Neurology Asia 2007; 12 (Supplement 1) : 87 – 90

DRUG TREATMENT

New antiepileptic drug efficiency: A 5 year study in Hamilton, New Zealand

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Background: The availability of new anti-epileptic drugs (AEDs) promised improved seizure control and superior tolerability for patients with treatment resistant epilepsy. In New Zealand a unique situation arose, because only 4 (vigabatrin, lamotrigine, gabapentin, and topiramate) of the new AEDs were listed for reimbursement on the pharmaceutical schedule, with the proviso that they were used as add on therapy in patients who were failing (or had failed) on appropriate doses of established AEDs. An additional requirement that a neurologist initiate the treatment via a "special authority" process was also imposed. Once granted, a "special authority" approval would expire after 18 months, and could only be renewed following re-application by the specialist, after review of each patient's progress. This procedure strongly encouraged regular specialist review and resulted in collection of efficacy and tolerability data for each patient, at least 18 monthly, spanning several years.

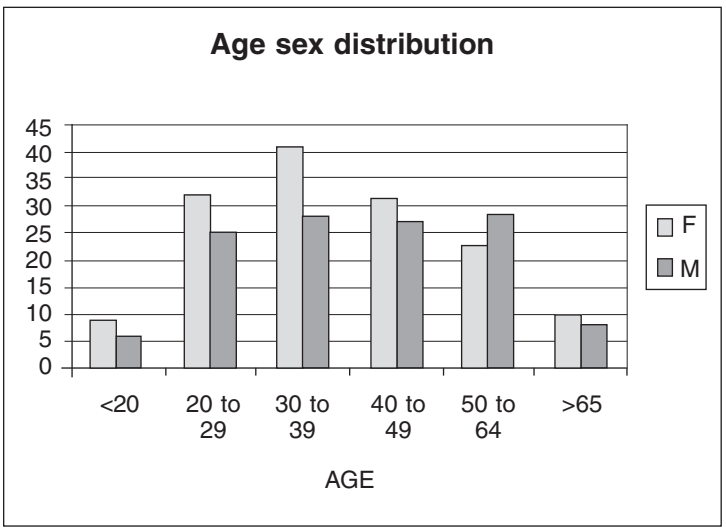
In the Waikato region, a small number of neurologists treated almost all adult patients receiving new AED therapy. Seizure types, syndromes (where known), efficacy, and retention on treatment information were recorded. The efficacy and retention data were of particular interest, as there are few long term comparative efficacy and retention "real world" studies in relation to new AEDs. Long-term efficacy is difficult to consistently quantify in terms of % seizure frequency reduction because of fluctuations in seizure frequency, a tendency for seizure frequency to regress to the mean and possible placebo responses. Seizure freedom as a marker of full efficacy is a more robust measure, and is probably the most relevant efficacy measure because seizure freedom allows resumption of "normal life" and enables a return to driving. Retention on treatment over a prolonged period also provides relevant data because if a patient continues with a therapy long term, the treatment must be both tolerable and effective. Adverse effects, if any, may be consciously or sub-consciously tolerated and "traded-off" against useful and sustained benefit. Thus, retention on treatment represents an excellent composite measure of AED "efficiency".

Methods: We selected the period from January 2000 to August 2005 for review. During this 5 year period 268 patients seen at our clinic with treatment resistant epilepsy were prescribed at least one new AED. Response and retention on treatment were recorded. Analyses by new AED prescription, seizure type, syndrome type, and long term efficacy were undertaken.

Results: The demographics are as in Figure 1. Of 268 patients, 54% were female. Ages ranged from 11-80yrs (mean 37.5). As for epilepsy type, 73% had partial epilepsy. 24% had generalised epilepsy, including 4% JME. At study end, 46 (17%) were taking new AED monotherapy (i.e. previous AED(s) had been withdrawn), 91 (34%) dual therapy, 95 (35%) triple therapy, 26 (10%) were taking 4 AEDs, and 10 (4%) were taking no AED. Some patients were prescribed more than one new AED. The percentages of patients trying each AED were: Gabapentin (10%), Lamotrigine (86%), Topiramate (37%), Vigabatrin (21%). In most patients given Vigabatrin, it was withdrawn due to concerns about visual field compromise. At conclusion of the review period, 57% of patients who had a new AED added were seizure free for at least 1 seizure type, and 38% were entirely seizure free. Figure 2 show actual numbers and proportions of patients seizure free, by drug, for tonic-clonic, or complex partial seizures.

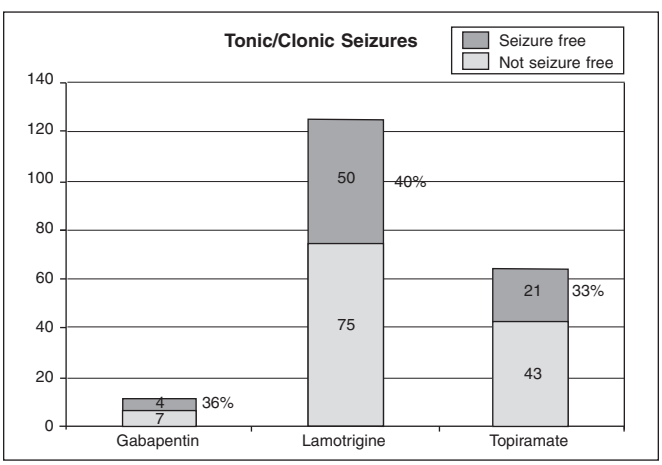
The retention rates (Figure 3) over the 5 year review period were: lamotrigine (79%, 8 yrs of data available on some patients), topiramate (70%), gabapentin (60%, data to 3 yrs, extrapolated to 5yrs). Most patients who were still taking a new AED 2 years after introduction continued on that therapy

Figure 1: Demographics of the study patients



F: female, M: Male

Figure 2: The numbers and proportions of patients seizure free, by drug, for tonic-clonic, or complex partial seizures.



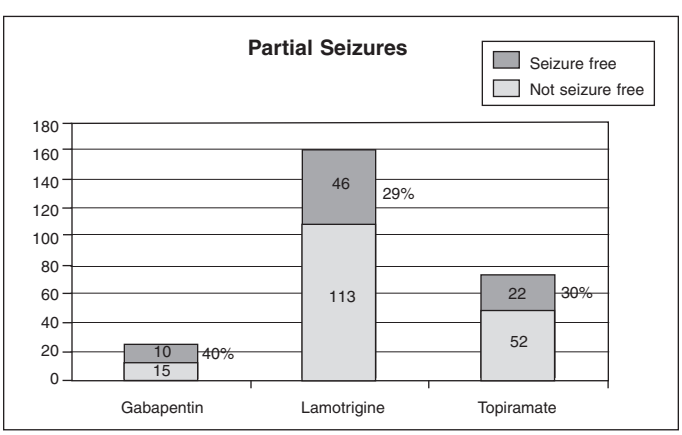
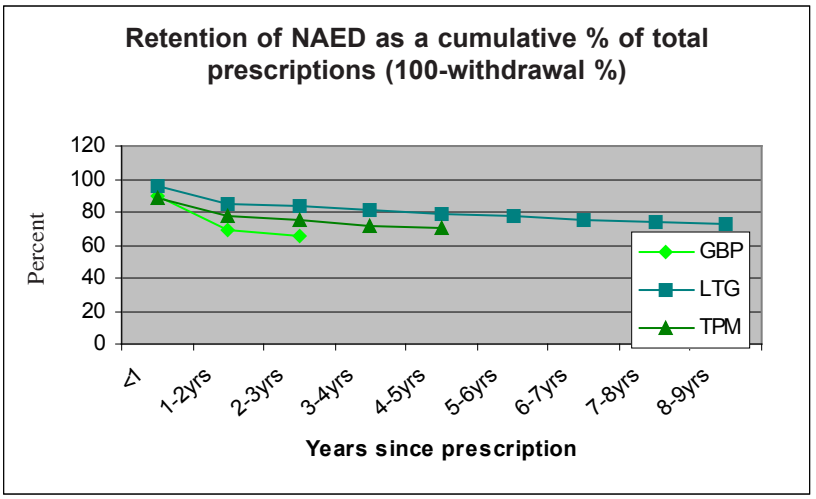
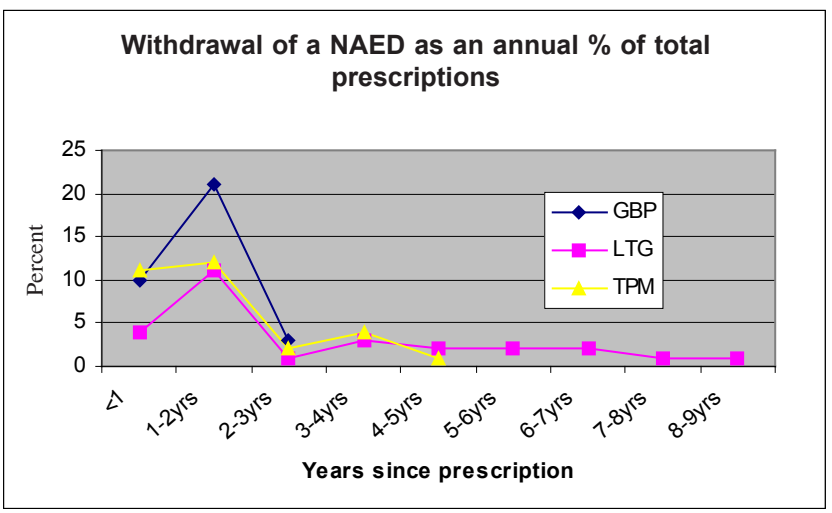


Figure 3: The retention rates over the 5 year review period



GBP: gabapentin, LTG: lamotrigine, TPM: topiramate

Figure 4: The probability of withdrawing from a new AED



GBP: gabapentin, LTG: lamotrigine, TPM: topiramate

long term. The probability of withdrawing from a new AED (Figure 4) was greatest in the first 2 years of treatment and varied between new AEDs, 34% for gabapentin, 25% for topiramate, and 16% for lamotrigine (at 2yrs).

Discussion: There are few long-term retention studies of new anti-epileptic drugs. Long term assessment of these patients is often hampered by significant numbers being "lost to follow-up", particularly follow-up by the therapy initiating clinic. In addition, "head to head" and relative efficacy data between the new AEDs are difficult to extrapolate from published studies, and often depend on complex meta analyses or "expert reviews". Retention on treatment, and seizure freedom are robust and reliable markers of treatment efficiency and collection of these data is relatively straightforward. They combine efficacy with tolerability by removing the variable of "percent seizure frequency reduction", (which can be difficult to consistently calculate), and thereby allow us to infer tolerability and continued net clinical benefit via overall retention. This may be expressed as new AED "efficiency".

Conclusion: The data record "non-clinical trial", "real world", "long term" NAED efficacy and tolerability in a cohort of treatment resistant patients. At conclusion of our review period 57% of patients who had a new AED added were seizure free for at least 1 seizure type, and 38% were entirely seizure free. Gabapentin efficiency in partial seizures appeared superior compared to its use in generalised tonic-clonic seizures, but total numbers were very small. In contrast, topiramate and lamotrigine appeared to be of similar efficiency in both partial and generalised tonic-clonic seizures. The 5 yr retention figures of 60 to 79% (depending on the new AED) illustrate that for these patients continued "net" benefit was obtained, and therefore the treatment might be said to have an "efficiency" of 60-79%. For these patients the addition of a new AED delivered long term efficacy and tolerability. That is to say; the long-term gain in Quality Of Life for these patients was sufficient for them to continue to take treatment spanning many years.

Reference

Sander JW. New antiepileptic drugs in practice - how do they perform in the real world? *Acta Neurol Scand* 2005: 112 (suppl 181): 26-9.