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New drugs for TB

New drugs, but also shorter, better-tolerated regimens are needed to tackle the high global burden of tuberculosis complicated by drug resistance and retroviral disease. This study, published in *The Lancet*, investigated new multiple-agent combinations over the first 14 days of treatment to assess their suitability for future development.

In this prospective, randomised, early bactericidal activity (EBA) study, treatment-naive, drug-susceptible patients with uncomplicated pulmonary tuberculosis were admitted to hospitals in Cape Town, South Africa, between 7 October 2010 and 19 August 2011. Patients were randomised centrally by computer-generated randomisation sequence to receive bedaquiline, bedaquiline-pyrazinamide, PA-824-pyrazinamide, bedaquiline-PA-824, PA-824-moxifloxacin-pyrazinamide, or unmasked standard antituberculosis treatment as positive control. The primary outcome was the 14-day EBA assessed in a central laboratory from the daily fall in colony-forming units (CFU) of *M. tuberculosis* per milliliter of sputum in daily overnight sputum collections. Clinical staff were partially masked but laboratory personnel were fully masked.

The mean 14-day EBA of PA-824-moxifloxacin-pyrazinamide ($n=13$; 0.233 [SD 0.128]) was significantly higher than that of bedaquiline (14; 0.061 [0.068]), bedaquiline-pyrazinamide (15; 0.131 [0.102]), bedaquiline-PA-824 (14; 0.114 [0.050]), but not PA-824-pyrazinamide (14; 0.154 [0.040]), and comparable with that of standard treatment (10; 0.140 [0.094]). Treatments were well tolerated and appeared safe. One patient on PA-824-moxifloxacin-pyrazinamide was withdrawn because of corrected QT interval changes exceeding criteria pre-specified in the protocol.

PA-824-moxifloxacin-pyrazinamide is potentially suitable for treating drug-sensitive and multidrug-resistant tuberculosis. Multi-agent EBA studies can contribute to reducing the time needed to develop new antituberculosis regimens.

Diacon AH, et al. *The Lancet*, Early Online Publication, 23 July 2012.

[[http://dx.doi.org/10.1016/S0140-6736\(12\)61080-0](http://dx.doi.org/10.1016/S0140-6736(12)61080-0)]

Walking speed and hypertension in older adults

Walking speed is emerging as an important measure of frailty in older adults. It's easy to measure, reproducible and associated with survival. Walking speed might also help identify older adults who need treatment for high blood pressure, according to an observational study from the USA. In a nationally representative cohort of 2 340 adults aged ≥ 65 years, systolic blood pressure of ≥ 140 mmHg predicted mortality in faster walkers (hazard ratio 1.35 (95% CI 1.03 - 1.77)) but not in slower walkers (hazard ratio 1.12 (0.87 - 1.45)). High blood pressure seemed protective in the small subset of adults who failed to complete the short walking test.

Doctors disagree about how to manage blood pressure in older adults, says a linked comment (doi:10.1001/archinternmed.2012.2642). Many are reluctant to accept that high blood pressure isn't always a bad sign. It may be a bad sign for those lucky enough to be well and physically fit (the kind of adults recruited to trials of antihypertensive drugs). But the direct association between blood pressure and



mortality breaks down, or even reverses, in older adults who are unable to walk 1.8 miles/hour for 20 feet (0.8 m/s for 6 m), which is the defining threshold used in this study.

The new data reinforce walking speed as a useful measure of frailty, says the comment, and remind us that there is no such thing as an average older person when it comes to blood pressure. Guidelines for treatment based on age alone will miss the mark and risk over-treating frail adults who may need

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their high blood pressure to perfuse vital organs, including the heart.

Odden MC, et al. *Arch Intern Med* 2012
[<http://dx.doi.org/10.1001/archinternmed.2012.2555>]

Spironolactone and the risk of breast cancer in women

In this paper in the *British Medical Journal* the authors report on a study that investigates whether exposure to spironolactone treatment affects the risk of incident breast cancer in women over 55 years of age.

The participants were 1 290 625 female patients, older than 55 years and with no history of breast cancer, from 557 general practices in the UK with a total follow-up time of 8.4 million patient years. We excluded patients with poor-quality data and those with no contacts with their general practitioner after their current registration date.

The exposed cohort included women who received at least two prescriptions of spironolactone after age 55 years, who were followed up from the first prescription (index date). The authors randomly selected two unexposed female controls for every exposed patient, matched by practice, year of birth, and socioeconomic scores (if information was available), and followed up from the same date.

The main outcome measure was new cases of breast cancer, using Read codes to confirm diagnoses.

Index dates for study patients ranged from 1987 to 2010, and 29 491 new cases of breast cancer were recorded in the study population (incidence rate 0.35% per year). The exposed cohort of 28 032 patients and control cohort of 55 961 patients had unadjusted incidence rates of 0.39% and 0.38% per year, respectively, over a mean follow-up time of 4.1 years. Time-to-event analysis, adjusting for potential risk factors, provided no evidence of an increased incidence of breast cancer in patients exposed to spironolactone (hazard ratio 0.99, 95% confidence interval 0.87 - 1.12).

These data suggest that the long-term management of cardiovascular conditions with spironolactone does not increase the risk of breast cancer in women older than 55 years with no history of the disease.

Mackenzie IS, et al. *BMJ* 2012;345:e4447.

Cranberries may be protective against urinary tract infection

Cranberry products probably do help prevent urinary tract infections, according to a meta-analysis of 13 randomised trials. A significant effect emerged from pooled analyses that excluded one outlying trial (risk ratio 0.62, 95% CI 0.49 - 0.80), confirming results from a previous much smaller meta-analysis.



Juice seemed to work best in subgroup analyses (0.47, 0.30 - 0.72), although only 4 of 13 trials tested non-juice products such as capsules or tablets. Cranberry products protected women with recurrent infections, children and anyone taking more than 2 doses a day. Results for older adults, pregnant women and people with neuropathic bladders were less clear-cut. The trials had limitations, including a tendency for participants to drop out before completing their treatment. They weren't well reported and tested a wide range of doses. Results are encouraging but not definitive, say the authors.

Cranberries (genus *Vaccinium*) have been used as a natural remedy for at least 100 years, and in the 1980s scientists discovered that the berries contain an active ingredient (possibly proanthocyanidins) that stops bacteria sticking to uro-epithelial cells. Future trials might usefully test different doses of cranberry and specify proanthocyanidin content from the outset. Many other potentially active ingredients are waiting to be investigated.

Wang C-H, et al. *Arch Intern Med* 2012;172:988-996.

SINGLE SUTURE

Elderly mice regain their memories

The forgetfulness accompanying the march of time may be reversible – in mice at least.

Hilmar Bading of the University of Heidelberg in Germany and his colleagues improved the memory of elderly mice by injecting a virus into their hippocampus – a part of the brain strongly involved in memory. The virus increased the presence of an enzyme called DNA methyltransferase.

Eighteen-month-old mice given the virus were able to perform in memory tasks as well as 3-month-old mice. When Bading halved the amount of the enzyme in the brains of young mice, their performance deteriorated to that of typical elderly mice.

New Scientist, 7 July 2012.