Neurology Research Review™

50th ISSUE

Making Education Easy

Issue 50 – 2018

In this issue:

Abbreviations used in this issue

ADAS-cog = Alzheimer disease assessment scale-cognitive subscale

AF = atrial fibrillation

ALS = amyotrophic lateral sclerosis

BACE-1 = beta-site amyloid precursor protein-cleaving enzyme 1

CGRP = calcitonin gene-related peptide

CSF = cerebrospinal fluid

TIA = transient ischaemic attack

PHARMACY GUILD OF NEW ZEALAND

NZMA New Zealand Medical Association

Welcome to the latest issue of Neurology Research Review.

I am pleased to present to you the 50th issue of Neurology Research Review. I have really enjoyed commenting on papers that I thought you would find instructive or at least entertaining. Neurology has always been a complex specialty, and we now have so many treatment options that even specialist neurologists sometimes struggle to keep up with new developments. Hopefully Neurology Research Review makes it easier to stay abreast.

This month we report that tenecteplase may be a better option than alteplase before thrombectomy for ischaemic stroke, and we report positive findings for the CGRP inhibitor fremanezumab in patients with migraine. On the downside, we present disappointing findings for rivaroxaban (vs aspirin) for recurrent stroke prevention and for verubecestat in patients with mild to moderate Alzheimer disease, and we report evidence of an association between some classes of anticholinergic drugs and dementia.

We hope you find these and the other selected studies interesting, and welcome your feedback.

Kind regards,

Dr Barry Snow
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Tenecteplase versus alteplase before thrombectomy for ischemic stroke

Authors: Campbell B et al., for the EXTEND-IA TNK Investigators

Summary: The EXTEND-IA TNK study compared the efficacies of tenecteplase and alteplase before endovascular thrombectomy for ischaemic stroke. 202 patients with ischaemic stroke who had occlusion of the internal carotid, basilar, or middle cerebral artery and who were eligible for thrombectomy were randomised to receive tenecteplase (0.25 mg/kg; maximum dose, 25mg) or alteplase (0.9 mg/kg; maximum dose, 90mg) within 4.5h after symptom onset. The primary outcome was >50% reperfusion of the involved ischaemic territory or an absence of retrievable thrombus at the time of the initial angiographic assessment. The primary outcome occurred in 22% and 10% of patients receiving tenecteplase and alteplase, respectively (p=0.03), and tenecteplase was associated with a better 90-day functional outcome (p=0.04). Symptomatic intracerebral haemorrhage occurred in 1% of patients in each group.

Comment: This is an exciting development in thrombolysis. We currently use alteplase for acute treatment of stroke. It requires an infusion, and this gets in the way of the rapid coordinated care that has become a feature of hyperacute stroke management. Tenecteplase is attractive because it is administered as a single injection. In this study, tenecteplase was also superior to alteplase with more reperfusion and less disability at 90 days with no more symptomatic intracerebral haemorrhage. More studies are necessary, but it is likely that we will move to tenecteplase for acute stroke thrombolysis.

Reference: N Engl J Med 2018;378:1573-82
Abstract

Effect of fremanezumab compared with placebo for prevention of episodic migraine

Authors: Dodick D et al.

Summary: This study investigated the efficacy of the CGRP inhibitor fremanezumab when administered subcutaneously for the prevention of episodic migraine. 875 patients with episodic migraine (6–14 headache days and at least 4 migraine days during a 28-day pretreatment period) were randomised 1:1:1 to receive monthly doses of subcutaneous fremanezumab (225mg at baseline, week 4, and week 8); a single higher dose of fremanezumab, intended to support a quarterly dose regimen (675mg at baseline; placebo at weeks 4 and 8); or placebo. From baseline to 12 weeks, mean migraine days per month decreased from 8.9 days to 4.9 days with monthly fremanezumab (p<0.001 vs placebo), from 9.2 days to 5.3 days with quarterly fremanezumab (p<0.001 vs placebo), and from 9.1 days to 6.5 days with placebo. The most common adverse events that led to discontinuation were injection site erythema or induration, diarrhoea, anxiety, and depression.

Comment: We have discussed CGRP as a migraine modulator previously. There are a number of drugs in advanced development that block the peptide or the receptor. They work, and there is considerable excitement that they might be the 'magic bullet' for migraine. Realistically, though, the reduction in migraine days per month is only 1–2 days more than placebo, which is similar to existing treatments such as topiramate and botulinum toxin. The new drugs will be a welcome addition to the treatments, and for some patients they will make a big difference, but they are unlikely to be game changers.

Reference: JAMA 2018;319(19):1999-2008
Abstract

Rivaroxaban for stroke prevention after embolic stroke of undetermined source

Authors: Hart R et al., for the NAVIGATE ESUS Investigators

Summary: The NAVIGATE ESUS trial compared the use of rivaroxaban and aspirin for the prevention of recurrent stroke in patients with recent ischaemic stroke of undetermined source. 7213 participants at 459 sites were randomised to receive rivaroxaban (15 mg/day) or aspirin (100 mg/day) for the prevention of recurrent stroke. The trial was terminated early after a median 11 months because of a lack of benefit with regard to stroke risk and because of bleeding associated with rivaroxaban. The primary efficacy outcome (first recurrence of ischaemic or haemorrhagic stroke or systemic embolism) occurred in 172 patients in the rivaroxaban group compared with 160 patients in the aspirin group (annualised rate, 5.1% vs 4.8%; p=0.52). Major bleeding occurred in 62 patients in the rivaroxaban group and 23 patients in the aspirin group (hazard ratio, 2.72; p<0.001).

Comment: About 20% of patients with non-lacunar stroke have normal large cerebral arteries, and we assume the cause is cardiac emboli. It is reasonable to assume that a portion of these are from otherwise undetected AF. The risk of stroke from known AF is reduced by about half with anticoagulation. This leads to the hypothesis explored in this study that anticoagulation might be better than aspirin for embolic stroke of undetermined source. The hypothesis was not proven, and there was more bleeding in the anticoagulated group. We will keep treating these patients with antiplatelet agents.

Reference: N Engl J Med 2018;378:2191-2201
Abstract

Randomized trial of verubecestat for mild-to-moderate Alzheimer's disease

Authors: Egan M et al.

Summary: This study investigated the effects of the oral BACE-1 inhibitor verubecestat in patients with Alzheimer disease. 1958 patients with mild to moderate Alzheimer disease were randomised to receive oral verubecestat 12 or 40 mg/day, or matching placebo, for 78 weeks. The trial was terminated early for futility, within 5 months of its scheduled completion. The estimated mean change from baseline to week 78 in the ADAS-cog score was 7.9 with verubecestat 12 mg/day, 8.0 with verubecestat 40 mg/day, and 7.7 with placebo (p=NS). Adverse events were more common in the verubecestat groups than in the placebo group, and included rash, falls and injuries, sleep disturbance, suicidal ideation, weight loss, and hair-colour change.

Comment: This is another disappointing anti-amyloid study for the prevention of Alzheimer disease. BACE-1 is an enzyme that cleaves amyloid precursor protein to produce amyloid-beta. Verubecestat blocks BACE-1. In this study, CSF beta-amyloid was reduced by 60–80%, so it did work. Clearly, reducing beta-amyloid like this is not enough to slow the progression of Alzheimer disease.

Reference: N Engl J Med 2018;378:1691-1703
Abstract

Anticholinergic drugs and risk of dementia

Authors: Richardson K et al.

Summary: This UK case-control study examined the association between anticholinergic drugs and dementia. 40,770 patients aged 65–99 years with a diagnosis of dementia between April 2006 and July 2015 were matched with 283,933 controls without dementia. 14,453 (35%) cases and 86,403 (30%) controls were prescribed at least one anticholinergic drug with an Anticholinergic Cognitive Burden (ACB) score of 3 (definite anticholinergic activity) during the exposure period. The adjusted odds ratio for incident dementia was 1.11 for any anticholinergic drug with an ACB score of 3. Dementia was associated with an increasing ACB score. The risk of dementia increased with greater exposure to antidepressant, urological, and antiparkinson drugs with an ACB score of 3, but not to gastrointestinal drugs with an ACB score of 3.

Comment: We have known for a long time that anticholinergics affect cognition, and their use should be reviewed carefully in any patient with impaired memory. What is of concern is the possibility that these drugs might have a long term and irreversible adverse effect on cognition. A number of studies have shown this association, but it is difficult to know if this is causative or merely reflects the association with the underlying disease; for example, depression in the elderly is a risk factor for dementia. This study is the most comprehensive study so far. It shows a link between previous use of anticholinergics for urology, depression and Parkinsonism. The increased risk is about 20%, and the association persists for up to 20 years after exposure.

Reference: BMJ 2018;361:k1315
Abstract

Time spent reading this publication has been approved for CME for Royal New Zealand College of General Practitioners (RNZCGP) General Practice Educational Programme Stage 2 (GPEP2) and the Maintenance of Professional Standards (MOPS) purposes, provided that a Learning Reflection Form is completed. Please **CLICK HERE** to download your CPD MOPS Learning Reflection Form. One form per review read would be required.

Time spent reading this publication has been approved for CNE by The College of Nurses Aotearoa (NZ) for RNs and NPs. For more information on how to claim CNE hours please **CLICK HERE**.

Dementia And Physical Activity (DAPA) trial of moderate to high intensity exercise training for people with dementia

Authors: Lamb S et al., on behalf of the DAPA Trial Investigators

Summary: The DAPA trial investigated the effects of a moderate- to high-intensity exercise training programme on cognitive function in patients with mild to moderate dementia. 494 people with dementia were randomised 2:1 to an aerobic and strength exercise programme or usual care for 4 months. At 12 months, the mean ADAS-cog score had increased to 25.2 in the exercise arm and 23.8 in the usual care arm (p=0.03), indicating greater cognitive impairment in the exercise group. Compliance with exercise was good, with >65% of participants attending more than three quarters of scheduled sessions. Six-minute walking distance improved by a mean 18.1m in the exercise group.

Comment: There is probably enough evidence to recommend an active exercise programme to reduce the risk of dementia. The question addressed in this paper is does it help established dementia? The answer is no, but the patients did get fitter. In fact, the four months of exercise may have worsened cognitive function. For now, probably the best advice for your cognitively impaired patients is to keep active, but don't engage in an otherwise stressful exercise programme with the sole expectation that it will improve dementia outcomes. Of course this does not exclude strengthening programmes for falls prevention.

Reference: BMJ 2018;361:k1675
Abstract

Five-year risk of stroke after TIA or minor ischemic stroke

Authors: Amarenco P et al., for the TIAregistry.org Investigators

Summary: This registry study examined the 5-year risk of stroke and vascular events after TIA or minor ischaemic stroke. 3847 patients with a TIA or minor ischaemic stroke in 2009–2011 were followed up for 5 years. The composite primary outcome (stroke, acute coronary syndrome, or death from cardiovascular causes) occurred in 469 patients during 5 years of follow-up (estimated cumulative rate, 12.9%), with 50.1% of events occurring in years 2–5. Strokes occurred in 345 patients (estimated cumulative rate, 9.5%), with 43.2% occurring in years 2–5. Multivariable analyses showed that ipsilateral large-artery atherosclerosis, cardioembolism, and a baseline ABCD2 score >4 for the risk of stroke were each associated with an increased risk of subsequent stroke.

Comment: Following a TIA, the risk of stroke or heart attack is about 6% in the first year, and 6% in the subsequent 4 years. This is a big improvement over the previous approximately 20% risk before the widespread uptake of standard risk factor management. The risk is highest in patients with ipsilateral atherosclerotic stenosis, AF and small vessel disease. We are doing well, but don't lose attention to aggressive blood pressure management and anticoagulation for AF.

Reference: N Engl J Med 2018;378:2182-90
Abstract

Projected stroke volumes to provide a 10-year direction for New Zealand stroke services

Authors: Ranta A

Summary: This study used health administrative and NZ Statistics data to predict stroke service demand up to 2028. The analyses showed that, despite improvements in stroke prevention and management, stroke volumes will increased by 40% by 2028 due to population growth and ageing. The projected increase will be accompanied by an increased need for hospital beds and staff resources.

Comment: We are doing well with risk factor management, which is producing a decline in the incidence of stroke. The problem is that we are now saving patients to live longer, and they are still getting strokes. When the rapidly increasing population is combined with the ageing demographic, the projected increase in the number of strokes is 40% in the next 10 years. We will need a concerted effort to further improve primary prevention and the development of highly organised networks for hyperacute stroke management to cope with this projected increase.

Reference: NZ Med J 2018;131(1477):15-28
Abstract

Impact of discontinuation of telestroke: the Nelson experience

Authors: Ranta A & Busch S

Summary: Telestroke services use remote expert support to improve out-of-hour patient access to intravenous thrombolysis in provincial hospitals. This article evaluated the impact of discontinuation of a telestroke service at Nelson Hospital. Three time-periods were compared: 6 months before the telestroke service, 6 months during the telestroke service and six months after discontinuing the telestroke service. Thrombolysis rates were 8.5%, 23.0%, and 7.9% during the respective periods, and rates for thrombolysis within 60 minutes of arrival were 50%, 64%, and 20%, respectively. The odds of receiving thrombolysis were 3-fold higher with vs without telestroke support (odds ratio, 3.33; p=0.006).

Comment: Hyperacute treatment with thrombolysis and clot extraction has revolutionised stroke management. It is not easy, however, and it is necessary to have highly skilled clinicians to diagnose stroke and to direct trained, rapid response teams with ready access to brain scanning. When skilled clinicians are not available on site, studies have shown that good decisions can be made by telemedicine. In this natural experiment, there was a tripling in the proportion of patients receiving thrombolysis during a 6-month trial of telestroke support. It is troubling to see that the effect disappeared when the telestroke support was withdrawn, indicating no learning effect. This study supports calls for a nationally-organised system of provision of stroke care.

Reference: NZ Med J 2018;131(1477):29-34
Abstract

Stage at which riluzole treatment prolongs survival in patients with amyotrophic lateral sclerosis

Authors: Fang T et al.

Summary: This retrospective analysis of a dose-ranging study investigated the disease stage at which the survival benefit of riluzole is seen in patients with ALS. In the original dose-ranging trial, 959 patients with probable or definite ALS were assigned to riluzole 50,100 or 200 mg/day, or placebo. Clinical stage at enrollment did not differ significantly between treatment groups. Time in stage 4 was longer for patients receiving riluzole 100 mg/day than for those receiving placebo (hazard ratio, 0.55; p=0.037). Time from stages 2 or 3 to subsequent stages or death did not differ between riluzole treatment groups and placebo.

Comment: Riluzole prolongs survival of ALS by 2–3 months and is funded in NZ for this use. It is the only medication that prolongs survival, but it does not improve motor function. The short increase means that not all patients, nor their clinicians, wish to use a drug that could just prolong the misery of a devastating disease. This study found that the prolongation of survival is in the last stages of the disease. This is in contrast to previous studies suggesting modification of earlier stages of disease. For now, riluzole is the only medication we have for ALS, but we desperately need a better treatment.

Reference: Lancet Neurol 2018;17(5):416-22
Abstract

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Independent commentary by Dr Barry Snow

Barry Snow was educated at Auckland Medical School. He spent his first house surgeon year at Rotorua Hospital where he learned to catch trout. After his FRACP examinations in 1983, he pursued geriatrics training before changing to Neurology training at Auckland Hospital. From 1998 to 2005 he taught at the UBC Medical School, Vancouver. There he was engaged in research into Movement Disorders, particularly Parkinson's disease; he has published over 100 papers in the area. He returned to NZ in 2005 to join the Department of Neurology at Auckland Hospital. He is currently Director of Adult Medicine at Auckland District Health Board. In addition to his general Neurology work, he runs a Movement Disorder Clinic and research programme.