Merritt-Putnam 2004
Prognosis of epilepsy

Symposium highlights
EPILEPSY SOCIETY OF AUSTRALIA, Annual Scientific Meeting

The 2004 Merritt-Putnam Symposium entitled Prognosis of epilepsy was held in Sydney, as part of the Epilepsy Society of Australia’s Annual Scientific Meeting. Pfizer Australia again sponsored this important symposium, as acknowledged by several of the speakers.

Prognosis of childhood epilepsy

Professor Anne T. Berg,
Northern Illinois University, IL, USA

More than a century ago, Sir William Gowers described epilepsy as a progressive disorder in which each attack facilitates the occurrence of the next, and spontaneous remission is too rare to be reasonably anticipated.

One of the most important pieces of work to counter that negative point of view was a population-based study in all age groups showing that after 20 years of follow-up, about 80% of neurologically intact individuals were in long-term remission (at least 5 years) compared with only about 40% of those with a deficit. ¹

The National General Practice Study of Epilepsy in the UK also reported that most patients experience significant periods of remission.² The best predictors of outcome were, two highly intercorrelated factors – neurological deficit and remote symptomatic aetiology.

An investigation looking specifically at children found that 58% achieved long-term remission and that the best predictor was symptomatic aetiology.³ Others have reported similar findings.⁴

One population-based study excluded children with ‘absence’ or ‘minor motor’ seizures (essentially most of the idiopathic generalised epilepsies and all of the epileptic encephalopathies).⁵ Approximately 70% of the remainder became long-term seizure-free, 55% without the need for medication. Predictive factors included age at onset, intelligence, neonatal seizures and number of seizures before treatment.

Overall, the literature consistently indicates that at least 50% of young people with epilepsy achieve long-term remission. Neurological deficit/remote symptomatic aetiology is the major determinant of outcome. However, beyond this one repeatedly confirmed factor, there is little else that consistently provides useful prognostic information.

... continued on page 3
Drs Merritt and Putnam

The Merritt-Putnam Symposium is named in honour of H Houston Merritt, a neurologist, and Tracy J Putnam, a neurosurgeon, whose collaborative research into anticonvulsive drugs during the 1930s resulted in the discovery of phenytoin.

The story began when work with barbiturates led Drs Merritt and Putnam to question the conventional wisdom that antiepileptic activity could not be obtained without sedation, and to look instead at molecules containing a phenyl radical. The pharmaceutical company Parke Davis provided the researchers with 19 such compounds, one of which was diphenylhydantoin, a very promising anticonvulsant. Clinical trials followed, and there was soon no doubt that the new agent, now dubbed phenytoin, was a valuable addition to the armamentarium of physicians treating epilepsy.

Since 1981, the US Merritt-Putnam Symposium has become established as a highly regarded forum for the communication of advances in epilepsy research. With the support of Parke Davis initially, and proudly continued by Pfizer, the International Symposium has built on that success in order to help physicians worldwide keep up with the rapid pace of change in the field including the development of new AEDs.

The Merritt-Putnam Symposium has been an important part of the Epilepsy Society of Australia’s annual scientific programme since 1996 and is also supported by Pfizer.

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### Abbreviations

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<td>Carbamazepine</td>
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<td>Vigabatrin</td>
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Most of this work was done before epilepsy syndromes were widely recognised as clinically and biologically coherent entities. The syndromic approach creates a diagnostic whole from factors such as mode of onset, seizure type, EEG patterns, underlying aetiology, and age at onset. The hope is that the whole will be of greater explanatory power than the sum of the parts.

A recent community-based study that looked at seizure outcomes with respect to syndromic diagnoses 5 years after diagnosis of epilepsy found substantial variation in seizure outcome as a function of syndromes. Since 1993, the Connecticut Study of Epilepsy has prospectively followed a community-based cohort of 613 newly diagnosed children. Clinical information was (and continues to be) gathered intensively and classified according to ILAE criteria for seizures, syndromes and aetiology.

After a median of 9 years of follow-up, it is becoming clear that outcomes such as remission are not so simple to characterise because patients remit and relapse repeatedly. A Markov process provides a convenient way to summarise these dynamic outcome states. The results suggest that, after the first four or five years, the proportion of patients in remission stays relatively constant, even though the specific individuals in remission may vary somewhat from year to year. The most parsimonious approach to summarising remission and relapse patterns was to consider the syndrome group.

Over the first 3-4 years, approximately 10% of the Connecticut group met predetermined criteria for intractable epilepsy (failure of at least two drugs and an average of at least one seizure a month for 18 months with a no more than 3-month seizure-free hiatus). An increased risk of developing intractable epilepsy during the first 3 years after diagnosis was seen in association with epileptic encephalopathies, high initial seizure frequency, and focal slowing on the EEG. Children with idiopathic syndromes were the least likely to develop intractable epilepsy. Poor outcome of nondescript partial epilepsies, either cryptogenic or symptomatic, was associated with a higher initial seizure frequency, focal slowing on the EEG, neonatal seizures, and a history of acute provoked status epilepticus.

While most investigators have assumed that intractability, if it occurs, will announce itself early in the course of the disorder, in fact, retrospective data indicate that, some forms of epilepsy may take an average of almost 10 years to become intractable. Up to three-quarters of adults who undergo surgery for refractory partial epilepsy have the initial onset of their epilepsy during childhood or early adolescence. Time to intractability depends on age at onset. Adults who are under 5 years old at the time of their first seizure take an average of 15 years to fail the second drug.

When interpreting the relationship between natural history and prognosis, it should be borne in mind that seizure outcomes are dynamic, not static. Short-term early outcomes may be deceptive, but both short- and long-term outcomes are important, particularly to the patient and family.

Mortality is greatly elevated in epileptic children compared with the overall population. Standardised mortality ratios (SMR) are reported to be of the order of 5-7. However, almost all deaths are due to the underlying condition (Figure). As discussed in more detail by other speakers, epilepsy has a variety of non-seizure outcomes that may have adverse effects on many aspects of a patient’s life.

In conclusion:

- Overall, the most likely outcome of childhood epilepsy is long-term remission
- Short-term outcomes are not always stable over time and may not predict long-term events

Figure. Mortality by aetiology.
• Approaching childhood epilepsy as a diagnostic whole rather than in terms of separate risk factors may provide more meaningful and parsimonious information about outcomes
• Intractable epilepsy affects a very important minority of children
• The hidden burdens of epilepsy – principally cognitive and behavioural comorbidities – may help explain poor long-term social and educational outcomes.

References

Prognosis of neonatal seizures

The literature indicates that seizures are relatively common in neonates. For example, an American study reported an incidence of 57.5/1000 among infants weighing less than 1500 g at birth, dropping with increasing weight and gestation to 2.8/1000 above 2500 g.1 More anecdotally, between November 2000 and November 2002, 122 neonates were diagnosed with seizures at the Royal Children’s Hospital in Melbourne.

Seizures are not disease entities in themselves, but symptoms, and prognosis depends largely on the underlying diagnosis.

Important information when establishing a diagnosis includes:

- time of onset
- history (eg, maternal drug abuse)
- examination findings (eg, focal neurological disorders)
- investigations (including examination of CSF for infection).

Conventional EEG is the gold standard diagnostic tool, but availability and convenience make new bedside monitors increasingly popular. Neuro-imaging helps improve diagnostic accuracy, and MRI is the technique of choice.

Most neonatal seizures are caused by hypoxic-ischaemic encephalopathy (HIE), followed by intracranial haemorrhage (principally affecting premature infants), intracranial infection, developmental defects, and metabolic disorders.

Abnormal signal from the posterior limb of the internal capsule (PLIC) on MRI appears to be highly predictive of neurodevelopmental disorders among infants with stage 2 HIE.2 Basal ganglia injury predicts spastic cerebral palsy in the same group.3

Work conducted in Melbourne has shown that a low apparent diffusion coefficient (ADC) in the PLIC correlates with poor motor outcome in term infants with asphyxia.4

It is generally agreed that neonatal seizures should be treated. The most popular current strategies involve phenobarbitone, phenytoin, and a
benzodiazepine (particularly midazolam). Overall, however, the results are disappointing. Case reports of the use of valproate, carbamazepine, vigabatrin, and topiramate have been published, but data are scarce in neonates.

In conclusion:

- Seizures are common in the neonatal ICU.
- They may be difficult to diagnose – approximately 50% are subclinical.
- New bedside tools improve recognition.
- Subtle seizures alone are associated with poor outcome.
- Seizures may be harmful, particularly in the context of HIE.
- Current therapies are effective in only about 50% of cases.

### References


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**Table. Prognosis of neonatal seizures – relation to neurological disease**

<table>
<thead>
<tr>
<th>Neurological disease</th>
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<td>Intraventricular haemorrhage</td>
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<td>Primary subarachnoid haemorrhage</td>
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<td>Hypoglycaemia</td>
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<td>Early onset</td>
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<tr>
<td>Later onset</td>
<td>100</td>
</tr>
<tr>
<td>Bacterial meningitis</td>
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</tr>
<tr>
<td>Hypocalcaemia</td>
<td>50</td>
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<tr>
<td>Developmental defect</td>
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**Prognosis of adult-onset epilepsy**

Dr Dan McLaughlin, University of Queensland, Brisbane, Qld

There are limited data on the prognosis of patients with epilepsy of adult onset. Mortality, morbidity, remission and influence of treatments are important outcomes for which some information is available. These outcomes should provide the rationale for treatment.

Over time these outcomes may be changing. Analysis of death certificates from England, Wales and the US for the period between 1954 and 1990 showed that the risk of epilepsy-related mortality declined dramatically among people under the age of 20. A less marked drop was seen in adults, and mortality among elderly people declined initially, but began to rise again in the mid-1970s.

Year of birth influenced outcome. In US patients, the risk dropped steadily from those born in 1905 to those born in 1940. In England and Wales, a similar pattern over the same period was seen in women, but was not apparent in men until the 1950 birth cohort.

A prospective study followed 107 patients (over 15 years of age) with newly-diagnosed adult onset epilepsy from 1985-87 to 1996. Approximately 40% were regarded as having generalised tonic/clonic seizures, of which 40% were idiopathic.

The standardised mortality rate (SMR) was 2.5 (3.3 in remote symptomatic cases, and 1.1 when seizures were idiopathic). The increased risk of mortality was most apparent in the early years (related to the underlying cause) followed by a decrease and then another rise around a decade.
after diagnosis (Figure). It has been suggested that this later increase may be attributable to seizures or their treatment.

Another study group determined cause-specific mortality in 9000 patients aged 17 and over with epilepsy included as a diagnosis at discharge from hospital. Average follow-up was for 6 years. The SMR was 3.6 overall, comprising: neoplasms (excluding those affecting the CNS) 2.6; circulatory disorders (mainly cerebrovascular disease) 3.1; respiratory disease (principally pneumonia) 4.0; and digestive disorders (including tumours) 5.0.

Sudden unexplained death in epilepsy (SUDEP) is a controversial area regards case ascertainment, but the risk may be increased in chronic refractory epilepsy. It may also rise with increasing seizure frequency and during sleep. The incidence of SUDEP is generally lower in data from community-based studies and among patients who are seizure-free.

A recent study compared 50 adults who died of SUDEP with 50 epilepsy patients who died of other causes. Younger patients were found to have been at more risk of SUDEP; many died in bed and evidence of a seizure at the time of death was common. Increased seizure frequency seemed to be a marker of risk.

An analysis of data of the US FDA found that over 938 patient-years there were no cases of SUDEP among patients in monotherapy studies (ie, receiving de novo treatment) compared with 3.8/1000 patient-years in those receiving add-on therapy for refractory epilepsy.

Many patients are treated in order to reduce the likelihood of accidents. The risks of illness and injury are reported to be significantly higher than among controls (those without epilepsy) in the first 12 months after diagnosis (illness 49% vs 39%; injury 17% vs 12%), and to become more apparent over 24 months (86% vs 75%, and 27% vs 17%, respectively).

There are few data concerning remission in adult onset epilepsy patients. It is generally agreed, however, that about 30% relapse following drug withdrawal, and the longer the subsequent seizure-free period, the lower the risk. The MRC Study randomised 1013 patients (children and adults) who had been seizure-free for at least 2 years to withdrawal or continuation of therapy. Factors predictive of relapse were: age over 16 years, more than one anti-epilepsy drug; secondary tonic/ clonic seizures; myoclonic seizures; and a short period of seizure freedom. The risk of relapse in patients with juvenile myoclonic epilepsy is estimated at 90% 1-2 years after drug withdrawal.

Although drug treatment prevents seizures, there is no evidence for an effect on mortality.

Although drug treatment prevents seizures, there is no evidence for an effect on mortality. Surgery (mainly temporal lobectomy) that provides seizure control probably reduces the risk. No real change in mortality has been observed in the first 2 years of vagal nerve stimulation.

In conclusion:

- Symptomatic epilepsy is a health hazard.
- Drug treatment suppresses seizures in some cases.
- Many patients are treated for longer periods than necessary.
- It is not clear that current anti-epileptic drugs do more than prevent seizures.

Against that background, physicians should be doing what they can to address the underlying causes of epilepsy.

**References**


**Discussion session 1**

**Q.** It seems clear that epilepsy never occurs in isolation. Have standardised mortality ratios ever been used to look at epilepsies plus (rather than versus) other disorders, such as depression?

**Professor Berg.** Comorbidity occurs not only in people with epilepsy but also control populations. However, more work is necessary in this area.

**Dr Neil Buchanan.** Once an adult patient is seizure-free, issues such as driving and employment mean that the decision about discontinuation of treatment becomes social rather than medical.

**Dr McLaughlin.** I agree. We treat most patients in order to meet current criteria to drive, without necessarily improving their lives substantially in other ways.

**Q.** We let people who have nocturnal epilepsy alone drive during the day, even though they are still having seizures. Are there any data on progression to daytime seizures in this group?

**Professor Berg.** I am not aware of any. Someone should look into it.

**Dr John Wilson.** As bedside monitors become increasingly common in NICUs, are there any dangers inherent in their use by people not trained to read EEGs? Is there a risk of overtreatment with anticonvulsants?

**Dr Hunt.** Neonatologists do not pretend to be neurologists or to have expertise in interpreting EEG. However, NICU patients have more seizures than we thought and – given limited access to conventional EEG – we are looking at ways of improving our ability to detect them. Trials aimed at determining how best to use the new equipment are planned, but in the meantime your point about the need for caution is well taken.

**Q.** What is the status of focal cooling as an antiseizure technique?

**Dr Hunt.** A number of RCTs are ongoing in term infants with HIE. A group from Auckland reported that infants with moderately abnormal amplitude-integrated EEG achieved some benefit in two-year outcome. We have published a small series from the Australian Cooling Study looking at imaging changes in asphyxiated term newborns. Cooling seems to selectively protect the cortex and reduce seizure frequency, but the basal ganglia are still affected – conferring a high risk of spastic cerebral palsy later in life.

**Q.** With regard to long-term epidemiology, has any work been done to classify seizures in terms of their visibility? Some parents may not see the more subtle types.

**Professor Berg.** Children visiting their physicians are usually given a hyperventilation challenge, and EEG is regularly checked. We use the information available from parents and physicians, but no specific scale is available. Other than 24-h monitoring, I am not sure what more we can do. It is a difficult disorder to study in that sense.

**Q.** What is the effect of medication and withdrawal on the remission and relapse pattern in partial seizures? Do they complicate assessments of the efficacy of new agents?

**Professor Berg.** Some relapse and remission is due to stopping medication; however, those patients least likely to relapse (children with benign rolandic epilepsy) are least likely to be treated at onset or most likely to stop medications after a short while, whereas those most likely to relapse (eg, children with symptomatic partial epilepsy) are most likely to be treated and to stay on medications. It is a complex issue that we are trying to tease out.
Prognosis of neuropsychiatric disorders in epilepsy

Contextual barriers to the diagnosis of psychiatric disorders in epilepsy include the emphasis given in epilepsy management to seizure control, and the regrettable divergence of neurology and psychiatry. In addition, psychiatric classifications are not designed to capture the psychological manifestations of epilepsy. Epilepsy syndromes often defy conventional definitions, many symptoms fluctuate, and symptoms that cause significant impairment may not reach threshold criteria for a psychiatric diagnosis.

The ideal classification system would cover both seizure-related conditions, and epilepsy-specific psychiatric disorders including:

- impaired awareness during complex partial seizures
- simple partial status
- psychologically-determined conditions (eg, nonepileptic seizures)
- affective anxiety and psychotic disorders, (either prodromal, ictal, postictal or interictal)
- personality disorders in association with epilepsy
- cognitive dysfunction
- psychosexual disorders.

Psychiatric disorders and epilepsy may be comorbid or independent. An underlying pathological substrate may predispose to both, or epilepsy may predispose a patient to psychological problems and vice versa. Psychiatric disorder may also be a secondary effect of treatment for epilepsy.

The comorbidity of depression with epilepsy is important as it is associated with reduced quality of life (QoL), increased seizure severity and slower self-reported recovery. Furthermore, suicide and deliberate self-harm attempts are 4-5 times more likely among people with epilepsy than in the general population, with the risk is greatest in surgically treated temporal lobe epilepsy (TLE).

Community studies report variable rates of depressive syndromes in epilepsy. The group at highest risk appears to be patients with intractable seizures, in whom there is a lifetime prevalence of 60% and a point prevalence of about 20-30%.

Although we are mostly concerned with interictal mood disorder, depressed mood can also be experienced as an acute preictal, ictal, or postictal phenomenon.

Preictal depression occurs in the minutes hours or days prior to a seizure. Its mechanism is largely unknown, but subclinical seizure activity may play a role. It has also been suggested that negative life events may lead to both low mood and an increased risk of seizures.

Approximately 10% of people with TLE will have ictal depression. It is seen with simple, partial or complex partial seizures, and may continue beyond the duration of the observable seizure. There is no association with laterality of seizure focus. Benzodiazepines may be useful in the control of preictal and ictal depressive syndromes, although hard evidence for their effectiveness is lacking and there is the potential for dependency.

Postictal depression immediately follows a seizure and should be distinguished from delirium and postictal psychosis. Its relationship to laterality is unclear, and no treatment guidelines are available. Conventional antidepressant medication (eg, an SSRI) may be of value when postictal depression is recurrent and severe, and judicious use of benzodiazapines can help.

Manifestations of interictal depression include the typical symptoms and signs of major depression major depression, as well as less typical symptoms of irritability, anxious mood, and somatic preoccupation.

Interictal depression is more common among men than women (the reverse is true of depression in the wider community). It is also associated with left-handedness, a family history of depression, general neurological conditions, intellectual dysfunction and learning disorders. Neurotransmitter and neuroendocrine changes post-seizure may impair control of mood.
No clear relationship has been established between interictal depression and age or duration of epilepsy. A reported association with complex partial seizures may be tenuous. The risk is increased with polypharmacy and with administration of older anticonvulsants due to folate deficiency and perhaps tryptophan depletion. Laterality (with left-sided focus predominating) and frontal lobe dysfunction play a role.

An interest in the bidirectional relationship between mood and epilepsy has emerged. There is some evidence that disturbance in mood may represent a risk for seizure disorder, with rates of depression in patients just prior to their first ever seizure being about four times higher than among controls. The risk is particularly high (17-fold) in TLE, suggesting an additive effect.

There is very little research on outcome of interictal depression. However, identification and treatment is clearly important. Both biological and psychological approaches have merit, and the ideal is a shared care model involving psychiatrists, psychologists, neurologists and GPs.

Treatment is effective in most cases. Where appropriate, biological treatments such as antidepressants or, for severe cases, electroconvulsive therapy can be used with relative safety in patients with epilepsy.

There are a number of factors to consider when evaluating drug treatment for someone with comorbid depression and epilepsy (Figure).

These include the:
- impact of current AEDs on mood and psychological status;
- possible impact of antidepressant choice on seizure threshold;
- side-effect profile of the antidepressant being considered;
- possible interactions between the antidepressant and AEDs;
- past antidepressant response; and
- the potential toxicity of the antidepressant during overdose.

The choice of anticonvulsant should take account of the potential impact on mood. For example, valproate, lamotrigine and carbamazepine are more helpful for mood control than vigabatin, phenobarbitone and phenytoin.

Dose-dependent induction of seizures is observed with most major classes of antidepressant. The highest risk regimens include bupropion and high-dose TCAs, particularly clomipramine.

Among the low-risk regimens are some SSRIs, low-dose amitriptyline, MAOIs. The risk of interaction between anticonvulsants and antidepressants is low with sertraline and citalopram. Antidepressants that are poorly tolerated or have a high risk of mortality in overdose (for example tricyclic antidepressants) are to be avoided as first-line agents. Taking all these factors into account, for antidepressant naïve patients who require drug treatment, drugs such as sertraline and citalopram are generally first line agents.

An under-recognised phenomenon is depression arising de novo post epilepsy surgery. About 25% of patients develop depression within 2 months of epilepsy surgery, but it is often transient. Excellent post-operative seizure control is necessary to minimise the likelihood of poor psychological outcome. A number of mechanisms have been proposed to explain the phenomenon of postsurgical mood changes.

Non-epileptic seizures (NES) range from those with a physiologic basis (eg, syncope, TIA and rarely, migraine) to those with a psychogenic cause (eg, conversion disorder, somatisation disorder, factitious disorder, malingering). NES are common, occurring in 5-20% of outpatients epilepsy clinics and in 10-40% of inpatient epilepsy services. The significant psychiatric comorbidity found in this patient group poses a diagnostic and management challenge.

Risk factors for nonepileptic seizures include: sexual and/or physical abuse; head trauma; psychiatric disorders (particularly personality disorder); lower intelligence; lower socioeconomic status; and lack of support. Outcome is very variable, but children tend to do better than adults, with about 50% achieving immediate seizure cessation and about 80% seizure-freedom after 2 years. On average, only 30% of adults...
remain seizure-free long-term. Good prognosis is associated with early detection and appropriate management, younger age, having an acute precipitant and with good psychosocial support.

Management of patients with non-epilepsy seizures should be approached in a non-adversarial way, with management shared between neurology and psychiatry services. Specialist services, for example psychotherapy, should be considered where NES are associated with complex personality disorders or a history of traumatic experiences such as childhood sexual assault. A psychotropic drug may be required to treat comorbidities such as depression and anxiety.

The historical relationship between psychosis and epilepsy has been a controversial one. However, the risk of schizophrenia-like psychosis in epilepsy (SLPE) is 6-12 times that among normal controls. Probable risk factors include temporal lobe focus, left or bilateral seizure onset, age at onset less than 20 years, duration of epilepsy of more than 10 years, absence of past febrile convulsions, complex partial seizures, and seizure clusters. A family history of psychosis increases the risk 40-fold.7

Other risk factors include female sex, left handedness, mild mental retardation, histologically abnormal mesial temporal lobe, and treatment with multiple antiepilepsy agents. MRI findings (such as contralateral amygdala volume loss) may also increase risk. An association has been noted between SLPE and PET/SPECT findings of reduced cerebral flow to the frontotemporal regions (particularly on the left) and increased dopamine binding in the striatum.

There is increasing recognition that postictal psychotic episodes may be a marker for later development of schizophrenia-like psychosis in epilepsy, with progression rates of 10-14%. Many hypotheses have been put forward concerning potential structural, functional and neurotransmitter correlates of increased risk of schizophrenia-like psychosis in epilepsy. The observation that in some cases EEG relatively normalises as behaviour or psychosis escalates has been used as evidence of an antagonistic relationship between psychosis and seizures (so called forced normalisation). However, this phenomenon is observable in a minority of patients.

The first priority when treating schizophrenia-like psychosis in epilepsy is to ensure a correct diagnosis. Management should be comprehensive and multidisciplinary. Appropriate medication is a low-dose high-potency antipsychotic with close observation of seizure frequency and side-effects.

In conclusion, psychiatric disorders in epilepsy:
- are common but not necessarily inevitable
- have a marked impact on daily function and QoL
- are associated with increased risk for the patient
- are usually amenable to treatment.

Better management of these patients requires a strong model of shared care.

References
Decades of research have shown that epilepsy can have far-reaching effects on a child’s life. It is not only a medical condition but also a social label – a stigmatising disorder.

Two types of stigma have been identified in this context: **Enacted stigma** refers to actual instances of discrimination (for example, rejection, bullying or teasing). **Felt stigma** refers to negative perceptions or beliefs related to the diagnosis of epilepsy, and fear of enacted stigma.

In 2002, more than 19,000 adolescents without epilepsy were surveyed using a questionnaire comprising 37 items looking at familiarity with epilepsy, knowledge about epilepsy, and perceptions related to stigma. Possible responses were ‘yes’, ‘no’, ‘don’t know’, and ‘unsure’. Almost 50% of all responses were ‘not sure’ or ‘don’t know’. Only 45% of respondents said they would tell their friends if they had epilepsy, but 69% would want a friend to tell them. Less than a quarter (24%) responded ‘no’ when asked whether children with epilepsy are likely to be picked on by their peers. Naïve views about epilepsy were common. For example, only 51% of respondents were sure it is not contagious.

Several studies indicate that children with epilepsy experience enacted stigma. Felt stigma is also widespread. According to one survey, half of all children with epilepsy keep their disorder secret, and 2/3 rarely if ever talk about it to others.

Parents and teachers report that children with epilepsy are more likely than peers or siblings to have social problems. They also tend to engage in more sedentary activities than their siblings. Even children with benign epilepsy are less socially active, despite fewer seizures and a favourable medical prognosis.

As a group, children with epilepsy exhibit elevated levels of depression, anxiety, and poor self-esteem, and are more likely to have an external locus of control. Estimates of psychiatric diagnosis range from 34% to 63%, but 67% of those with a disorder receive no treatment. Problems of this kind tend to be stable over time. Patients whose seizures are well controlled have a better psychological prognosis than those with refractory seizures, but still do not do as well as normal controls.

The Figure illustrates the causes of psychological difficulties in epilepsy. Most studies focus on the link between psychological well-being and clinical variables, particularly young age at onset, long duration, high frequency of seizures, intractable and severe seizures, and the need for multiple drugs. Psychosocial variables implicated are as listed in the Figure.
A recent study followed families of children with new onset seizures for 24 months. Both at onset and 2-year follow-up, behavioural problems were associated with low levels of family mastery (lack of cooperation and organisation). Declining family mastery over the two-year period led to escalation of behavioural problems.

Less democratic and more autocratic parenting is associated with increased anxiety and depression. Children more dependent on their parents in novel situations are also prone to depression, as are those in families with negative perceptions of the child’s health status.

Multiple regression analysis shows that epilepsy-related clinical variables are mediated by psychosocial variables and have weak explanatory power on their own.

The impact of epilepsy goes beyond the psychosocial issues mentioned above. Epilepsy also affects learning, cognition and physical function.

The adult literature focuses increasingly on quality of life (QoL) as a measure of the broader impact of epilepsy. QoL takes account of physical, social and psychological factors, overall life satisfaction/well-being, and health status. It is defined by the WHO as ‘Individuals’ perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns.

Several epilepsy-specific QoL scales for children have recently become available, including the Quality of Life in Childhood Epilepsy Questionnaire (QOLCE), a 77-item parent-rating instrument for children aged 14-18 years.

Studies using the QOLCE have confirmed that severe seizures are associated with poor levels of functioning. Importantly, 36% of the variance in QoL is explained by parents’ perceptions of the severity of their child’s seizures. In order to improve QoL in children with epilepsy it is therefore necessary to address not only seizures but also attitudes within the family.

In conclusion:

- Childhood epilepsy has a significant impact on psychosocial functioning and QoL.
- Children with well controlled seizures and relatively benign syndromes may have psychosocial difficulties.
- Most psychological disorders in children with epilepsy go untreated.
- The impact of epilepsy on a child’s QoL can be reduced by:
  - decreasing the burden of epilepsy medically and surgically
  - counselling and educating families
  - reducing enacted stigma by educating the general public
  - reducing felt stigma with psychological interventions such as cognitive behavioural therapy.

References

Psychosocial research is by nature patient-centred. Its primary focus is adjustment, taking account of the complex interactions between physical health and mental and social well-being. In this context it is concerned with how people with epilepsy perceive their condition, and its effects on their day-to-day activity. As in clinical research, the most fruitful approach is to take a lifetime perspective and follow changes over time; however, longitudinal data are generally lacking.

Although health-related quality of life (HRQoL) has become synonymous with psychosocial outcome, there are crucial differences between them. HRQoL is a measure of well-being derived from the social psychology literature. The questionnaires with which it is generally assessed measure well-being, but may not accurately consider distress (for example, depression and anxiety).

Further, HRQoL questionnaire frequently do not assess family adjustment. Patients do not operate in isolation and it is important to find out how the family is adjusting to the epilepsy and how, in turn, this affects the patient’s psychosocial adjustment.

Few alternatives to questionnaires are available, but clinically valuable information that facilitates targeted intervention can be gained through face to face interviews with the patient and their family members. This qualitative, phenomenological approach is formalised in the semi-structured Austin Comprehensive Epilepsy Programme (CEP) Interview.

Common psychosocial issues in chronic adult epilepsy fall into three main groups as shown in the Figure. The question of when and how they begin is being addressed in the ongoing First Seizure Study. Semi-structured interviews one month after patients suffered a first seizure revealed psychological difficulties very similar to those seen in chronic epilepsy:

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<tr>
<th>Psychological (Psychological difficulties)</th>
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<tbody>
<tr>
<td>Memory complaints</td>
<td>33%</td>
</tr>
<tr>
<td>Increased vulnerability</td>
<td>53%</td>
</tr>
<tr>
<td>Increased social dependence</td>
<td>67%</td>
</tr>
<tr>
<td>Perceived stigma (employment)</td>
<td>10%</td>
</tr>
<tr>
<td>Increased anxiety</td>
<td>70%</td>
</tr>
</tbody>
</table>

Findings of this kind underscore the need to identify patients with a poor long-term psychosocial prognosis and then intervene early – preferably as soon as the diagnosis is made.

Traditionally, factors predictive of poor adjustment fall into two main categories: neurobiological and medical factors specific to epilepsy; and psychosocial factors. However, we know that there is a complex interaction between these factors. Indeed, recent evidence indicates that psychosocial issues may mediate the influence of medical factors.

With regard to type of seizures, the conventional wisdom is that partial epilepsy, particularly temporal lobe epilepsy (TLE), is far more likely than generalised epilepsy to be associated with psychosocial problems, especially mood disturbance. Little work, however, has been done on variations in psychosocial outcome in different partial epilepsies.

A recent study in patients undergoing surgery reported a preoperative lifetime history of depression in 53% of those with extra-temporal epilepsy, compared with 33% of those with TLE. One month after undergoing seizure surgery, 26% of the TLE group had clinically relevant depression (many with no prior history) whereas none of the extra temporal patients was suffering from a psychosocial problem.

Psychological: decreased self-esteem; illness self-concept (a feeling of being defined by the illness); and cognitive complaints (particularly relating to memory, often despite normal objective neuropsychological testing).

Sociological: perceived stigma; low level of education and greater risk of unemployment; decreased rate of marriage, and lack of independence (for example, the inability to drive).

Affective function: up to 50% of epilepsy patients suffer from depression and anxiety. Their rate of suicide may be as high as five times that in normal populations.

Figure. Common psychosocial outcomes in adults with chronic epilepsy.
mood disorder. Mechanisms are difficult to determine, but disruption to mesotemporal structures such as the amygdala and hippocampus may play a role.

Seizure frequency is considered a predictive factor in almost all the adult literature concerning psychosocial outcomes, and poorly controlled epilepsy has been linked to lower HRQoL, increased rates of mood disturbance and adverse social outcomes. Recent work suggests that almost complete seizure freedom is required in order to achieve a psychosocial benefit.\(^6,7\)

Among the psychosocial factors that may mediate medical factors is an external locus of control – a perception that one’s life is controlled by fate, luck or powerful others (such as family members or medical practitioners). People with an increased seizure frequency are more likely to have an external locus of control, and consequently generally poor adjustment.

Poor treatment adherence has been linked to perceived stigma, low socioeconomic status, and lack of support.

Even complete seizure freedom may not eliminate psychosocial difficulties. After epilepsy surgery, patients must adjust their self-concept from sickness to health, and face the new challenges and demands inherent in that. This so called ‘burden of normality’\(^1,8\) is felt in four psychosocial domains: psychological, sociological, affective and behavioural. Features develop over the early postoperative phase, but the ultimate outcome is not necessarily poor.

In one study, patients were asked to rate their psychosocial adjustment 2 years postsurgery.\(^9\) Most (58%) reported a good outcome that was highly predicted by improved family dynamics, enhanced vocational and social functioning, and ability to drive. Poor outcome (31%) was predicted by anxiety 1 month postoperatively. The remaining 11% experienced minimal change.

These findings add to the argument that long-term benefit requires early intervention.

A patient’s psychosocial context has a crucial impact on outcome. Someone who is isolated and lonely is at increased risk of poor adjustment. The same is true of people who feel overprotected by their family. Patients with epilepsy are disproportionately likely to be unemployed, and the resulting socioeconomic stress can have a marked impact on adjustment.\(^10\) Just the perception of future financial stress can affect adjustment, even when epilepsy is well controlled.

In conclusion:

- In general, patients invest great effort in managing their own psychosocial concerns – often with very limited support from medical practitioners.
- The likelihood of a poor outcome can be decreased by assistance with:
  - employment and education
  - maintaining a sense of control over their lives
  - social networks
  - decreasing the sense of stigma and illness perception
  - prevention and early intervention.

Unfortunately, psychosocial interventions are yet to be part of the routine management of epilepsy in many international centres.

References

What can or will genetics tell us about the prognosis of epilepsy?

As yet, benign familial neonatal seizures is the only epilepsy syndrome in which the molecular basis is essentially solved. Ninety percent of affected families exhibit mutations of potassium channel genes, \textit{KCNQ2} and \textit{KCNQ3}.\footnote{Singh NA, et al. \textit{KCNQ2} and \textit{KCNQ3} potassium channel genes in benign familial neonatal convulsions; expansion of the functional and mutation spectrum. \textit{Brain} 2003; 126: 2726-37.}

In these individuals, the genetic aetiology provides helpful guidance with regard to prognosis. However, most epilepsies are more complex, involving polygenic inheritance with or without an environmental contribution.

Nevertheless, there is promise for the future. It is hoped that pharmacogenetic findings will enable epilepsy treatment to be individually tailored to the patient. Particular attention is being paid to single nucleotide polymorphisms (SNPs), variations in the sequence of DNA that occur in more than 1% of the population. It is thought that specific SNPs that affect drug metabolising enzyme receptors and drug transporter genes may provide information regarding efficacy and metabolism of specific agents in patients. Molecular epidemiological work may also allow for more precision in epilepsy management.

In conclusion:

- Genetics will answer many questions about epilepsy syndromes, including how refractory a patient will be and the likely prognosis.
- Pharmacogenetics will guide which drug to give, when, and at what dose.
- Side-effects will be minimised by taking account of an individual’s metabolic genetic profile.
- Teratogenicity will be elucidated.
- Eventually, we will be able to prevent epilepsy by targeting specific genes or ‘turning off’ epileptogenesis in response to a neurological insult.

Reference


Discussion session 2

**Q.** I was surprised by your recommendations about antidepressants in epilepsy and the evidence that some are relatively good or bad in precipitating seizures. My sense is that there are no good data to suggest that any one class is any better than any other.

**Dr Trollor.** There is some evidence of a differential effect of antidepressants on seizure threshold. However, most of this is an older literature and from post-marketing surveillance. Most of this work is not methodologically rigorous, but it provides an impression.

**Q.** What is your clinical experience?

**Dr Trollor.** I am conservative in prescribing, and most patients I treat do not have a definite increase in frequency. I usually start with sertraline or citalopram and do not find it a problem. I would not hesitate to give these drugs to people who need them, even if they have intractable seizures.

**Q.** I was intrigued by the high rate of psychosocial problems within the first month of diagnosis; have those data been broken down by seizure type?

**Ms Wrench.** Results are preliminary. The data will be analysed more thoroughly in due course and questions like yours will be answered.

**Dr Hunt.** The first stop in achieving cost-effectiveness is the neurologist’s office. Stigma can develop over the course of the condition as family dynamics change. Educating families about what to look out for in the future can be very cost-effective.

**Ms Wrench.** We should not be looking only at cutting cost. The scale and importance of these issues warrant the development and implementation of good interventions.