long-term follow-up. The implications of second generation effects in the management of women of childbearing potential are discussed in Section 6.1.

Examples of irreversible adverse effects associated with postnatal exposure include (i) coarsening of facial features following long-term treatment with phenytoin in infancy and childhood (Falconer and Davidson, 1973); (ii) severe Dupuytren's contracture and some other connective tissue disorders in patients on phenytoin and barbiturates (Pojer et al., 1972); (iii) development of cerebellar degeneration in patients on phenytoin. The latter is characterized by permanent cerebellar deficits associated with Purkinje cell degeneration and astrocytic changes following prolonged exposure to phenytoin, but it has been occasionally described following a single episode of phenytoin intoxication (Kuruvilla and Bharucha, 1997). The actual incidence of this syndrome is unclear, but it is probably very rare in view of the large number of patients who are exposed to long-term phenytoin therapy. Furthemore, because seizures may also cause cerebellar damage, it is also possible that at least some of the reported cases are due to the underlying disorder rather than to phenytoin.

One seemingly irreversible effect which has caused special concern recently is the occurrence of visual field defects (VFDs) in patients treated chronically with vigabatrin (Eke et al., 1997; Wild et al., 1999). Typically, the defects affect mostly the peripheral fields, do not cause loss of visual acuity, and they may be associated with electroretinographic changes consistent with a reduced inner retinal cone response (Krauss et al., 1998). Severe symptomatic visual field constriction seems to be rare ($\leq 2\%$), but at perimetric testing asymptomatic VFDs have been described in as many as 13 out of 32 patients (42%) randomized to long-term vigabatrin monotherapy compared to none of 20 patients randomized to carbamazepine (Kalviainen et al., 1999). Since the disorder develops slowly, even patients with relatively severe constriction may partly compensate through adjustment in eye movements and therefore may remain unaware of their condition, even though their visual impairment could place them at risk in special situations, such as driving a car.

3.3. Reversible side effects

Hypersensitivity reactions range from mild maculo-papular rashes (affecting up to 15% of patients started on carbamazepine, lamotrigine or phenytoin) to serious but fortunately rare immune-mediated disorders such as systemic lupus erythematosus (Weinstein, 1980). In chronically treated patients, the most common side effects involve the central nervous system (CNS) and include cerebello-vestibular and oculomotor symptoms (ataxia, dysarthria, dizziness, tremor, diplopia, blurred vision and nystagmus), drowsiness, fatigue, impairment of cognitive function, and disorders of mood and behavior (Battino et al., 2139). Many of these side effects are dose-dependent and they are usually more prominent in patients on multiple drug therapy, although it has been suggested that neurotoxicity relates more to total drug load (in terms of sum of defined daily doses for each drug) than to the actual number of drugs taken (Deckers et al., 1997). Examples of chronic non-CNS side effects include cosmetic disorders (hirsutism, gum hyperplasia) with phenytoin, shoulder–hand syndrome with barbiturates, weight gain with valproate and vigabatrin, nephrolithiasis with topiramate, and endocrine disturbances with a variety of AEDs.

In different studies, the proportion of patients with side effects from AED therapy range from less than 10% to over 70% depending on ascertainment methods, characteristics of the patients, AED dosage and duration of follow-up. These effects may affect adversely quality of life to an important extent, especially in patients with refractory epilepsy (Gilliam et al., 1999). Although no single AED emerges as having fewer side effects than all the others, there are clearly important differences in the spectrum of adverse effects produced by specific agents (Battino et al., 2000). This clearly influences drug selection in the individual patient: for example, topiramate tends to cause weight loss and it may not be the best choice in a thin, anorexic patient, while the reverse is true for valproic acid.

It has been suggested that some of the newer AEDs are overall better tolerated than older agents, but this claim should be regarded cautiously because in many comparative studies the choice of titration schedules or dosing regimens were biased in favour of the innovative product (Perucca, 1996a). Moreover, clinical exposure to the newer drugs is still relatively limited and experience shows that it may take many years for important adverse effects to be discovered (Table 1).

4. Benefits associated with AED therapy

4.1. Seizure control

The efficacy of AEDs in suppressing and preventing seizures in most patients is remarkable. Several studies in the community or in referral patients reported 1 and 2-year remission rates of up to 98 and 78% respectively in the 5 years following initiation of treatment (Collaborative Group, 1992; Elwes et al., 1984; Cockerell et al., 1995, 1997). In addition to the obvious benefit in terms of suppression of the manifestations of the disease, there are reasons to believe that epilepsy-related morbidity and mortality may also be decreased by AED treatment (see Section 3).

Comparative trials have failed to detect important differences in efficacy between carbamazepine, phenytoin, phenobarbital, and valproate in patients with partial and/or generalized tonic-clonic seizures (Mattson et al., 1985, 1992; Richens et al., 1994; Heller et al., 1995; Verity et al., 1995; De Silva et al., 1996), although in one study phenobarbital was somewhat less effective than carbamazepine or phenytoin in controlling partial seizures (Mattson et al., 1985). Likewise, the efficacy of valproate against absence seizures is similar to that of ethosuximide (Callaghan et al., 1982; Sato et al., 1982). Most studies comparing old and new AEDs as monotherapy in newly diagnosed epilepsy also failed to detect differences in efficacy (Brodie et al., 1999; Perucca and Tomson, 1999; Steiner et al., 1999) or, when a difference in efficacy was found, this was not in favour of a new drug (Chadwick et al., 1999). Although the lack of a proven difference in efficacy does not always mean equivalence (Jones et al., 1996), these findings reinforce the view that choice between AEDs effective in a given seizure type should be based primarily on assessment of their comparative tolerability profile.

Table 1
Latency between the introduction of AEDs in the market and the discovery of important adverse effects

Drug	Adverse reaction	Incidence	Year of marketing	Year of discovery
Phenobarbital	Shoulder-hand syndrome	Up to 12%	1912	1934
Phenytoin	Rickets and osteomalacia	Up to 5%	1938	1967
Carbamazepine	Aplastic anemia	1:200 139	1963	1964
Valproic acid	Hepatotoxicity	1:600–1:50 000	1967	1977
Vigabatrin	Visual field defects			
	-Asymptomatic	30%	1989	1997
	-Symptomatic	Up to 3%	1989	1997

To date, there is no evidence that AEDs can prevent the development of epilepsy in patients with severe head trauma, brain surgery or other epileptogenic conditions (Shinnar and Berg, 1996; Temkin, 1999). While AEDs can prevent acute symptomatic seizures (i.e. seizures occurring in the proximity of the event) after head trauma, they have not been found to be effective in preventing late unprovoked seizures or post-traumatic epilepsy (Temkin et al., 1990; Shierhout and Roberts, 1998). In other studies, AEDs were not effective in preventing seizures in patients with head tumors (Glantz et al., 1996) or after neurosurgery (Foy et al., 1992), although a significant reduction in seizure frequency has been observed up to the 10th postoperative week (North et al., 1983). While some of these negative findings could be related to methodological drawbacks and inadequate sample size leading to low statistical power, it is clear that risk to benefit ratio is against prophylactic use of AEDs in most patients who never had an unprovoked seizure but are at increased risk of developing epilepsy.

Continuous pharmacological prophylaxis is also unwarranted in children older than 1 year who presented with febrile seizures (American Academy, 1999). In fact, the risk of these children developing epilepsy later in life is not affected by prevention of febrile seizures with benzodiazepines or phenobarbital (Knudsen, 1985; Wolf and Forsythe, 1989; Rosman et al., 1993).

4.2. Quality of life

The efficacy of AEDs is traditionally assessed by measuring their impact on seizure frequency and, sometimes, seizure severity (Baker et al., 1998). While these measures are regarded as gold standards in quantifying treatment benefits, seizure control does not always fulfil entirely individual needs in the patient's perspective. Seizure-related measures also fail to take into account the impact of AED side effects on patient's well being. Therefore, it is not surprising that in recent years quality of life measures have become a valid and important feature of clinical trials and medical practice (Cramer et al., 1983; Baker, 1995; Baker et al., 1998).

There is no doubt that AEDs can improve quality of life through their ability to control seizures. Complete seizure freedom is by far the most important predictor of improved quality of life (Van Hout et al., 1997). In patients who underwent epilepsy surgery, major differences in quality of life measures have been found between a state of complete seizure control and that of even a few minor seizures or auras (Vickrey et al., 1995). Whether the same holds true also for medical treatment has not been exhaustively investigated, but there is little doubt that complete seizure suppression should be always the ultimate goal (Walker and Sander, 1996).

Studies in patients with refractory epilepsy suggest that beneficial effects of AEDs on quality of life may be independent from the reduction in seizure frequency (Baker et al., 1993; Smith et al., 1993). One explanation may be found in the observation that certain AEDs attenuate the severity of the seizures (Smith et al., 1993), even though this has been little investigated. Another possibility is that some AEDs produce positive psychotropic effects, such as mood elevating or mood stabilizing actions. Indeed, preliminary studies seem to confirm that after adjusting for seizure frequency, age and gender, certain medications may improve quality of life measures to a greater extent than others (Gillham et al., 1996; Cramer et al., 1998). However, quality of life measures are still heavily dependent on subjectivity and, in their present form, they are not yet accepted by the regulatory authorities as primary end-points to test treatment efficacy.

4.3. Pharmacoeconomic considerations

The efficiency of diagnostic and therapeutic strategies must be confronted always with the limited resources allocated by governmental agencies and public and private institutions. These aspects are even more important in developing countries, where resources are significantly lower. Analysis of the costs of a medical intervention differs depending on whose perspective (patient, third party payer, health provider, or society) and which source of expenditures (medical and nonmedical costs or loss of productivity) is being

considered. All these factors should be included in the analysis of the costs compared to the efficacy of any medical intervention, including AEDs.

The new AEDs are significantly more expensive than conventional agents. A cost-minimization study comparing lamotrigine, gabapentin and vigabatrin failed to document differences in cost-effectiveness among the three drugs, although fewer adverse effects with gabapentin could explain the lower costs of the first year of treatment with this drug (Hughes and Cockerell, 1996). A cost analysis of epilepsy surgery versus vigabatrin in patients with refractory partial seizures showed that if the costs of surgery are distributed over the expected lifetime, its yearly cost is comparable to that of treatment with vigabatrin (Malmgren et al., 1996). Although some studies comparing old and new AEDs in newly diagnosed patients suggested that new drugs may be better tolerated (Perucca and Tomson, 1999), there is no evidence that this translates into cost savings or overall improved patient well-being. Long-term prospective studies are needed to determine how old and new AEDs compare in terms of efficacy, tolerability, costs, and health-related quality of life.

5. Factors affecting risk to benefit ratio

5.1. Epilepsy syndrome

As discussed in Section 2.4, syndromic form is a major determinant of long-term prognosis (Sander, 1993). This clearly influences the decision about risks to which the patient may be reasonably exposed. In self-remitting seizure disorders, most notably simple febrile seizures and idiopathic partial epilepsy with centro-temporal spikes (benign rolandic epilepsy), the condition is so benign that treatment is usually not justified. In fact, in most of these patients the benefit of controlling seizures is outweighed by the risk of adverse effects on cognitive function and behavior (Perucca, 1996b). Conversely, severe encephalopathies such as the Lennox–Gastaut syndromes, which is associated with high morbidity and mortality, warrant aggressive treatment and even drugs with a high toxicity risk such as felbamate

may be justified in these conditions (French et al., 1999).

5.2. Predictors of AED responsiveness

If patients showing the best response to individual drugs could be identified beforehand, the benefit to risk ratio of any AED would be significantly improved. Because the efficacy spectrum of AEDs differs, seizure type and syndromic form provide the most important predictors of response. Evidence, however, is accumulating that other variables, such as seizure etiology and MRI findings, may provide additional prognostic clues (Semah et al., 1998). For example, there is suggestive evidence that infantile spasms associated with tuberous sclerosis respond better to vigabatrin than spams associated with other etiologies (Chiron et al., 1997; Vigevano and Cilio, 1997). In preliminary studies, seizures associated with glial tumors responded well to tiagabine (Dean et al., 1998). The development of tools that allow prediction of response to individual AEDs is one of the greatest challenges in epilepsy research.

5.3. Risk factors

Identification of risk factors is of paramount importance to minimize the probability of adverse drug reactions. A comprehensive discussion of the many conditions that affect the susceptibility to specific adverse reactions to AEDs is beyond the purpose of this article. A number of examples are listed in Table 2, and others are discussed in the sections below. Certain disease states may represent contraindications to use of specific drugs, as in the case of some congenital metabolic disorders for valproate or intermittent acute porphyria for most AEDs. A good knowledge of clinical pharmacology is essential to avoid selection of the incorrect drug or inappropriate dosing regimen in these situations.

5.4. Alternative treatment options

It is clear that the risk to benefit ratio of a given treatment must be weighed against that associated with alternative management strategies. This is

Table 2
Examples of conditions leading to increased susceptibility to specific adverse effects of AEDs[a]

Drug	Adverse reaction	Predisposing condition	Reference
Carbamazepine	Liver toxicity	Old age	Horowitz et al., 1988
Phenytoin	Skin rashes	Malignant gliomas	Mamon et al., 1999
Valproate	Liver toxicity	Age below 2 years, metabolic disorder, polytherapy	Bryant and Dreifuss, 1996
Felbamate	Aplastic anemia	Autoimmune disease	Pellock and Brodie, 1997
Gabapentin	Behavioral disturbances	Mental retardation	Khurana et al., 1996
Lamotrigine	Skin rash	Valproate comedication	Li et al., 1996
Tiagabine	Sedation, dizziness, incoordination	Liver disease	Lau et al., 1997
Vigabatrin	Sedation, confusion, encephalopathy	Old age, impaired renal function	Haegele et al., 1988; Ifergane et al., 1998

[a] For some of the conditions, evidence should be regarded as preliminary.

true not only with respect to availability of other pharmacological agents, but also to alternative therapies such as epilepsy surgery, the ketogenic diet or vagal stimulation. At least in some countries, epilepsy surgery is considered far too late in the treatment algorithm. As a result of this, patients that could be cured readily by surgical intervention are unnecessarily exposed for many years to the adverse medical and social consequences of seizures and AED medication.

6. Risk to benefit assessment in special situations

6.1. Infants and children

6.1.1. Age-specific aspects of epilepsy-related risks

Seizures that occur in young children and exclusively at home, primarily during sleep, usually have no significant psychosocial impact on the child. On the other hand, in older children, the unpredictability of even infrequent seizures can be extremely difficult to cope with, and self-esteem has been shown to be directly related to seizure control in adolescents (Hopkins et al., 1988). Unjustified restriction of everyday life is common in children with epilepsy, and specific guidelines have been produced to minimize this problem (Commission, 1997).

The risk of seizure-related injuries is moderate in children. Among 138 children with epilepsy followed over a 10-year period, only six sustained seizure-related physical injuries, none of which produced sequelae (Ziegler et al., 1994). Four of these injuries were the first manifestation of epilepsy.

The neurological risk of repeated seizures is to produce progressive motor, sensorial or cognitive impairment. Brain damage and sequelae from short seizures are very unusual, and prospective studies failed to demonstrate any brain damage from short seizures (Ellenberg et al., 1986). However, while any neurological impairment resulting from repeated short seizures is generally reversible (Jambaqué and Dulac, 1989), this is not always the case: in Rasmussen syndrome, the contribution of seizures to deterioration seems to be significant (Dulac, 1996). In some conditions which can be diagnosed soon after birth, the risk of neurological worsening due to severe seizures in the 1st year of life may be prevented by early therapy, and pharmacological treatment may be considered even before the occurrence of a first seizure. One example is represented by tuberous sclerosis, where early therapy may be taken into consideration to prevent the occurrence of infantile spasms. In other instances and particularly in idiopathic partial epilepsy with centro-temporal spikes, repeated seizures pose no risk of brain damage or physical injury: in these cases, many

authors advise against treatment unless seizures become frequent enough to have psychosocial consequences (Ambrosetto et al., 1987).

A high risk of cognitive, motor or sensorial deterioration also characterizes epileptic encephalopathies, particularly West syndrome, Lennox–Gastaut syndrome, myoclonic-astatic epilepsy, and epileptic encephalopathy with continuous spike waves in slow sleep. Risk factors are determined by etiology, including tuberous sclerosis and perinatal infectious or ischemic brain damage. The cognitive risk is clearly reduced by AED treatment, provided it is chosen properly and administered early enough in the course of the disease. The mental impact of infantile spasms due to tuberous sclerosis has been shown to be partially reversible with vigabatrin (Jambaqué et al., 2139). Persistence of partial seizures without major cognitive effects represents a great improvement over persistence of generalized epilepsy with severe cognitive impairment. Epileptic encephalopathies represent another example of conditions where early preventive treatment may be considered, and a prospective controlled study on the impact of such treatment on long-term prognosis is clearly warranted.

The risk of serious sequelae following status epilepticus is related mainly to the underlying cause of the status (Maytal et al., 1989), and mortality is lower in children than in adults (Maytal et al., 1989). However, brain damage may be caused by the epileptic activity itself, and the occurrence of hemiconvulsion-hemiplegia syndrome is higher in the first year of life than in older children (Aicardi and Chevrie, 1970). In Sturge–Weber disease, prophylactic treatment has been suggested to prevent status epilepticus and hemiplegia as a result of a first seizure (Dulac et al., 1982; Salman, 1988). Other conditions at risk of hemiconvulsion–hemiplegia syndrome include tuberous sclerosis and callosal agenesis.

For febrile convulsions, views on the benefit to risk ratio of pharmacological treatment has changed significantly over the last decades. Chronic pharmacological prophylaxis after the first seizure is advised when the seizure occurred early, i.e. in the 1st year of life. An additional justification for starting chronic treatment in infants with early onset febrile seizures is the higher risk of severe epilepsy, that may be due to hippocampal atrophy after long-lasting focal febrile seizures or to development of severe myoclonic epilepsy in infancy (Dravet et al., 1992). After the first year of life, the risk of status epilepticus and severe epilepsy decreases, and the risk to benefit ratio is against chronic AED prophylaxis in children who had simple febrile seizures. Intermittent prophylaxis with diazepam during the febrile illness may be indicated in these older children (Knudsen, 1996).

6.1.2. Altered susceptibility to adverse effects

Valproate-induced liver failure affects mainly infants with intractable epilepsy receiving polytherapy, especially those with associated metabolic disorders. There is growing evidence that a number of these patients at risk for liver failure suffer from Alper's disease (Dreifuss et al., 1989; Dreifuss, 1995). Early recognition of liver failure, which is important to improve outcome, can be achieved by informing the parents that vomiting, somnolence or increased seizure frequency should call for immediate medical attention and measurement of prothrombin time and liver enzymes (König et al., 1994).

The risk of phenobarbital-induced mental deterioration is increased in children. As confirmed by experimental data (Mikati et al., 1994), risk is greater in the presence of brain damage, but children without preexisting brain damage may be also affected (Vining et al., 1987; Farwell et al., 1990). Hyperactivity can be a major side effect of many AEDs in school age children and it is particularly prominent with phenobarbital (Vining et al., 1987) benzodiazepines and, to a lesser extent, with vigabatrin (Dulac et al., 1991) and gabapentin (Mikati et al., 1998). For the latter drugs, a previous history of hyperkinesia or psychomotor retardation are major risk factors.

Carbamazepine-induced intermittent ataxia is particularly marked in infants after intake of syrup formulations which produce high postabsorptive peaks in serum drug concentrations, especially when high doses are ingested to compensate for the high drug clearance in this age group (Liu and Delgado, 1994). The carba-

mazepine-10,11-epoxide to carbamazepine ratio is particularly high in infants and children, and this metabolite can contribute to adverse effects. Carbamazepine intoxication in children may be caused by metabolic interactions with frequently prescribed comedication, particularly macrolide antibiotics (Mesdjian et al., 1980).

Lamotrigine-induced mild skin rashes are particularly frequent in children, partly because valproate comedication (an identified risk factor) is common in these patients (Schlumberger et al., 1994), particularly those with generalized epilepsies which may benefit from the combined use of these drugs (Ferrie and Panayiotopoulos, 1994). The risk of Stevens–Johnson syndrome from lamotrigine is also much higher in children than in adults (see Section 3.1).

The tolerability profile of many other AEDs differs in children compared to adults. A major risk of sudden death due to pharyngeal hypotonia affects children given nitrazepam doses over 0.7 mg/kg (Lim et al., 1992). Acute but insidious intoxication is a frequent complication of phenytoin treatment in newborns and young infants (Sicca et al., 2139). The cosmetic side effects of phenytoin (gingival hyperplasia, coarsening of facial features, hirsutism and acne) may be particularly troublesome in children and adolescents.

The occurrence of vigabatrin-induced irreversible visual field defects (see Section 3.2) is of special concern in young children in whom standard perimetric examination of the visual field cannot be performed (Wild et al., 1999). The precise incidence of these defects in a pediatric population exposed to vigabatrin is unknown, but it might be lower than in adults because no symptomatic case appears to have been reported to date in children despite extensive use of the drug in these patients and questioning by physicians. Provided that parents are made aware of this issue and that visual fields are assessed, whenever possible, before and at 6 months intervals during treatment, the fear of visual field defects should not preclude the use of vigabatrin in West syndrome, and in partial epilepsies with frequent seizures that do no respond to other drugs. Since vigabatrin-induced visual field defects appear to be related in part to the cumulative dose administered, limiting duration of treatment to the shortest necessary period may be crucial for a safer use of the drug.

6.1.3. Risks associated with inappropriate drug choice

Inappropriate drug choice may result in worsening of seizures and this seems to be more common in children, possibly because the seizure types involved are those associated more often with pediatric epilepsies (Guerrini et al., 1998a; Perucca et al., 1998). Absence and myoclonic seizures may be worsened by carbamazepine, phenobarbital, phenytoin, vigabatrin and, possibly, gabapentin. Drug-induced worsening seems to affect especially epileptic encephalopathies. Thus, carbamazepine may aggravate infantile spasms (Talwar et al., 1994), myoclonic-astatic epilepsy (Kaminska et al., 1999) and continuous spike waves in slow sleep (Lerman, 1986). Vigabatrin may aggravate myoclonic-astatic epilepsy (Luna et al., 1989), and lamotrigine may worsen severe myoclonic epilepsy (Guerrini et al., 1998b).

It must be emphasized that, in some instances, the initial seizure type presented by the child may be misleading. For example, atypical absence seizures may be caused by the syndrome of continuous spike-waves in slow sleep, which responds poorly to valproate and requires treatment with benzodiazepines (Marescaux et al., 1990; Roulet-Perez et al., 1993). The same syndrome may be precipitated by carbamazepine given after an initial seizure to children with benign partial epilepsy. In infants, severe myoclonic epilepsy often begins with unilateral or partial motor seizures, and may be worsened by carbamazepine. In the 1st year of life, only patients with proven localization-related epilepsy (based on focal neurological defects and neuroradiological data) should be given carbamazepine as a first-line drug. In children and adolescents, idiopathic generalized epilepsies associated with photosensitivity may produce visual illusions (micropsia, macropsia) or elementary hallucinations that are often considered to be a manifestation of partial epilepsy, leading to incorrect prescription of carbamazepine or phenytoin.

For childhood cryptogenic partial epilepsies and for infantile and childhood symptomatic partial epilepsies, the drug of choice is generally a sodium channel blocker such as carbamazepine. Valproate is preferred in other cases, unless a precise syndromic and etiologic diagnosis indicates more specific compounds, such as vigabatrin for infantile spasms, benzodiazepines for epileptic encephalopathy with continuous spike waves in slow sleep and ethosuximide for infantile absence epilepsy.

6.1.4. Risks associated with inappropriate management

There are many situations when risks arise out of incorrect clinical management. One example is the unnecessary modification of drug dosage in well-controlled patients simply because the serum concentration of the drug is outside the 'therapeutic range'. Many patients can be optimally treated at serum drug levels outside this range, and dosage should only be adjusted when there is a clear indication such as persisting seizures or signs of toxicity. Another common therapeutic error is the discontinuation of the AED when a mild increase in liver enzymes is seen shortly after starting treatment: unless other indicators signal otherwise, these minor abnormalities are not clinically relevant, even with valproate.

Failure to maintain adequate drug administration in patients temporarily unable to take oral medication may precipitate an increase in seizure frequency or even status epilepticus. Similarly, too rapid changes in AED treatment may increase seizure frequency, even when the drug did not seem to be helpful: this is particularly relevant with carbamazepine, phenobarbital, vigabatrin and clonazepam. Another incorrect practice is the prolonged prophylactic use of phenobarbital following occasional convulsions in the newborn. There are no obvious reasons to continue treatment when there are no persisting seizures or spikes in the EEG, and unjustified prescription over several months may cause problems when later these patients develop infantile spasms (Hellström-Westas et al., 1995).

In conclusion, it is important for each child to be given the correct medication at the right dosage and according to appropriate indications. For newer AEDs, indications in children are often difficult to define because regrettably adequate pediatric trials are seldom performed prior to registration. Even the limited data available from pediatric exposure are not reported in the package insert when use in children has not been approved officially by regulatory authorities. This lack of information (or lack of disclosure) may result in inappropriate AED use in children, with avoidable morbidity and even mortality risks.

6.2. Women of childbearing potential

For a woman intending to become pregnant, uncontrolled seizures not only jeopardize her own well-being but also impose risks on the fetus. Generalized tonic-clonic seizures may affect the fetus through lactacidosis, hypoxia or direct trauma during the seizure. Fetal asphyxia manifested by prolonged bradycardia has been recorded after maternal seizures (Teramo et al., 1979; Yerby, 1987). In addition, a case of fetal intracranial hemorrhage has been observed after a seizure (Minkoff et al., 1985). However, it seems likely that, in most cases, isolated seizures are harmless. Tonic-clonic status epilepticus is associated with fetal death in approximately 50% of the cases (Teramo and Hiilesmaa, 1982). Other seizure types such as partial seizures or absences are unlikely to have detrimental effects on the fetus. Unfortunately, assessment of fetal risks associated with maternal seizures mainly relies on case-reports, and we have no reliable estimates of the incidence of such adverse outcomes. However, from existing accounts, intrauterine death of a healthy fetus after a maternal seizure must be considered a rare occurrence. Whether maternal seizures have more subtle effects on the psychomotor development of the child or increase the risk for malformations has not been determined, but is is difficult to envisage what mechanisms might apply.

Maternal and fetal risks associated with uncontrolled seizures have to be weighed against the increased risk of adverse outcomes in the offspring imposed by maternal use of AEDs during pregnancy. Major malformations, minor anoma-

lies, intrauterine growth retardation and impaired postnatal psychomotor development have all been reported at increased rates among children exposed prenatally to AEDs (see Section 3.2). Although the pathogenesis of these adverse outcomes is multifactorial, available data strongly suggest that exposure to AEDs is the dominating cause for at least major birth defects (Lindhout and Omtzight, 1994; Steegers-Theunissen et al., 1994; Waters et al., 1994; Samren et al., 1997; Canger et al., 1999; Kaneko et al., 1999). Although, as discussed in Section 3.2, individual AEDs may differ in teratogenic patterns, as far as teratogenic effects in total are concerned, none of the established drugs can be claimed to be safer than others. The safety of the newer AEDs in this respect is also unknown (see Section 3.2).

Despite the documented teratogenicity of AEDs and the scarce documentation of risks imposed by maternal seizures, most physicians believe that uncontrolled tonic-clonic seizures present greater risks than drug therapy to the fetus, especially in late pregnancy. Hence, AEDs are indicated for the treatment of epilepsy during pregnancy if this is considered necessary to control tonic-clonic seizures. The risk to benefit equation may be slightly different for other seizure types during early pregnancy: however, although such seizures may not need to be treated as aggressively as tonic-clonic seizures, there is a risk that uncontrolled partial seizures undergo secondary generalization. Since evidence is lacking for major safety differences between drugs, the drug of choice should be the most appropriate for the patient's seizure type and epilepsy syndrome (Tomson et al., 1997). However, where there is a family history of neural tube defects, valproate and carbamazepine are best avoided. New AEDs should be used in women planning a pregnancy only when they are considered as the most efficacious and best tolerated in the individual patient. Whenever possible, AEDs should be used in monotherapy and at the lowest dosage and serum level that protects against tonic-clonic seizures. Folic acid administration is also recommended, and should be started preferably before conception. Any major change in drug therapy should also be accomplished before conception, and drug withdrawal should be considered before pregnancy in women who have been seizure free for more than 2 years. Should this not be possible, titration to the lowest effective dose or conversion from polytherapy to monotherapy should be attempted. When pregnancy is established, the risks associated with drug withdrawal or changes between drugs probably outweigh potential benefits to the fetus.

The above considerations underline the importance of planning pregnancies and the issue of effective and reliable contraception. The potential for enzyme inducing AEDs to interact with contraceptive pills is discussed in Section 6.9.

Risk to benefit ratio may be influenced favorably by use of appropriate methods for prenatal diagnosis of malformations. Malformation-directed ultrasonography may detect more than 90% of neural tube defects and the majority of cleft lip/palate and heart anomalies. Determination of alpha-fetoprotein in maternal serum or in amniotic fluid may also be appropriate in selected cases (Tomson et al., 1997).

6.3. The elderly

Although in general the treatment of epilepsy in the elderly follows the principles that are applied to other adults, there are some age-specific issues that need to be taken into account.

Compared with seizure disorders with a younger age of onset, epilepsy developing after 60 years of age is more likely to be associated with partial seizures (Hauser et al., 1993; Forsgren et al., 1996a) and with a known etiology (Hauser et al., 1993; Forsgren et al., 1996a; Olafsson et al., 1996). Partial and remote symptomatic seizures are factors associated with a high recurrence rate after a first unprovoked seizure (Berg and Shinnar, 1991), and particularly high recurrence rates have been reported after a first seizure caused by stroke (Luhdorf et al., 1986). The elderly are thus likely to be at higher risk of recurrence after a single unprovoked seizure. Indeed, in a prospective population-based study, the recurrence rate after a first seizure among patients aged 60 or older was 83% by 36 months (Hart et al., 1990). The incidence of status epilepticus is also increased in the elderly (Hesdorffer et al., 1998).

Uncontrolled seizures are likely to be more hazardous in an elderly patient. The systemic effects of tonic-clonic seizures may impose higher risks in patients with cardio-respiratory disorders, and the old, fragile patient would be more susceptible to suffer from fractures as a consequence of seizure-induced falls. Although epidemiological studies indicate that SMRs among people with epilepsy are highest in the younger age groups, most studies demonstrated an increased mortality also in the elderly (Hauser et al., 1980; Cockerell et al., 1995; Nilsson et al., 1997). SUDEP is an issue mainly among young and middle-aged patients (Ficker et al., 1998), but mortality in status epilepticus is much higher in the elderly (De Lorenzo, 1997).

Old patients may have an increased sensitivity to the effects of AEDs, due to age-dependent changes in pharmacokinetics and pharmacodynamics. Pharmacokinetic changes may include a lower degree of drug binding to plasma proteins and decreased metabolic and renal drug clearance (Bernus et al., 1997; Scheuer, 1997). Most of these alterations can be managed with dose adjustments guided by therapeutic drug monitoring, with the important caveat that in elderly patients with hypoalbuminemia or impaired renal function the total concentration of highly protein-bound drugs such as phenytoin and valproic acid may underestimate the concentration of free, pharmacologically active molecules in the circulation. Pharmacodynamic changes also need to be taken into consideration. Older patients are more sensitive to sedation induced by benzodiazepines (Feely and Coakley, 1990), but information concerning more frequently used AEDs is scarce. Results of the Veterans Administration (VA) trials, comparing different treatments in adults with new onset seizures, showed that older patients were more likely to drop out because of adverse effects than younger patients (Ramsay et al., 1994; Ramsay, 1998). Adverse effects were quantitatively but not qualitatively different from those experienced by younger patients. Recently, a multicentre, double-blind trial compared the efficacy and safety of lamotrigine and carbamazepine in 150 elderly patients with newly diagnosed epilepsy (mean age 77 years)(Brodie et al., 1999). Lamotrigine (median dosage 100 mg/day) was similarly effective but better tolerated than carbamazepine (400 mg/day): in particular, patients on lamotrigine had a lower incidence of skin rashes (3 vs. 19%), somnolence (12 vs. 29%) and dizziness (10 vs. 17%), and drop-out rate for adverse events was 18% for lamotrigine compared with 42% for carbamazepine. These data suggest that lamotrigine may be a better choice for initial treatment in the elderly, although the toxicity of carbamazepine might have been overestimated by giving a non-sustained release formulation twice daily.

While dose-dependent adverse effects seem to be more frequent in the elderly, the VA studies also suggest that patients over 65 years of age are more responsive to AEDs than younger adults (Cloyd et al., 1994; Ramsay et al., 1994; Ramsay, 1998), and may respond well at lower serum drug concentrations and dosages. Unlike acute side effects, manifestations of chronic toxicity may be less likely in patients started on treatment late in life because overall drug exposure will be shorter in these patients.

Admittedly, there is suboptimal information for a rational assessment of the risk to benefit ratio of AED therapy in the elderly. If one considers the high recurrence risk after unprovoked seizures, the potential for serious consequences of uncontrolled epilepsy and the favorable response to conventional AEDs, treatment is generally indicated if an elderly patient develops recurrent unprovoked seizures. AED treatment should also be considered more often than in the younger patients after single unprovoked seizures. As always, individualized assessment is necessary, taking into account the possible complications of associated disease and comedication (Section 6.8 and Section 6.9). Whenever possible, treatment should be started with a low dose followed by slow titration according to response. Special caution is recommended in considering the possibility of withdrawing AED therapy in successfully treated elderly patients. In fact, the risk of relapse after drug withdrawal is probably higher in these patients in view of the high proportion of cases with a known underlying etiology in this age group (Berg and Shinnar, 1994a). Moreover, potential

benefits of successful AED withdrawal may be less marked in these patients.

6.4. Newly diagnosed seizure disorders

In patients who had a single unprovoked tonic-clonic seizure, the risk of recurrence is comparably lower (about 42% by 2 years)(Berg and Shinnar, 1991) than that following a second (73%) or a third seizure (76%) (Hauser et al., 1998). Because many patients who had a single seizure will not have a recurrence (First Seizure Trial Group, 1993) and because treatment after a first seizure does not improve long-term prognosis (Musicco et al., 1997), AED therapy is generally considered to have a favorable benefit to risk ratio after at least two seizures have occurred. Treatment after a first seizure may be considered in special situations, for example when prognostic factors (for example, the presence of interictal epileptiform EEG abnormalities and/or a known and persisting etiology of the seizures) indicate a high risk of recurrence, or when it is felt that the physical or psychosocial consequences of a recurrence outweigh the risks associated with chronic AED treatment (Beghi and Cornaggia, 1997; Beghi and Perucca, 1995). By contrast, treatment may be withheld in patients with seizures occurring at prolonged intervals (e.g. 12 months or longer) and in those epileptic syndromes with a very benign course and excellent prognosis (Beghi et al., 1997; Sander, 1993).

Despite differences in outcome between studies, about 50% of newly diagnosed children and adults achieve remission immediately after onset of treatment and another 20% or more enters remission after a limited number of seizure recurrences with or without treatment changes (Annegers et al., 1979; Collaborative Group, 1992; Elwes et al., 1984; Cockerell et al., 1995, 1997; Sillanpää et al., 1998). Patients with seizures caused by known epileptogenic conditions tend to have a lower rate of remission. The chance of remission does not seem to be significantly affected by factors such as sex, age, or abnormal EEG findings at the time of the diagnosis. The proportion of newly diagnosed patients with side effects leading to withdrawal of the initially pre-scribed AED varies depending on the drug, dose, and physician's and patient's attitude to side effects. Patients with mid-to-high serum AED concentrations tend to have higher rates of withdrawal (Mattson et al., 1985) than those with serum AED concentrations in the middle of the target ranges (Mattson et al., 1992).

Optimal initial maintenance AED dosages have not been precisely defined in newly diagnosed patients, but in most cases it is reasonable to aim at the lower end of the effective dosage range and, if necessary, make further adjustments based on clinical response (Beghi and Perucca, 1995). With most AEDs, escalation to the initial target maintenance AED dosage should be gradual to minimize potential intolerance. Most physicians regard carbamazepine as the agent of choice for the treatment of partial seizures, and valproate as the first choice for generalized epilepsies. Other AEDs, however, may be selected preferentially based on physician's preference, individual characteristics of the patient, and cost factors.

6.5. Well controlled epilepsy

In patients who achieved complete seizure control for at least 2 years (or even shorter periods in children) (Peters et al., 1998), the need to continue AED treatment should be evaluated. The possibility of gradually discontinuing AEDs is especially important in childhood epilepsies, many of which show higher rates of permanent remission compared to adult epilepsies (Pedley, 1988). In different studies, the overall probability of relapse following discontinuation of AED ranged from 10 to 60%, with a pooled estimate of 25% at 1 year and 29% at 2 years (Berg and Shinnar, 1994b).

The risk to benefit ratio of discontinuing AED therapy should be assessed on a case by case basis and discussed throughly with the patient or his/her family. Such evaluation should take into account the tolerability of treatment, the medical and psychosocial implications of seizure recurrence, and prognostic factors for relapse. Of these, syndromic form is probably the most important: relapse rates vary from close to 0% in idiopathic partial epilepsy with centro-temporal spikes to 0–25% in childhood absence epilepsy, 25–75% in

non-idiopathic partial epilepsies, and over 85% in juvenile myoclonic epilepsy (Beghi and Perucca, 1995). Other factors associated with an increased risk of relapse include a prolonged duration of epilepsy and a high seizure frequency prior to control, symptomatic epilepsy, associated neurological handicaps and epileptiform activity in the EEG (Berg and Shinnar, 1994a; Beghi and Perucca, 1995; Peters et al., 1998). Algorithms designed to help physicians in deciding indications for starting and withdrawing AEDs have been published (Beghi and Perucca, 1995).

6.6. Chronic refractory epilepsy

Although management strategies in patients with epilepsy refractory to initial monotherapy vary between and within countries (Baldy-Moulinier et al., 1998), increasing evidence indicates that these patients have an up to 30–50% chance of achieving seizure freedom with an alternative monotherapy (Hakkarainen, 1980; Tanganelli and Regesta, 1996; Camfield et al., 1997; Perucca, 1998). Because side effects are minimized with prescription of a single drug, the benefit to risk ratio is probably in favour of restricting the use of polytherapy to those patients who failed two or three sequential monotherapies at the maximally tolerated dosages (Perucca, 1997).

Randomized trials of new AEDs in refractory epilepsy demonstrated a statistically significant benefit when these drugs were added as second or third medication to patients uncontrolled by older agents (Kramer, 1997; Marson et al., 1997). However, the impact of these treatments on long-term prognosis is unknown and there is evidence that the majority of patients receiving new AEDs tend to stop them after a limited number of months or years (Sander, 1996). Despite these limitations, the use of new AEDs should be considered in patients refractory to other agents, with choice of specific agents being determined by their efficacy spectrum against different seizure types and their tolerability profile. While the suggestion has been made that combining AEDs with different modes of action may be advantageous, in practice current knowledge on the mechanisms by which AEDs exert their effects is insufficient to allow a fully rational approach to multiple drug therapy in epilepsy (O'Donoghue and Sander, 1997). In spite of this, clinical experience has indicated that some combinations seem to have a better therapeutic index than others, the best examples being the combination of valproate with ethosuximide in absence seizures (Rowan et al., 1983) or valproate with lamotrigine in partial and generalized seizures (Ferrie et al., 1995; Brodie et al., 1997; Pisani et al., 1999).

Prior to the discovery of visual field defects associated with its use (Kalviainen et al., 1999), vigabatrin was prescribed early in the therapeutic algorhitm for partial epilepsy. In view of its considerable efficacy against refractory partial seizures (Marson et al., 1997), this drug retains an important role in the management of epilepsy, but in adults its prescription, under close ophthalmological monitoring, should be reserved to partial epilepsies that failed to respond to other AEDs of the older and newer generations. The broader indications of vigabatrin in infants and children are discussed in Section 6.1.

A final comment is required about felbamate, whose use has been curtailed in recent years due to the risk of aplastic anemia and fatal hepatitis (French et al., 1999). Felbamate should not be used until all other AEDs effective in the patient's specific seizure type have been tried and failed. In patients refractory to other agents, and particularly in those with catastrophic epilepsies associated with high morbidity and mortality, a trial of felbamate is clearly justified.

In cases not benefiting from different AEDs and their combinations, and for whom surgery is not an option, a reasonable compromise is to select AED dosages and combinations that give the best seizure control with the lowest incidence of adverse effects. It should be remembered that all too often patients are exposed to an inacceptable burden of side effects, disproportionate to benefits in terms of seizure control.

6.7. Previous hypersensitivity reactions

Hypersensitivity reactions occur most commonly with carbamazepine, phenytoin, barbiturates, lamotrigine, oxcarbazepine and felbamate

(Battino et al., 2139). At least for skin reactions, there is considerable cross-reactivity among these drugs: in one study, 20 of 42 patients (48%) who had a rash from phenytoin or carbamazepine also developed a rash after switching to either drug (Hyson and Sadler, 1997). Of 51 patients who had a rash from carbamazepine, 14 (27%) also had a rash from oxcarbazepine (Jensen et al., 1986). Although lamotrigine is structurally unrelated to conventional aromatic anticonvulsants, Gudin et al. (1997) reported six patients in whom a rash induced by phenobarbital and phenytoin recurred when lamotrigine was given. Especially in patients who developed serious hypersensitivity reactions, it would be wise to avoid, if possible, AEDs associated with a high allergenic potential and/or high risk of cross-reactivity. Valproate or clobazam seem to be safe alternatives in patients who had a rash from aromatic anticonvulsants (Hyson and Sadler, 1997), although recurrence of the reaction is occasionally seen even with these drugs. Other AEDs associated with a low risk of hypersensitivity reactions include gabapentin (Chadwick, 1994), topiramate (Shorvon, 1996), tiagabine (Adkins and Noble, 1998) and vigabatrin (Grant and Heel, 1991).

6.8. Associated disease

Concurrent diseases and AED treatment can interact in several ways. AEDs may aggravate a concurrent disease, but the same may be seen with uncontrolled seizures. Patients with a specific co-morbidity may be more likely to develop adverse effects of AEDs. Disorders affecting gastrointestinal, hepatic or renal function may alter the pharmacokinetics of AEDs; although these alterations seldom have a major impact on risk to benefit assessment, they do require adjustments in dosage. Some AEDs may have beneficial effects on concurrent conditions such as neuropathic pain (carbamazepine, gabapentin), bipolar disorder (carbamazepine, valproate, lamotrigine), migraine (valproate) and other neurological disorders (Van Valkenburg et al., 1992; Beghi, 1999).

6.8.1. Mental retardation

More than 20% of all patients with epilepsy have intellectual disabilities, and the severity of the seizure disorder increases with the degree of disability. Seizure frequency is often high and mixed seizure types occur, with potentially serious consequences for the physical and mental well-being of the patient. Patients with mental retardation are at particular risk of SUDEP (Nashef et al., 1995b) and epilepsy-related mortality in general (Forsgren et al., 1996b). Although this points to the importance of effective treatment, management may be complicated by the fact that these patients tend to be more vulnerable to adverse effects of AEDs on cognitive function and behavior. In particular, complex polytherapies including AEDs (and/or other psychoactive agents) in mentally retarded patients may impair alertness and cognition without improving seizure control and behavior (Fischbacher, 1982; Beghi et al., 1987). Patients with intellectual disabilities are also at particular risk for paradoxical effects of AEDs (Bauer, 1996; Perucca et al., 1998). Carbamazepine may aggravate atypical absences in symptomatic generalized epilepsies, benzodiazepines have been reported to induce tonic seizures in the Lennox–Gastaut syndrome, and sedative AEDs may also contribute to seizure induction in multi-handicapped patients (Brodtkorb, 1999). The use of these AEDs is not contraindicated, but patients should be monitored closely for possible deterioration in seizure control. Assessment of seizure response as well as side effects may be made more difficult by the patient's intellectual deficits. In the light of risk of visual field defects and the difficulties in assessing this side effect in mentally retarded patients, vigabatrin should be used very cautiously in these patients.

In general, over-treatment and unwarranted polytherapy should be avoided due to the risk of seizure exacerbation and adverse effects that may easily be overlooked. Although mental retardation has been identified as a risk factor for seizure recurrence on withdrawal of AED therapy (Berg and Shinnar, 1994a), withdrawal may be considered in selected cases after several years of seizure control.

6.8.2. Psychosis

Although some AEDs have additional indications in the management of certain psychiatric conditions (especially bipolar disorder), virtually all AEDs have been implicated in the occasional precipitation of adverse psychiatric reactions, and patients with a previous history of psychiatric disorders may be at particular risk (Wong et al., 1997). Available data do not allow an accurate assessment of the incidence of psychiatric side effects of different AEDs, but phenobarbital and vigabatrin seem to be associated with a comparatively higher risk (Wong et al., 1997). Zonisamide, topiramate, felbamate, tiagabine and lamotrigine have also been associated with the precipitation of psychosis in patients with epilepsy (Ferrie et al., 1996; Trimble, 1996; Matsuura and Trimble, 1997; Matsuura, 1999). These AEDs should be used with caution in patients with concurrent psychosis, where carbamazepine and valproate may be preferred. If AEDs with a potential to induce psychosis are considered necessary, low initial doses should be used and a thorough follow-up is recommended. Changes in AED regimens should be made gradually and drastic alterations avoided (Wong et al., 1997; Matsuura, 1999).

6.8.3. Liver disease

Although many AEDs undergo hepatic metabolism, their clearance is seldom affected to an extent that it influences the risk to benefit ratio, except for severe hepatic failure (Aminoff and Parent, 1997). Similarly, decreased protein binding of phenytoin and valproate has little bearing on risk assessment, even though it is relevant for a correct interpretation of total serum drug concentrations.

Valproate should be avoided if possible in patients with liver dysfunction due to its potential hepatotoxic effects (Asconapé and Penry, 1982). Phenobarbital and benzodiazepines should be avoided in advanced stages of hepatic failure because of the risk of induction or aggravation of hepatic encephalopathy (Plum and Hindfelt, 1976). Although theoretically non-metabolized drugs such as gabapentin and vigabatrin offer attractive option for treating patients with hepatic

impairment, potential alterations in the pharmacodynamic sensitivity to these drugs cannot be excluded.

6.8.4. Porphyria

Seizures may be a component of an attack of acute intermittent porphyria, but porphyria and epilepsy may also co-exist independently. Most of the established AEDs can precipitate attacks of porphyria. Hence, barbiturates, phenytoin, carbamazepine, valproate, clonazepam, primidone and ethosuximide should all be avoided (Larson et al., 1978; Reynolds and Miska, 1981). In vitro studies furthermore suggest that felbamate, lamotrigine, and tiagabine may be porphyrogenic and should thus be avoided (Hahn et al., 1997). Gabapentin and, possibly, vigabatrin, do not induce the cytochrome P450 system and may be safer alternatives (Krauss et al., 1995; Tatum and Zachariah, 1995).

6.8.5. Renal failure

Renal failure is associated with a decreased protein binding of phenytoin (Odar-Cederlof and Borga, 1974) and valproate (Orr et al., 1983), resulting in lower optimal ranges of the total serum concentration of these drugs. The clearance of AEDs that are eliminated completely (vigabatrin, gabapentin) or largely (primidone, topiramate) unchanged by the renal route will be reduced in these patients. This may necessitate dose adjustments, but it does not preclude the use of these AEDs in renal failure.

6.8.6. Cardiac disease

Uncontrolled generalized tonic-clonic seizures are likely to be more hazardous in patients with severe heart disease and the risks associated with untreated active epilepsy are probably increased in these patients. Some AEDs, however, may have adverse cardiac effects in predisposed patients. Carbamazepine should be avoided in patients with pre-existing disturbances in the cardiac conduction system or cardiomyopathies. Intravenous administration of phenytoin should be made only with caution in patients with cardiac disturbances. Routine ECG should be obtained to identify cardiac disease before starting treatment with these

drugs, especially in elderly patients and in those with a history suggestive of heart disease (Kennebäck et al., 1991; Tomson and Kennebäck, 1997).

6.9. Concomitant medication

AEDs are frequently involved in drug–drug interactions, particularly of the pharmacokinetic type. Most of these are of little clinical relevance and can be successfully managed with dose adjustments guided, if appropriate, by serum drug level monitoring (Loiseau, 1998). However, some interactions may have serious clinical consequences or can be difficult to control with individualized dosing. Most metabolic interactions can be predicted based on available knowledge of the effect of individual drugs on cytochrome P450 isoenzymes, and it is often possible to select a type of comedication that prevents or minimizes any risk of interference with preexisting therapy.

The inhibitory effect of dextropropoxyphene on the metabolism of carbamazepine is a good example of an interaction that is clinically relevant and difficult to control because the intake of dextropropoxyphene will vary depending on patients' needs (Loiseau, 1998). Dextropropoxyphene should therefore be avoided and other analgesics used in patients treated with carbamazepine. Similarly, verapamil, diltiazem, macrolide antibiotics and isoniazid increase the serum levels of carbamazepine and induce clinical toxicity. When possible, other calcium antagonists and antibacterials should be used in patients treated with carbamazepine (Loiseau, 1998).

Interactions between enzyme inducing AEDs (phenytoin, barbiturates and carbamazepine) and anticoagulants may have severe consequences. Adding phenobarbital or carbamazepine may lead to reduced effects of dicumarol or warfarin and withdrawal of these AEDs may result in bleeding complications (see Section 3.1). Phenytoin, on the other hand, may enhance the effect of warfarin. Although these interactions can be monitored by determination of the prothrombin index, it might be more advantageous to avoid them by using a non-inducing AED if appropriate for the patient's type of seizures.

Phenobarbital, phenytoin, carbamazepine, oxcarbazepine, felbamate and topiramate induce the metabolism of steroid oral contraceptives (Back et al., 1988; Loiseau, 1998). Contraceptive failure is an infrequent but potentially serious consequence, not least taking into account the teratogenic effects of AEDs. It has been suggested that women who require oral contraceptive steroids should receive preparations with higher content of ethinylestradiol (more than 30 μg) if they are treated with inducing AEDs (Tomson et al., 1997; Zahn et al., 1998). If insufficient protection is suggested by bleedings, it is reasonable to consider changing to a non-inducing AED such as valproate, lamotrigine, gabapentin or tiagabine depending on the patient's seizure disorder.

7. Conclusions

The purpose of this review is to increase the awareness of the risk to benefit assessment that should precede any decision concerning institution of AED therapy, choice of drugs and mode of treatment monitoring. In some instances this assessment is unequivocal. For example, the risks and drawbacks associated with prophylactic treatment of patients who never had a seizure but are at high risk of developing epilepsy clearly outweigh potential benefits in most instances. This is also generally the case after acute symptomatic and single unprovoked seizures and in patients with some benign idiopathic partial epilepsies of childhood. In contrast, risks associated with epileptic encephalopathies such as the Lennox–Gastaut syndrome are so severe that treatment even with drugs with potential for serious toxicity may be warranted. Likewise, the good response to vigabatrin in West syndrome may justify its first-line use in these patients, despite the risk of visual field defects, also partly due to the serious adverse effects associated with the treatment alternatives.

Careful individual assessment of the risk to benefit equation is necessary for every patient in whom AEDs are considered. Such evaluation should take into account the prognosis of the seizure condition; the risks if the epilepsy is untreated; the risks associated with different thera-

peutic alternatives; the potential for AEDs to control seizures and to reduce the risks associated with the epileptic disorder; the measures that could be taken, in terms of individualised dosing strategies and monitoring of side effects, to improve the risk to benefit ratio. For obvious ethical and legal reasons, it is important that the implications of this evaluation be discussed throughly with the patient or his/her family, and that the patient be integral part of the decision process.

Syndromic classification and etiology presently appear to be the best predictors of prognosis and response to treatment. Risk factors for adverse drug reactions have been associated with age, comorbidity and comedication. Improved knowledge of such predictors and risk factors would improve the benefit to risk ratio of AED therapy. To this purpose, the conduction of syndrome-oriented trials, and trials focused on specific epilepsy sub-populations are highly desirable. Further mechanistic and epidemiological studies of risk factors for adverse drug reactions are also needed.

Risk to benefit assessment would also gain from a better understanding of how AED therapy affects the serious consequences of epilepsy such as associated morbidity and excess mortality. Although these areas are difficult to incorporate in clinical trials, long-term follow-up studies should aim at assessing other aspects of outcome in addition to seizure frequency and quality of life. Large scale comparative studies of different AEDs including follow-up of chronic adverse reactions and teratogenic effects would also be useful for a more rational choice among different treatment options.

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