The concept that “seizures beget seizures” was originally coined by Sir William Gowers in 1881, who warned that evidence for the efficacy of therapies in epilepsy is nothing but a fallacy, a position that has largely persisted up until today. Therapy of chronic epilepsy remains bedevilled by the lack of good, controlled data. Thus, there is no real evidence base from which to work.

What is ‘chronic epilepsy’ and is it always refractory?

The traditional view is that epilepsy occurs with the first seizure, with 50–80% of patients succumbing to further seizures over the next 2 years; this is defined as early epilepsy. This stage is characterised by good outcomes on monotherapy, with 60–80% of seizures stopping. However, 20–40% of these patients will remain uncontrolled at 5 years and are referred to as having chronic epilepsy. Among these patients, the response to mono or polytherapy is not as good, with many remaining refractory to multiple therapies, with a diminishing return on introducing new medications. This probably tends to make clinicians pessimistic about introducing new treatments, if they perceive that after achieving a certain point with a number of medications, little benefit will be gained by introducing additional therapies.

Chronic epilepsy is defined as epilepsy enduring 5 years or more after the initiation of therapy. However, it is not always necessarily resistant. In Prof. Cook’s view, drug resistant epilepsy is a poor term, as it has to be retrospective and it obscures those patients who can still have a good outcome.

The International League Against Epilepsy (ILAE) Taskforce recently defined drug resistant epilepsy as failure of adequate trials of two tolerated and appropriately chosen and used antiepileptic drug (AED) schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom. However, there are many criticisms of this sort of definition and it is true that many patients achieve long term remission even after trying multiple medications. Prof. Cook adds that even patients with structural pathologies may enter long term remission. Although this is correctly recognised as being a poor prognostic factor, many patients with extensive cerebral pathologies can do well in the long term. An alternative suggestion has been to add a number to the level of refractoriness, i.e., ‘Level 1, 2, 3 refractoriness’, which corresponds to the number of drugs that have been tried.

None of these definitions are entirely satisfactory. Notably, large, population-based studies of the natural history of epilepsy have shown that substantial proportions of patients do very well. The Rochester Minnesota5 study followed 474 patients for >5 years and found that the probability of being in remission (at least 5 consecutive years seizure-free) was 42% at 6 years after diagnosis, 65% at 10 years and 74% at 15 years, with 6% relapsing after a 5-year remission. In the Tonsbridge Kent study, which followed 122 patients for 11–14 years, 68% had 10 or fewer seizures, 50% had >2-year remission within 5 years, 10% relapsed after a 2-year remission, and 22% had no remission at all. Clearly, a great proportion of patients who develop seizures enter long-term remission.

In the largest ever such study, the UK National General Practice Study of Epilepsy, 564 patients were followed for up to 9.5 years from the time of diagnosis. The study showed that newly diagnosed patients have a good chance of entering long-term seizure remission. At 10 years after the index seizure, 84% of those with definite epileptic seizures were in 1-year remission and 54% were in 5-year terminal remission (see Figure 1). As depicted in the graph, the greater the number of seizures, the less likely is remission to occur. Factors related to a higher likelihood of seizure recurrence are a high frequency of seizures in the first 6 months, aetiology (structural pathology symptomatic of epilepsy such as trauma or tumour), and partial onset.

Figure 1: The percentage achieving remission for patients with onset at the age of 5 years or older who had experienced 1 (dashed line), 2 (solid line), 5 (dotted line), or 10 (dashed and dotted line) seizures from the index seizure to 6 months.
Factors associated with intractability

• Many clinical features of chronicity have been identified in epidemiological/clinical studies:
  • Severe epilepsy (>1 seizure/month)
  • Symptomatic epilepsy
  • Structural cerebral damage
  • Certain epilepsy syndromes (e.g. juvenile myoclonic epilepsy)
  • Additional neurological disability
  • Learning disability
  • Certain aetiologies (e.g. neoplasms)

A high seizure frequency before therapy commences is more likely to be more difficult to control.

Is there such a thing as drug resistance and tailored drug therapy?

Pharmacogenomic and clinical trial investigations have been keen to investigate genetic variation in drug transporter genes or targets, in the hopes of identifying drug-refractory patients. However, this appears to be an over-simplistic concept, as so many factors are involved for each individual:

- Disease factors
  - aetiology and syndrome
  - extent/position of lesion (e.g. frontal lesions are typically more refractory)
  - severity of seizures

- Personal/environmental factors
  - lifestyle (alcohol, nutrition, sleep, stress etc.)
  - hepatic enzymes – induction/inhibition

- Drug factors
  - dose
  - not all drugs have the same mechanisms of action
  - multiple actions imply multiple genes and a single drug action can be determined by >1 gene.

In 2000, Alan Roses declared that pharmacogenetics would be widely used within 3 to 5 years; a commonplace tool to deliver patient-specific therapy. This has proven to be too optimistic and moreover, practical tools that use pharmacogenetics are still lacking in the clinical armamentarium. The only current example of pharmacogenetic influence in epilepsy is that of carbamazepine-induced Stevens-Johnson syndrome, but this only applies to certain Asian groups. Prof. Cook added that this test is not widely available or applied in Australia and that international research into this susceptibility has produced conflicting results.

Drug resistance is currently not explained on simple genetic basis. Almost certainly, multiple factors involved in determining drug response, some genetic (likely to be polygenic) and some environmental.

Another motive that makes clinicians apprehensive about giving new medications to drug-refractory patients is due to monotherapy and polytherapy patients, and that AEs did not correlate with AED load, possibly as a result of physicians’ interventions in individualising treatment regimens. They added that taking into account the study limitations of a cross-sectional survey, their findings are consistent with the hypothesis that AEs are determined more by individual susceptibility, type of AEDs used, and physicians’ skills, than the absolute number or load. This is a very important result.

Approach to the treatment of refractory epilepsy

The number of AEDs has grown exponentially over the last 20 years (see Figure 2), yet the proportion of patients who remain inadequately controlled is still around 30%. Thus, although the range of available drugs is much greater nowadays, and clinicians have a far greater ability to choose side effect profiles best suited to the individual, we have not managed to significantly alter the number of patients who are not controlled.

Factors that make monotherapy and polytherapy patients more likely to be refractory:

- Drug factors
  - AED nature
  - drug interactions

- Personal/environmental factors
  - lifestyle (alcohol, nutrition, sleep, stress etc.)
  - hepatic enzymes – induction/inhibition

- Disease factors
  - aetiology and syndrome

- Learning disability

- Certain aetiologies (e.g. neoplasms)

In many cases, patients requiring treatment with AEDs for epilepsy may be suffering from more than one disease and therefore, may present with multiple neurological conditions.

Recent clinic-based studies of therapy in chronic epilepsy

Luciano and Shorvon analysed the success rate of adding previously untried AEDs to the treatment regime of 155 adults with chronic epilepsy (defined as epilepsy active after >5 years of initiation of therapy), who had at least one AED added, and were followed-up for a median of 18 months. Patients who wished to change medication to improve seizure control were rotated through a planned sequence of drug changes until satisfactory improvement was obtained. The choice of drug was based on clinical judgement (seizure type, response to previous therapy, efficacy, potential side effects) and the concomitant medication varied according to usual clinical practice usually at least 1-2 drugs were chosen to leave unchanged. A total of 265 drug introductions by addition (125) or substitution (140) of the previously unused drug were studied.

Strikingly, 28% of patients were rendered seizure free (defined as seizure free at last follow-up for >12 months) by a drug introduction. About 16% of all drug introductions resulted in seizure freedom; 21% of drug introductions resulted in 50%-99% seizure reduction. Clinical factors associated with a better effect were fewer previously used antiepileptic drugs, shorter duration epilepsy, and idiopathic epilepsy. Encouragingly, even in those who had used ≥5 AEDs, 11% became seizure free, which compares well with the 24% of those who had used <5 AEDs.

Similar studies that have assessed outcome in chronic epilepsy include a US-based study that followed 246 patients with chronic epilepsy for 36 months. At 6 months, 19% of all cases had achieved remission. A negative outcome was associated with young age, history of status epilepticus, long duration of therapy, and number of previous failed treatments. The study concluded that no matter how many AEDs have failed, there is always hope of a meaningful seizure remission with change. Very similar findings were reported by a study involving 613 children, who were followed for a median 9.7 years. A total of 23% developed intractable epilepsy (failure of 2 AEDs) and 74% of intractable cases had early remission. Notably, 20.5% of cases entered remission after intractability and 13.3% were in remission at last follow-up.

The prognosis of epilepsy improving?

Many believe that treating epilepsy early will result in a better prognosis. However, the available evidence from large clinical trials conducted in third world countries reveals that instead, when medication was introduced to patients with longstanding epilepsy in Kenya and Ecuador, they responded just as well as those with more recent onset. Thus, there was scant support for Gowers’ contention that seizures began seizures. The FIRST and MESS studies examined whether immediate or deferred treatment affected the long-term outcome, and found no effect.

It has been noted that these studies looked at ‘first line’ AEDs, so it is unclear whether this is true for the newer agents.

Currently, the evidence does not show that treatment influences the long-term outcome of epilepsy. Has the much greater range of treatment now available had an impact on overall prognosis? Short-term regulatory studies in severe chronic epilepsy show seizure-free rates of up to 6% in the placebo arm of therapies.

The range of antiepileptic drugs has increased significantly, but Prof. Cook doubts that we are sure that any of these agents act in a protective manner or prevent the process of epilepsy per se, besides having an ability to treat seizures. Different individuals respond differently.

Figure 2: Change in drug treatment over the last 20 years

Prof. Cook pointed out that drug response varies widely between individuals and is not predictable. Therefore, in patients who want better seizure control, the only logical approach to active therapy is to try new drugs sequentially. An active treatment strategy involves a series of what is in effect ‘n=1’ clinical trials. The choice of drug and order of trials depends entirely on individual factors – ‘clinical tailoring’ of therapy.
to individual drugs; an active treatment policy of trials of sequential therapy is the only logical approach.

Prospective hospital clinic studies show that about 15%–25% of previously intractable patients (with a more limited range of medications) enter remission with changes on therapy. However, no large population-based studies have as yet demonstrated this phenomenon. Prof. Cook concurs with the view of Callaghan and colleagues; no matter how many AEDs have failed, there is always hope of meaningful seizure remission with alterations.9

**Prof. Cook’s experience with Vimpat® (lacosamide)**

In Australia, lacosamide is available in both tablet and intravenous (IV) formulations. Based on the results of 3 randomised placebo-controlled studies, lacosamide at doses of 200, 400 and 600 mg/day reduced seizure frequency in patients with uncontrolled partial-onset seizures with or without secondary generalisation despite 1–3 concomitant AEDs.9–11 These pivotal trials demonstrated that little additional benefit was achieved above doses of 400 mg/day. Thus, a maximum ceiling of 400 mg/day exists in Australia on prescription. In the pivotal trials, lacosamide use was generally well-tolerated and was associated with dose-related CNS and GI AEs. There was no clinically relevant influence of lacosamide on laboratory results or vital signs. A small, dose-related PR prolongation was observed on ECGs, but this has turned out to be not very important. The other AEs were either similar to placebo (somnolence, cognitive disorders) or uncommon; weight gain, oedema and rash.

Prof. Cook has 103 patients on lacosamide, which has been available in Australia since December 2009, initially on a compassionate use scheme through to May 2010 and thereafter available on the Pharmaceutical Benefits Scheme (PBS), with the following restrictions:

- Patients must have tried ≥2 new AEDs
- For continuing lacosamide therapy, current treatment consists of ≥2 AEDs.

Lacosamide is authorised in Australia and in New Zealand for use as adjunctive therapy in intractable partial-onset seizures. Prof. Cook has used lacosamide for a variety of aetiologies.

- 103 patients (48 male; age range 17–72 years)

**Concomitant medications:**

- 40% on 3 medications
- 19% on 4 (or more) medications
- 31% on 2 medications
- 10% on 1 medication (from compassionate use phase)

**Vimpat – introduction:**

50mg bd for 1 week (breaking 100mg tablets). Please note that 50mg x 14 packs are available in New Zealand.

- Then 100mg bd
- Increasing in 50mg steps (to maximum allowable dose of 400 mg/day)
- Some patients went for 2–4 weeks on 50mg
- 2 patients have returned to 25mg bd (having achieved a response at this dosage)

**Response:**

Effect generally evident early (in the first few weeks or months of treatment)

- A few patients stayed on effective dose of 50mg bd.
- Majority are on 150–200mg bd.

**Response rates (n=81):**

About 15% of patients have stopped lacosamide due to tolerability issues, but around 12% are completely seizure free – a very significant proportion and akin to that seen with levetiracetam, which is very reassuring, in Prof. Cook’s opinion. Notably, over 30% of patients have achieved a >50% reduction in seizure rates.

**Inducers vs non-inducers**

It has been suggested that those on enzyme inducers may differ in response. However, Prof. Cook has not found any evidence for this amongst his patients. Some recent data point to differences relating to the use of different sodium channel-blockers. It is true that patients who are intolerant to lacosamide are more likely to respond best to reducing doses of concomitant sodium-channel-blockers. It appears that the mechanism of lacosamide may compound the side effects of sodium channel-blockers, so reducing the doses of carbamazepine or phenytoin before initiating lacosamide seems to be a wise strategy for improving the side effects profile.

**Tolerability**

Lacosamide is associated with the usual tolerability issues of drowsiness, sedation, tiredness and ataxia. No rashes or other skin issues have been reported, and no cases of weight gain.

Forty percent of patients complained of sedation; usually a transient phenomenon, but the commonest reason reported by patients who stopped lacosamide. Two patients stopped because of intolerable behavioural/psychiatric side effects (self-reported as ‘crazy in the head’ ‘really depressed’), which were not reversed by dose reduction of concomitant AEDs. Most side effects resolved spontaneously or with small changes in concomitant medications.

**Concluding remarks**

- Lacosamide is an effective and generally well tolerated drug
- Easy to introduce
- No ‘surprises’ amongst the adverse effects
- No cardiac problems encountered. Prof. Cook does not perform routine ECGs prior to, after, or during lacosamide therapy. He has not heard of lacosamide causing any significant cardiac complications.
- Sedation is a major side effect, but is generally self-limiting and may respond best to reduction of concomitant sodium channel-blockers
- Lacosamide is a little more like using an ‘old’ drug than a ‘new’ drug in the sense of AEs (e.g. akin to phenytoin or carbamazepine causing sedation or unsteadiness with over-large doses)
- No particular synergies/interactions noted as yet by Prof. Cook.

**Q&A Session**

**Q:** Are the IV and oral doses exactly comparable? Will there be evidence on drug levels at some stage?

**A:** The IV formulation is an identical dose to the oral formulation. Prof. Cook has found the IV formulation to be very well tolerated. He has administered lacosamide to a few patients for primarily generalised epilepsies and found it worked very well. A paediatric colleague has reported almost instantaneous benefits with IV lacosamide in children with generalised epilepsy, particularly in those with West syndrome. Prof. Cook surmises that lacosamide’s use in the generalised syndromes and above all in the childhood syndromes will become a major use of the agent.

There is no available evidence as to drug levels and no suggestion that there will be in future. In earlier work, levels have not been found to correlate with the drug’s effect.

**Q:** Early reports attest to lacosamide producing numbness in the mouth. Might lacosamide play a role in producing neuropathy?

**A:** Prof. Cook is unaware of any such data and has not seen any suggesting that lacosamide has a damaging effect on nerves. Perhaps more longer-term use data are needed.

**Q:** Yousef has proposed that epileptologists should be using polytherapy much more often, on the basis of combination therapy in other diseases such as hypertension improving treatment efficacy with fewer side effects compared with monotherapy. Has Prof. Cook found lacosamide to work best alongside particular therapies?

**A:** Prof. Cook agrees and, in his opinion, polytherapy works much better than poisonous doses of monotherapies. He has found that if he lets patients drive therapy changes, they will often tailor their medication into a polytherapy regimen according to what they have experienced on previous regimes. Prof. Cook has not noticed that any particular drugs work better than others with lacosamide. Longer-term data may prove otherwise.

**Q:** It appears that polytherapy was given bad press in the 1980s, when the newly available carbamazepine was added to phenytoin, resulting in undesirable side effects. Also, many patients at that time were receiving phenobarbital and did better when this was removed. However, this evidence does not seem to be relevant to the newer drugs in current use, with different modes of action. What is the authorised age range for lacosamide in Australia and will it become available for use in children?

**A:** Prof. Cook agrees with this summation of the evidence. In Australia, lacosamide is authorised for patients aged ≥16 years. No information as to whether or when it will become available for use in children.

**Q:** Why is lacosamide not marketed for use in primary generalised epilepsy?

**A:** Because of a lack of evidence.
Lacosamide belongs to a new class of anticonvulsants called ‘functionalised amino acids’, meaning that different functional groups have been added to the amino-acid D-serine, allowing for specific characteristics and functions within the body.1,2 The R-enantiomer of lacosamide exhibits the anticonvulsant potency, while the S-enantiomer is inactive. Lacosamide has a low molecular weight (250.3 g/mol), allowing the molecule to cross the blood-brain barrier. The agent is highly soluble in water, allowing it to go easily into solution and facilitating an IV preparation.

**Novel mode of action**

The precise mechanisms by which lacosamide exerts its antiepileptic effects in humans remain to be fully elucidated. Whereas lacosamide selectively enhances slow inactivation of voltage-gated sodium channels, resulting in stabilisation of hyperexcitable membranes, and facilitating an IV preparation.

Compared with other AEDs (carbamazepine, phenytoin, valproate, lamotrigine, topiramate, gabapentin and levetiracetam), lacosamide showed the highest potency at a 50% dose in induced seizure models. Interestingly, lacosamide showed activity in some models in which classical sodium channel blocking AEDs do not, implying further therapeutic potential.

- Severe renal impairment (CL CR ≤30mL/min) and those with end-stage renal disease
- No dosage adjustment is considered necessary in mildly and moderately renally impaired (CLCR ≤80mL/min): Titrate cautiously
- Renally impaired (CLCR 50-80mL/min): Titrate cautiously
- Severe renal impairment (CLCR <30mL/min) and those with end-stage renal disease: a maximum dosage of 250 (EU) or 300 (US) mg/day is recommended.

**Efficacy of lacosamide in animal models**

UCB data on file demonstrates lacosamide to have antiepileptic activity in a broad range of rodent seizure models for generalised and complex partial-onset seizures and status epilepticus, i.e., maximal electroshock seizures (MES), hippocampal kindling, audiogenic seizures (AGS), self-sustaining status epilepticus (SSSE), and in one of the chemosensitive-induced seizure models.

Interestingly, lacosamide showed activity in some models in which classical sodium channel AEDs do not. While lacosamide showed no effect when given subcutaneously in the pentylenetetrazole (PTZ) model (like other sodium channel AEDs), it did show activity in the intravenous PTZ model (a model thought to represent efficacy in primary generalised seizures), and also in the MDMA where most classical sodium channel blocking AEDs do not, implying further therapeutic potential.

Compared with other AEDs (carbamazepine, phenytoin, valproate, lamotrigine, topiramate, gabapentin and levetiracetam), lacosamide showed the highest potency at a 50% dose in the 6 Hz-induced seizure model in mice (a model for treatment-resistant limbic epilepsy).2 Furthermore, motor side effects of AED combinations were not increased by the addition of lacosamide, as assessed by the rotarod test.

**Lacosamide: clinical pharmacology**

The pharmacokinetics of lacosamide have been studied in 25 Phase I studies in a variety of populations (epilepsy and also diabetic neuropathy), in a total of 683 subjects (667 healthy persons aged 18–87 years, female and male, and persons with hepatic and renal impairment. Lacosamide appears to have no abuse potential in persons with a history of recreational CNS drug use.

**References**

7. Canevini MP et al. Relationship between adverse effects of antiepileptic drugs, number of co-prescribed drugs, and drug load in a large cohort of consecutive patients with drug-refractory epilepsy. Epilepsia 2010;51(5):797-804.
Most patients had longstanding epilepsy with uncontrolled seizures (>22 years since diagnosis) despite multiple medication trials and current use of at ≥2 concomitant AEDs with or without vagal nerve stimulation (VNS).

Two primary variables were defined in each of these trials. For the US FDA, the primary variable was the change in partial seizure frequency per 28 days from baseline to the maintenance phase. For the European regulatory agencies, the primary variable was the response (improvement) to treatment of ≥50% from baseline to the maintenance phase.

**Ben-Menachem study**

In the Ben-Menachem study, based on the intent-to-treat (ITT) analyses (i.e. all patients with ≥1 post-baseline efficacy assessment), the median percent reduction in seizure frequency from baseline to maintenance was 10% in the placebo, 26% in the lacosamide 200 mg/day, 39% in the 400 mg/day, and 40% in the 600 mg/day treatment groups. Proportions of patients with ≥50% reduction in seizure frequency during maintenance for lacosamide 400 mg/day (41%) and 600 mg/day (38%) was statistically significant when compared to placebo (22%). Similarly, significantly greater proportions of patients had ≥75% reduction in seizure frequency during maintenance for lacosamide 400 mg/day (22%) and 600 mg/day groups (16%), compared with placebo-treated patients (6%). AEs associated with lacosamide were mild to moderate in intensity and there was an apparent dose-related effect, with the highest number of patients reporting AEs in the 600 mg/day treatment group. The most commonly reported treatment-emergent AEs included dizziness, headache, nausea, and fatigue.

**Chung study**

Reassuringly, similar outcomes have been reported by this study.9 The ≥50% responder rate was 18% in the placebo arm, 38% in the lacosamide 400 mg/day arm and 41% in the 600 mg/day; the between-group differences were highly significant for the 400 and 600 mg/day arms, compared with placebo (p=0.0004 and p=0.0005, respectively). The AE profile was also similar; CNS and GI events were the most common AEs and, in general, appeared to be dose-related. Diplopia was also a common side effect (10% and 19% of patients in the 400 and 600 mg/day treatment groups, respectively), as was visual blurring (11% and 16%, respectively). Dizziness (9%) and co-ordination problems (2%) were the most common AEs leading to discontinuation.

**Halász study**

Again, very similar ITT results were obtained from this study.10 The ≥50% responder rate was 18% in the placebo arm, 38% in the lacosamide 400 mg/day arm and 41% in the 600 mg/day; the between-group differences were highly significant for the 400 and 600 mg/day arms, compared with placebo (p=0.0004 and p=0.0005, respectively). The AE profile was also similar; CNS and GI events were the most common AEs and, in general, appeared to be dose-related. Diplopia was also a common side effect (10% and 19% of patients in the 400 and 600 mg/day treatment groups, respectively), as was visual blurring (11% and 16%, respectively). Dizziness (9%) and co-ordination problems (2%) were the most common AEs leading to discontinuation.

**Pooled data analyses**

In the pooled data analyses, the median percent seizure reductions were 33%, 37% and 39% in the lacosamide 200 mg/day, 400 mg/day and 600 mg/day groups, respectively, and 18% in the placebo group. Corresponding ≥50% responder rates were 34%, 40% and 40% in the lacosamide groups, versus 23% for the placebo group. Each of the lacosamide doses tested was significantly different from placebo.

Seizure freedom was a secondary outcome measure in each trial. Higher lacosamide doses were associated with better outcomes (see Figure 3). During the maintenance phase, 3%, 3% and 5% of patients in the lacosamide 200, 400, and 600 mg/day groups, respectively, were seizure free, compared with 0.9% of patients in the placebo group. In individual trials, the corresponding median percent increase in seizure-free days during the maintenance phase was 7%, 9%, and 12% versus 5%; the between-group differences were significant for lacosamide 400 and 600 mg/day compared to placebo.

In all the pooled data from the studies, the primary reason for study discontinuation was the occurrence of an AE (184 patients; 14%), the AE being a side effect that typically occurred during the titration period.

The overall percentage of patients who discontinued treatment was 13% in placebo-treated patients, and was similar for lacosamide 200 mg/day (18%) and 400 mg/day (23%), and higher in the lacosamide 600 mg/day group (38%). The percentage of patients discontinuing due to AEs increased with increasing doses of lacosamide (10%, 17%, and 29% for lacosamide 200, 400, and 600 mg/day, respectively, in comparison to 5% of placebo-treated patients).

The most common side effects were dizziness, headache, nausea and diplopia.

**In summary:**

- Based on the results of these three studies, lacosamide at doses of 200, 400 and 600 mg/day appears to improve seizure freedom and responder rate in patients with uncontrolled partial-onset seizures with or without secondary generalisation who are receiving 1–3 concomitant AEDs.
- Lacosamide is well tolerated and side effects are primarily dose-related CNS and GI AEs. There is no clinically relevant influence of lacosamide on laboratory results or vital signs. Lacosamide induced a small, dose-related PR prolongation across all studies (approximately 0.3–0.7%), but this was not clinically relevant.
- AEs were similar to placebo (somnolence, cognitive disorders), with no cases of weight gain or rash.

**Cardiac safety**

Extensive ECG evaluations have shown that lacosamide:12

- Did not affect heart rate
- Did not prolong the QT interval (n=247)
- Was not associated with a dose-related or clinically relevant effect on QRS duration

The use of lacosamide is associated with dose-related increase in the PR interval. Adverse reactions associated with PR interval prolongation (e.g. atrioventricular [AV] block, syncope, bradycardia) may occur. In patients with partial-onset seizures, the incidence rate of first-degree AV block being reported as an AE is uncommon.

The following contraindication and warnings are in the labelling in relation to cardiac safety:

- Lacosamide should be used with caution in patients with known conduction problems (e.g. marked first-degree AV block, second-degree or higher AV block and sick sinus syndrome without pacemaker);
- Prolongations in PR interval with lacosamide have been observed in clinical studies. Lacosamide should be used with caution in patients with known conduction problems or severe cardiac disease such as a history of myocardial infarction or heart failure. Caution should especially be exerted when treating elderly patients as they may be at an increased risk of cardiac disorders or when lacosamide is used in combination with products known to be associated with PR prolongation.

**Lacosamide: long-term follow-up data**

An ongoing open-label extension study is investigating the long-term efficacy (maintenance of seizure reduction) and safety of lacosamide.11 This study has continued for 5.5 years so far and involves patients that completed phase II trials, with uncontrolled partial-onset seizures and a stable regimen of AEDs. The optimal lacosamide dose (100 mg/day to 800 mg/day) and concomitant AED optimal dose is determined by the investigator.

Lacosamide has shown a good efficacy and safety profile: 77% of the patients were still continuing lacosamide after ≥1.5 years of treatment; 56% of patients remained in the study at >30 months.

At 3 years’ follow-up, the overall seizure reduction from baseline was 45.5% (see Figure 4 next page). Over time, this rate reduction seems to continuously increase up to 24 to 30 months of treatment, reaching 65.4%. However, Dr D’Souza notes that this interpretation is slightly deceptive, as it appears that the numbers of patients has decreased from 370 at baseline to 24 at >10–24 months’ follow-up. He suggests that these results can be interpreted as meaning that over time, seizure reduction appears to be maintained (the response to lacosamide does not diminish).

Treatment-emergent AEs were generally mild to moderate in intensity, with no change in pattern or safety measures from those reported in the previous studies.

Figure 3. Pivotal trials: seizure freedom during maintenance (pooled data)
In summary:

- Lacosamide at doses of 200, 400 and 600 mg/day reduced seizure frequency in patients with uncontrolled partial-onset seizures.
- Lacosamide has shown a good tolerability profile and is associated with dose-related CNS and GI AEs.
- Most common AEs include dizziness, headache, nausea and diplopia.
- No clinically relevant influence of lacosamide on laboratory results or vital signs was observed in the pivotal trials (small increase in PR interval).

Q&A Session

Q: Does the tablet cut in half?
A: No. In Australia, the clinician can ask the pharmacist to cut the tablets.

Q: If lacosamide is an amino acid, does it have a specific transporter system from the gut and is it overdispersed if the drug dose is taken with food?
A: No data exist to show that absorption is impaired when the dose is taken with food.

Q: Are there any red flags or concerns about teratogenicity for women of childbearing age?
A: No human clinical data regarding teratogenicity and lacosamide exist as yet and nothing has emerged from the animal models so far. In-human data is being compiled using the Australian Pregnancy Register, which can enrol patients taking AEDs.

Q: How do we represent lacosamide to patients? How good a drug is it?
A: Similarly to other clinical studies, the placebo response rate in lacosamide trials has been reported to be as high as 25%. Nevertheless, when this has been accounted for, lacosamide has still been associated with a greater response rate, both in the percentage of seizure reduction and >50% number of responders. Rates are very consistent across the studies, around 24% in the lacosamide 400 mg/day regime and approximately 21% with lacosamide 600 mg/day. Interestingly, around 85% in the active arms versus 70% in the placebo arm have reported AEs.

Dr D’Souza has almost 100 patients on lacosamide; he has not examined the data to determine how many are seizure free. Notably, the seizure freedom proportion of 12% in Prof. Cook’s group is similar to that observed in Simon Sharvon’s study, a pragmatic study in which the clinician was allowed to add or take away an AED. Dr D’Souza warns his patients of the AEs associated with lacosamide; these AEs disappear when he takes away the other drugs. This amelioration encourages the patients to stay on lacosamide.

Q: Can Dr D’Souza comment on indications of lacosamide in any other therapeutic areas, such as is the case for other AEDs?
A: Dr D’Souza has had no experience in the treatment of headache. He is aware that lacosamide has been used for neuropathic pain, but he has yet to see the data. Theoretically, lacosamide could be beneficial.

Dosage and administration

Lacosamide is available in various strengths and various forms for oral and intravenous use:
- as 50, 100, 150 and 200 mg tablets
- as 20 mL solution for infusion containing 10 mg/mL lacosamide.

Lacosamide must be taken twice a day. The recommended starting dose is 50 mg twice daily, which should be increased to an initial therapeutic dose of 100 mg twice daily after one week.

Depending on response and tolerability, the maintenance dose can be further increased by 50 mg twice daily every week, to a maximum recommended daily dose of 400 mg (200 mg twice daily). Lacosamide may be taken with or without food.

In accordance with current clinical practice, if lacosamide has to be discontinued, it is recommended this be done gradually (e.g. taper the daily dose by 200 mg/week).

References