

Neurology Research Review

Making Education Easy

Issue 9 - 2009

In this issue:

- *Lipid management for stroke prevention*
- *The Paracetamol In Stroke trial*
- *Prior antiplatelet use does not affect outcome after ICH*
- *Adverse antiepileptic drug effects: taxonomy*
- *Aetiology of musician's dystonia*
- *Deep brain stimulation for primary generalised dystonia*
- *Heterogeneity in response to interferon beta in MS*
- *Alcohol consumption and risk of essential tremor*
- *Conversion from valproic acid to topiramate in epilepsy*
- *Cognitive function after foetal exposure to antiepileptics*

Welcome to the latest edition of **Neurology Research Review**, a unique New Zealand publication bringing you some of the most important research from around the world every month.

We hope you enjoy the latest edition from Dr Barry Snow and welcome your comments and feedback.

Kind regards,

Dr. Chris Tofield

christofield@researchreview.co.nz

Lipid management in the prevention of stroke: review and updated meta-analysis of statins for stroke prevention

Authors: Amarenco P et al

Summary: Statin therapy is considered to be the most important advance in stroke prevention since the introduction of antihypertensive therapies and aspirin, and has been shown to lower the risk of stroke in high-risk populations despite there being an inconsistent association between cholesterol and stroke. A large meta-analysis (n = 165,792) of randomised trials of statins combined with other preventive treatments found that the relative risk of stroke fell by 21.1% for every 1 mmol/L decrease in LDL cholesterol (p = 0.009). When used for secondary preventions of non-cardioembolic stroke, intense reduction of LDL cholesterol levels by statins reduced the risk of recurrent stroke by 16% (p = 0.03) and major cardiovascular events by 20% (p = 0.002). Future directions for investigation include the benefits of reducing LDL cholesterol levels below 1.8 mmol/L, the effects of triglyceride-lowering agents alone or combined with a statin, and the benefits of elevating HDL cholesterol levels.

Comment: Statins are a standard part of stroke therapy. The NZ guidelines recommend that all TIA patients receive a statin and that the optimal LDL level is <4 mmol/L. Compared with other first line therapy, however, the effect is quite small. For example the number of patients needed to be treated with a statin for one year to avoid one stroke is 112-143, compared with aspirin (NNT: 100), blood pressure control (NNT: 45) and smoking cessation (NNT: 43).

Reference: *The Lancet Neurology* 2009;8(5):453-463

[http://dx.doi.org/10.1016/S1474-4422\(09\)70058-4](http://dx.doi.org/10.1016/S1474-4422(09)70058-4)



PHARMACY GUILD OF NEW ZEALAND (INC)



COMING SOON to South Africa

SUBSCRIBE NOW TO RECEIVE YOUR COPY

This publication is a sample copy from New Zealand. The opinions expressed are specific to the New Zealand health environment. South African versions will be available soon.

The Paracetamol (Acetaminophen) In Stroke (PAIS) trial: a multicentre, randomised, placebo-controlled, phase III trial

Authors: den Hertog HM et al on behalf of the PAIS Investigators

Summary: The multicentre PAIS trial investigated whether early reduction of body temperature (and thus prevention of fever) with paracetamol improves functional outcome in patients with acute stroke. 1400 patients with ischaemic stroke or intracerebral haemorrhage and body temperature 36–39°C were randomised to receive paracetamol 6 g/day or placebo within 12 h of symptom onset. The primary outcome (improvement beyond expectation on the modified Rankin scale at 3 months) was reached by 37% of paracetamol recipients compared with 33% of placebo recipients (adjusted odds ratio 1.20, 95% CI 0.96–1.50). A post-hoc analysis of patients with body temperature 37–39°C at baseline showed improved outcome in paracetamol recipients (adjusted odds ratio 1.43, 95% CI 1.02–1.97). The number of serious adverse events did not differ significantly between the 2 groups. In conclusion, these findings do not support routine use of high-dose paracetamol in patients with acute stroke, although the drug might benefit patients admitted with a body temperature 37–39°C.

Comment: Fever is associated with a poor outcome following stroke, and normalising body temperature with paracetamol is part of acute stroke management. This study extended the question to examine whether it is useful to lower normal body temperature, and the answer is that it is not worth doing. This is an extension of other thinking in stroke management. For example, following a stroke it is beneficial to lower high blood pressure, but it is also beneficial to treat normal blood pressure and lower it further. The numbers needed to treat to avoid one stroke are higher in the normal group (NNT: 118) than the hypertensive group (NNT: 45), but lowering normal blood pressure is at least as beneficial as using a statin (NNT: 112–143).

Reference: *The Lancet Neurology* 2009;8(5):434–440

[http://dx.doi.org/10.1016/S1474-4422\(09\)70051-1](http://dx.doi.org/10.1016/S1474-4422(09)70051-1)

Prior antiplatelet use does not affect hemorrhage growth or outcome after ICH

Authors: Sansing LH for the CHANT Investigators

Summary: This analysis of data from the placebo arm of The Cerebral Hemorrhage and NXY-059 Treatment trial examined the effects of prior antiplatelet therapy on haemorrhage growth and outcome after spontaneous intracerebral hemorrhage (ICH). 282 patients were included in the analysis, 24.8% of whom were taking antiplatelet medications at the time of ICH onset. Antiplatelet use at ICH onset was not found to be correlated with initial ICH volume, ICH growth in the first 72 hours, or initial oedema volume or oedema growth. Multivariate analysis found no association between use of antiplatelet medications and any haemorrhage expansion, haemorrhage expansion >33%, or clinical outcome at 90 days. In conclusion, based on these findings, attempts to reverse antiplatelet medications after ICH may be unwarranted.

Comment: A major concern in stroke management is bleeding into a cerebral infarct. This has led to caution in several situations for example avoiding aspirin before CT scanning in case of a haemorrhage. This can cause important delays in therapy, and we know that early treatment of TIA or small stroke substantially decreases the chance of a second stroke that could be devastating. In addition, when patients present with cerebral haemorrhage and are taking antiplatelet agents, we are left wondering if the haemorrhage has been made worse. This and other studies are reassuring. We are much less concerned about aspirin and cerebral haemorrhage than we have been in the past. If the patient presents with an acute cerebral event, and there is no strong pointer to cerebral haemorrhage such as headache or drowsiness, then it is reasonable to give aspirin acutely.

Reference: *Neurology* 2009;72:1397–1402

<http://dx.doi.org/10.1212/01.wnl.0000342709.31341.88>

View the latest job listings at
Healthcare Jobs

<http://www.researchreview.co.nz/jobs.cfm>

Adverse antiepileptic drug effects: toward a clinically and neurobiologically relevant taxonomy

Authors: Perucca P et al

Summary: This study evaluated specific patterns and clinical relevance of adverse events associated with antiepileptic drug therapy. 200 patients with epilepsy were enrolled in the study and completed self-reported health assessments (including the Adverse Event Profile [AEP] and Quality of Life in Epilepsy Inventory [QOLIE]-89). The 19 AEP items were grouped into 5 categories of adverse events: cognition/coordination, mood/emotion, sleep, weight/cephalgia and tegument/mucosa. On average, each patient reported 6.5 adverse events. Higher scores in the adverse event categories were associated with lower QOLIE-89 scores. Multivariate analysis adjusted for depression and seizure frequency found that cognition/coordination scores were the strongest predictor of QOLIE-89 scores. In a subgroup of 62 subjects enrolled in a randomised trial, improvements in cognition/coordination, mood/emotion and tegument/mucosa scores were all found to be associated with improvements in QOLIE-89 scores. In conclusion, quality of life can be significantly improved when specific classes of adverse events are identified and attempts are made to reduce them.

Comment: Anticonvulsants are often associated with side effects, and many of these develop gradually. In particular, many cause mild cognitive impairment. This is often initially obscured by the cognitive changes associated with a seizure and the emotional reaction to a diagnosis of epilepsy. It can be some time before it becomes apparent that the patient's mentation has slightly slowed. Weight gain, particularly with valproate, can take months. Osteoporosis develops over years, but can be severe with enzyme-inducing drugs such as carbamazepine and phenytoin. Consider these side effects in your patients on anticonvulsants as it might be time to consider withdrawal or change to another anticonvulsant. We routinely prescribe vitamin D for patients on enzyme-inducing anticonvulsants.

Reference: *Neurology* 2009;72:1223–1229

<http://www.neurology.org/cgi/content/abstract/72/14/1223>

Independent commentary by
Dr Barry Snow, Neurologist,
Auckland Hospital

COMING SOON to South Africa

SUBSCRIBE NOW TO RECEIVE YOUR COPY

This publication is a sample copy from New Zealand. The opinions expressed are specific to the New Zealand health environment. South African versions will be available soon.

Etiology of musician's dystonia: familial or environmental?

Authors: Schmidt A et al

Summary: This study investigated whether the aetiology of musician's dystonia (MD) is familial or environmental. The families of 28 patients with MD underwent a telephone screening interview using a modified version of the Beth Israel Dystonia Screen. Participants who screened positive then underwent neurological examination. All 28 of the index patients and 19 out of 97 examined relatives were diagnosed as having dystonia (5 of the latter group were related to an index patient with no known family history of MD). 27 of the 47 affected individuals had additional forms of dystonia, and 23 patients had other movement disorders. A total 18 families had 2–4 affected members. All affected patients had an absent GAG deletion in DYT1. There did not appear to be any potential environmental triggers. In conclusion, these results suggest a genetic contribution to the aetiology of musician's dystonia.

Comment: Musician's dystonia is a fascinating movement disorder. Professional musicians occasionally develop abnormal involuntary posturing of the vital hand. Thus the fingers may pull away from the keyboard or the hand twist on the neck of the string instrument. This often means the end of the professional career. Musician's dystonia is a subtype of task-specific dystonia. The most common is writer's cramp. The cause is unclear but it probably represents a disorder of brain plasticity. Leaned activities that become automatic, such as writing, develop an abnormal pattern with disabling hand postures or movements. The disorder is often diagnosed as Occupational Overuse Syndrome and leads to unhelpful physiotherapy or even hand surgery. The management is difficult and often unsuccessful. The first step is a neurological assessment to make an accurate diagnosis.

Reference: *Neurology* 2009;72:1248-1254

<http://www.neurology.org/cgi/content/abstract/72/14/1248>

Deep brain stimulation for primary generalized dystonia: long-term outcomes

Authors: Isaías I et al

Summary: This study evaluated long-term clinical outcomes after pallidal deep brain stimulation (DBS) in patients with disabling primary generalised dystonia (PGD). 30 consecutive patients were followed for at least 2 years after pallidal DBS implantation for intractable PGD. Clinical outcome was measured by changes in the Burke-Fahn-Marsden dystonia scale, adverse events, total electrical energy delivered, and implant longevity. Overall improvement at 1 year in patients was maintained in all subsequent annual examinations. There were no intraoperative complications, and adverse events related to hardware were infrequent. Stimulation-related adverse events were rare and mainly affected speech. Patients initially stimulated using 130-Hz frequency had their implantable pulse generators replaced every 24 months on average, but no batteries were replaced (for up to 48 months) in 20 patients who received initial stimulation at 60-Hz frequency. Clinical outcome was not dependent on high-energy stimulation. In conclusion, pallidal DBS is a safe and effective treatment for PGD; low energies of stimulation were associated with longer battery life.

Comment: This is an extension of the use of DBS, which has now become a standard treatment for a subgroup of patients with Parkinson's disease. Movement disorders are associated with complex neuronal connections within the basal ganglia. Blocking these connections with either lesions or electrical impulses via deep brain electrodes can interrupt the abnormal circuitry and re-establish normal movement patterns. The range of disorders treatable with DBS is steadily increasing, and we are now submitting some of our patients with dystonia for DBS. The treatment is complicated, costly and, despite the optimism expressed in this report, the outcome is unpredictable.

Reference: *Arch Neurol.* 2009;66(4):465-470

<http://archneur.ama-assn.org/cgi/content/abstract/66/4/465>

Heterogeneity in response to interferon beta in patients with multiple sclerosis: a 3-year monthly imaging study

Authors: Chiu AW et al

Summary: This study used magnetic resonance image (MRI) to evaluate the heterogeneity in response to interferon beta in patients with relapsing-remitting multiple sclerosis (MS). 15 patients were included in the study and were given SC interferon beta-1b, 250µg every other day for 3 years. Patients underwent monthly MRIs and clinical examinations during a 6-month pretherapy phase and a 36-month therapy phase. Responders were defined as those with ≥60% reduction in the total number of contrast-enhancing lesions on MRI during each semester of therapy. 8 (53.3%) patients were classed as MRI responders and 7 (46.7%) as nonresponders. Of the 7 nonresponders, 3 only had an initial response, 2 never had an optimal response, and 2 had a delayed optimal response. Bimonthly neutralising antibody tests showed no clear association between neutralising antibody profile and MRI response. In conclusion, these findings show that only about half the patients treated with interferon beta achieve and maintain a full response to the drug over time.

Comment: Not so long ago, there were very few effective interventions for MS. We now have multiple drugs all of which modulate the immune system in some way. They are expensive and usually involve the patient receiving injections at least weekly for years. Some are associated with severe side effects. Some patients appear to have an excellent response to treatment, while others do not. Assessing response is complicated in a disease with natural remissions. To complicate matters further, there is pathological evidence suggesting that what we call MS may be a mixture of conditions with different pathophysiological processes. All this means that we need good ways of picking which patient will respond best to which therapy; and we cannot yet do that.

Reference: *Arch Neurol.* 2009;66(1):39-43

<http://dx.doi.org/10.1001/archneur.66.1.noc80047>

Subscribing to Research Review

To subscribe or download previous editions of Research Review publications go to www.researchreview.co.nz

To unsubscribe reply to this email with unsubscribe in the subject line.

COMING SOON to South Africa

SUBSCRIBE NOW TO RECEIVE YOUR COPY

This publication is a sample copy from New Zealand. The opinions expressed are specific to the New Zealand health environment. South African versions will be available soon.

Population-based study of baseline ethanol consumption and risk of incident essential tremor

Authors: Louis ED et al

Summary: This population-based study investigated alcohol consumption as a risk factor for the development of essential tremor (ET). 3285 elderly participants living in central Spain had their lifetime alcohol consumption assessed at baseline (1994–1995) and were then followed for up to 4 years, during which time 76 people developed incident ET. A Cox proportional hazards model adjusted for smoking, depression and community, showed that the baseline number of drink-years was marginally associated with a higher risk of incident ET (relative risk 1.003, $p = 0.059$). Compared with non-drinkers, people in the highest drink-year quartile had twice the risk of incident ET (relative risk 2.29, $p = 0.018$), while those in the other quartiles had nonsignificant elevations in risk. The risk of incident ET increased by a mean 23% with each higher drink-year quartile ($p = 0.01$ for trend). In conclusion, people with a higher alcohol intake at baseline had an increased risk of developing ET.

Comment: Essential tremor is diagnosed clinically. It is a postural tremor and therefore appears on action. These are the people who rattle cups in saucers. The cause is usually genetic, but it often does not appear until the 6th or 7th decade. Alcohol, often in small amounts, can be a very effective treatment for essential tremor, and we suggest that patients use it in appropriate situations to control the tremor that is socially embarrassing. Alcohol benefit is also helpful diagnostically, but patients often misinterpret our questioning as they are of the view that tremor is a sign of too much alcohol. We try to reassure them that this is not the case, but this paper suggests we may be wrong!

Reference: *J of Neurology, Neurosurgery & Psychiatry* 2009;80:494-497

<http://dx.doi.org/10.1136/jnnp.2008.162701>

Conversion from valproic acid onto topiramate in adolescents and adults with epilepsy

Authors: Schreiner A et al

Summary: This multicentre open-label study investigated outcomes associated with conversion from valproic acid to topiramate in 147 patients (aged ≥ 12 years) with epilepsy who were switching because of unacceptable efficacy (61%) and/or tolerability (81%). Topiramate was added to the existing antiepileptic regimen at a dose of 25mg once daily. The dose was gradually titrated in 25 mg/day increments to a final dose of 50-200 mg/day. The treating physician decided when and if the existing antiepileptic regimen could be withdrawn. Patients were followed for a mean 20.3 weeks during which time 70% of patients achieved the shift to topiramate monotherapy (median dose 150 mg/day). 75% of patients had $\geq 50\%$ seizure reduction in the last scheduled period (week 8-20); 51% of patients entering the last trial period remained seizure-free. Quality of life improved significantly from baseline for all QOLIE-10 domains. In conclusion, conversion to topiramate led to improved seizure control and quality of life in patients with epilepsy insufficiently treated with valproic acid.

Comment: Topiramate is the latest generally available anticonvulsant. It can be very effective, but there are significant side effects. Despite the outcome of this study, we find that many patients cannot tolerate topiramate because of cognitive side effects or a curious halting speech pattern. Most patients develop tingling of the limbs, and occasional patients develop kidney stones. The best way to avoid side effects is a very gradual introduction. I recommend 25mg alternate days for the first two weeks and increase by 25mg two weekly or even more slowly.

Reference: *Acta Scand Neurol* 2009;119(5): 304-312

<http://dx.doi.org/10.1111/j.1600-0404.2008.01130.x>

Cognitive function at 3 years of age after fetal exposure to antiepileptic drugs

Authors: Meador KJ et al for the NEAD Study Group

Summary: This observational study examined the cognitive effects of foetal exposure to antiepileptic drugs. Cognitive outcome was evaluated in 309 three-year-old children born to women treated with antiepileptic monotherapy (carbamazepine, lamotrigine, phenytoin or valproate) while pregnant. Children exposed to valproate in utero had significantly lower IQ scores than those exposed to other antiepileptic drugs. After adjustment for confounding factors, children exposed to valproate had a mean IQ score 9 points lower than that of children exposed to lamotrigine ($p = 0.009$), 7 points lower than that of children exposed to phenytoin ($p = 0.04$), and 6 points lower than that of children exposed to carbamazepine ($p = 0.04$). The association between IQ and valproate use was dose dependent. In conclusion, in utero exposure to valproate is associated with an increased risk of impaired cognitive function at 3 years of age compared with other commonly used antiepileptic drugs.

Comment: This is another reason why we are becoming increasingly cautious about valproate in women with child bearing potential. Data are difficult to accumulate on the effects of drugs on pregnancy, but the risk of foetal abnormalities appears to be over 10% in pregnancies exposed to valproate in contrast to 2-4% with carbamazepine. We had thought that the risk was largely confined to early pregnancy, but late trimester exposure to valproate is a risk factor for low IQ and learning difficulties. Valproate is sometimes the only effective drug for some forms of epilepsy, particularly with myoclonus. Women taking valproate should see a neurologist or maternal medicine specialist before they plan to conceive.

Reference: *NEJM* 2009;360:1597-1605

<http://content.nejm.org/cgi/content/abstract/360/16/1597>

Privacy Policy: Research Review will record your email details on a secure database and will not release it to anyone without your prior approval. Research Review and you have the right to inspect, update or delete your details at any time.

Disclaimer: This publication is not intended as a replacement for regular medical education but to assist in the process. The reviews are a summarised interpretation of the published study and reflect the opinion of the writer rather than those of the research group or scientific journal. It is suggested readers review the full trial data before forming a final conclusion on its merits.

COMING SOON to South Africa

SUBSCRIBE NOW TO RECEIVE YOUR COPY

This publication is a sample copy from New Zealand. The opinions expressed are specific to the New Zealand health environment. South African versions will be available soon.