

## Medibytes

Medibytes offer readers short, informative synopses of important or interesting papers published in specialty and other general medical journals. They are edited by Dr J Ferguson.

**LIST OF ABBREVIATIONS** Acute respiratory failure syndrome (ARFS), bis in die – twice a day (BID), methicillin-resistant staphylococcus aureus (MRSA), National Institute for Clinical Excellence (NICE), physician-assisted dying (PAD), Scottish Medicines Consortium (SMC), standardized mortality ratio (SMR), transient ischaemic attacks (TIA)

### PSYCHIATRY

#### *Depressive syndromes and adverse life events*

This major study explored associations between 12 diagnostic depressive symptoms and nine types of adverse life event. Over 12 years almost 5,000 people in the general population were recruited. Clear-cut differences in depressive syndromes were found in a between-persons analysis depending on whether an adverse life event was reported or not, and what type of life event had occurred. Death of a loved one or romantic break-up was associated with sadness, inability to feel pleasure, anorexia and guilt; chronic stress and failure with fatigue and sleepiness; lack of any life accent with fatigue and appetite gain. These differences were replicated when an independent, within-persons analysis was undertaken of subjects who reported several episodes of depression associated with different types of life event. This provides strong evidence of a causal association.

*From* Keller MC, Neale MC, Kendler KS. Association of different adverse life events with distinct patterns of depressive symptoms. *Am J Psychiatry* 2007; 164: 1521–1529.

G Masterton

#### *Mortality in schizophrenia*

It might be anticipated that improvements in the management of patients with schizophrenia would have led to a reduction in their higher rate of premature death. Sadly, a systematic review of 37 studies from 25 countries on this topic published between 1980–2006 shows the opposite. The median SMR was 2.58 (10-90% quantiles 1.18-5.76); analysis confirmed the difference from the general population was widening, with all-cause mortality having increased ( $p=0.03$ ) in recent years. At 12.86, the SMR was greatest for suicide, which is not unexpected, but excess mortality was found in many other diseases not directly associated with schizophrenia.

*From* Saha S, Chant D, McGrath J. A systematic review of mortality in schizophrenia. *Arch Gen Psychiatry* 2007; 64: 1123–1131.

G Masterton

#### *Participant distress in psychiatric research*

There is particular ethical concern about medical research that involves vulnerable people such as prisoners, refugees or the mentally ill. This systematic review evaluated whether taking part in research has adverse effects on the mental health of psychiatric patients when the study involves assessment of their mental state or associated risk factors. Forty-six studies were included, but few were controlled, so the findings are not robust. There were no long-term adverse consequences evident, while in the short term more subjects reported benefit than harm. Distress was most common in studies that investigated traumatic events, and needs to be specifically addressed in this field of research.

*From* Jorm AF, Kelly CM, Morgan AJ. Participant distress in psychiatric research: a systematic review. *Psychol Med* 2007; 37: 917-926.

G Masterton

### RESPIRATORY

#### *Safety of talc pleurodesis in malignant pleural effusion*

Talc is the most popular and effective sclerosing agent used for induction of pleurodesis. There is a controversy about the safety of talc as ARFS has been reported following pleurodesis. Some reports link occurrence of ARFS to the particle size of the talc. This multicentre, international prospective study looked at the safety of large-particle talc for pleurodesis in malignant pleural effusion. Thirteen European and one South African centre participated. The primary endpoint was ARFS after talc poudrage pleurodesis. Secondary endpoints were other side effects (e.g. fever, hypoxaemia and respiratory failure without ARFS) and death within 30 days.

Five hundred and fifty-eight patients aged 30–96 years, (mean 64.4 years) were included. Pleurodesis was carried out at thoracoscopy, 4g of large size particle talc was administered by a pneumatic atomiser, followed by chest drain insertion. Chest radiographs were taken at baseline and within 24 hours of pleurodesis. Additional images were done according to local treatment protocols. No ARFS occurred after talc pleurodesis. There were small increases in temperature and oxygen

demands which were not clinically significant. Large-particle talc can be used safely for pleurodesis in malignant pleural effusion.

*From* Janssen JP et al. Safety of pleurodesis with talc poudrage in malignant pleural effusion. *Lancet* 5 May 2007; 369(9572): 1535–1539

A Mohammed

## INFECTIOUS DISEASE

### MRSA – it's everywhere now

This study investigated invasive MRSA infection (isolation from normally sterile sites) in nine sites across the US representing 16.5 million people (5.6% of the US population) over 18 months (2004–5). A total of 8,987 invasive infections was identified, of which 7,639 (85%) were healthcare-related, 1,234 (13.7%) were community infections, and 114 (1.3%) were of unknown origin. Of the healthcare-related infections 5,250 (68.7%) started in the community and 2,389 (31.3%) began in hospital.

Healthcare-related risk factors were previous hospital admission, previous surgery, long-term care residence and past MRSA infection/colonisation. Infections occurred without healthcare-related risk factors, but most were with MRSA strains of healthcare origin. Mortality related to the manifestation of the infection; septic shock (55.6%), pneumonia (32.4%), endocarditis (19.3%), bacteraemia (10.2%), and cellulitis (6.1%). Vancomycin was the drug most used and equal proportions of patients received 1, 2, and >2 drugs.

An editorial (Bancroft EA, Antimicrobial resistance: it's not just for hospitals. *JAMA* 2007; **298**:1803) commented that the community and hospitals are both important sources of MRSA, and estimations from this study suggest that more people die in the US from MRSA than from HIV infection.

*From* Klevens RM, Morrison MA, Nadle J, Petit S et al. Invasive methicillin-resistant *Staphylococcus aureus* (MRSA) infections in the United States. *JAMA* 2007; **298**:1763–71.

N Finlayson

## NEUROLOGY

### Move quickly on TIAs and small strokes

In this sequential trial, phase 1 patients (n=634) had 'usual care' and phase 2 patients (n=644) had urgent assessment and immediate standard medical treatment (aspirin and clopidogrel). Patients in the two phases were similar though more patients in phase 2 had received statins, clopidogrel or hypotensive drugs (too few for separate

analysis). The primary outcome was the risk of stroke at 30 days.

Recurrent strokes were less in phase 2 patients (4.2%) than in phase 1 patients (9.9%) (p<0.0001), irrespective of referral to hospital or outpatient clinic or treatment in the community. There were no adverse consequences of immediate treatment, particularly intracranial bleeding. Standard medical treatment applied immediately prevented 80% of early recurrent strokes. Differences in long-term outcome are unknown.

An editorial (Dean N, Shuaib A, A Transient ischaemic attacks: unstable, treatable, neglected. *Lancet* 2007; **370**:1398) notes that 30–40% of ischaemic stroke patients have an initial TIA or minor stroke, and 10.5% of TIA and minor stroke patients overall have a further stroke within 90 days. Standard currently available treatment applied quickly could save lives and function.

*From* Rothwell PM, Giles MF, Chandratheva A et al. Effect of urgent treatment of transient ischaemic attack and minor stroke (EXPRESS study): a prospective population-based sequential comparison. *Lancet* 2007; **370**:1432–42.

N Finlayson

## PREVENTIVE MEDICINE

### Varenicline (Champix) for smoking prevention approved by the SMC and NICE

Nicotine and related natural products in various formulations (gum, spray and patches) have been the mainstay of drugs for smoking cessation for two decades, yet approximately 25% of the population continues to smoke and the number quitting has shrunk to about 0.4% per annum. Although legislation against smoking in work and public places might be a new incentive to stop, the introduction of varenicline (by Pfizer) should be seen as a new opportunity for the medical profession to become involved.

Varenicline is a selective  $\alpha 4\beta 2$  acetylcholine partial agonist that acts at the same receptor as nicotine. However, as a partial agonist, the stimulatory effect of varenicline is much less than that of nicotine, but importantly the effect does not desensitise and, as a result, the effect of additional nicotine is blocked for some hours. Thus varenicline is thought to produce a modest and long-lasting release of dopamine in the forebrain, which is presumed to create a feeling of well-being that remains at the same level for some time in the absence or presence of top-up doses of nicotine.<sup>1</sup>

Undoubtedly the most impressive data to date comes from two trials in Asia, where approximately 39% of men smoke. In a double blind, placebo-controlled, randomised parallel group study in Japan in which two doses of

varenicline were compared to a placebo for 12 weeks varenicline was associated with abstinence during the last four weeks of treatment and in the longer term over 40 weeks of non-treatment.<sup>2</sup> In a second study in Taiwan and Korea, where the rates of smoking for men may be even higher, varenicline 1mg BID was again efficacious over a 12-week period and after a 12-week follow-up. At follow-up 9-24 weeks post treatment cessation was 46.8% in the treatment group and 29% in the placebo group. In this study, at the dose recommended by NICE, adverse effects caused a dropout rate of 10%, about 5% greater than in the placebo control. The main adverse effects were predominantly nausea, insomnia, increased appetite, constipation and abnormal dreams.<sup>3</sup> Although the trial reported side effects are relatively trivial, there have been reports of a manic attack in a patient with a bipolar disorder<sup>4</sup> and an activated psychotic relapse in a patient with schizophrenia.<sup>5</sup>

Although neuropharmacologists working on animal models would not be surprised if varenicline would have a beneficial effect on other drug-related addictions, it is surprising to note that in many trials smokers with alcohol-related addictions were excluded.<sup>6</sup> Indeed, varenicline has been shown in animal models to reduce ethanol seeking and preference.<sup>7</sup>

Finally it is worth noting that varenicline is an analogue of cytosine, a natural insecticide present in several plants, and that cytosine, marketed as Tabex at very low cost, has been used in Eastern and Central Europe for smoking cessation since the late 1960s and was found to be effective with minimal behavioural support in three placebo-controlled trials.<sup>8</sup> Unfortunately, almost nothing is known of the compound's safety, abuse liability and efficacy.

1. Rollema H, Coe JW, Chambers LK, et al. Rationale, pharmacology and clinical efficacy of partial agonists of alpha(4)beta(2) nACh receptors for smoking cessation. *Trends in Pharmacological Sciences*, 2007; 28: 316–325.
2. Nakamura M, Oshima A, Fujimoto Y, et al. Efficacy and tolerability of varenicline, an alpha(4)beta(2) nicotinic acetylcholine receptor partial agonist, in a 12-week, randomized, placebo-controlled, dose-response study with 40-week follow-up for smoking cessation in Japanese smokers. *Clinical Therapeutics*, 2007; 29: 1040–1056.
3. Tsai ST, Cho HJ, Cheng HS, et al. A randomized, placebo-controlled trial of varenicline, a selective alpha(4)beta(2) nicotinic acetylcholine receptor partial agonist, as a new therapy for smoking cessation in Asian smokers. *Clinical Therapeutics*, 2007; 29: 1027–1039.

4. Kohen I & Kremen N. Varenicline-induced manic episode in a patient with bipolar disorder. *American Journal of Psychiatry*, 2007; 164: 1269–1270.
5. Freedman R. Exacerbation of schizophrenia by varenicline. *American Journal of Psychiatry*, 2007; 164: 1269.
6. Leeman RF, Huffman CJ, O'Malley SS. Alcohol history and smoking cessation in nicotine replacement therapy, bupropion sustained release and varenicline trials: A review. *Alcohol and Alcoholism*, 2007; 42: 196–206.
7. Steensland P, Simms JA, Holgate J, et al. Varenicline, an {alpha}4beta2 nicotinic acetylcholine receptor partial agonist, selectively decreases ethanol consumption and seeking. *Proceedings of the National Academy of Sciences*, 2007; 104: 12518–12523.
8. Etter JF, Lukas RJ, Benowitz NL, et al. Cytisine for smoking cessation: A research agenda. *Drug and Alcohol Dependence*, In Press, Corrected Proof.

JS Kelly

## ETHICS

### *No pressure in Oregon or the Netherlands*

Fears that vulnerable people might be (or feel) pressurised into accepting a physician-assisted death has led to resistance to the legalisation of this way of ending life. Physician-assisted dying is legal in Oregon and the Netherlands and official reports and additional surveys are available. This study, relying mainly on the 2006 Oregon report and cumulative study and the 2005 Netherlands nationwide study, found no evidence of increased risk of dying by PAD in vulnerable groups including; elderly, women, poorly educated, poor, physically disabled, chronically ill, minors, psychiatric illness, racial/ethnic minorities, and uninsured (Oregon only). Those with HIV infection in Oregon were 30 times more likely to die by PAD, but numbers were small. Those dying by PAD were, in general, socially privileged.

*From* Battin MP, Van der Heide, Ganzini L et al. Legal physician-assisted dying in Oregon and the Netherlands: evidence concerning the impact on patients in 'vulnerable' groups. *Journal of Medical Ethics* 2007; 33:591–7.

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