

Behavioural activation cost-effective alternative to CBT for depression

The best-evidenced therapy for depression in adults – cognitive behavioural therapy (CBT) – is complex and costly. A randomized, controlled, non-inferiority trial compared the clinical efficacy and cost-effectiveness of behavioural activation (a simpler therapy) and CBT (Richards et al, 2016).

Participants were randomly allocated to behavioural activation ($n=221$) or CBT ($n=219$). The primary outcome was depression symptoms according to the Patient Health Questionnaire 9 at 12 months. Behavioural activation was non-inferior to CBT in treating adults with depression, and the researchers concluded that behavioural activation can be delivered by junior mental health workers with less intensive and costly training, with no lesser effect than CBT.

Richards DA, Ekers D, McMillan D et al (2016) Cost and outcome of behavioural activation versus cognitive behavioural therapy for depression (COBRA): a randomised, controlled, non-inferiority trial. *Lancet* (doi: 10.1016/S0140-6736(16)31140-0)

Men who have sex with men willing to use HIV rapid result self-test

A mixed methods research study was undertaken to explore preparedness for the HIV self-test among men who have sex with men and those involved in HIV prevention and care (Flowers et al, 2016).

Among men who have sex with men, self-test awareness was moderate (55%) but willingness to use the test was high (89%) and associated with meeting sexual partners online. Self-testing was understood as convenient, discreet, accessible, and with a low burden to services.

Flowers P, Riddell J, Park C et al (2016) Preparedness for use of the rapid result HIV self-test by gay men and other men who have sex with men (MSM): a mixed methods exploratory study among MSM and those involved in HIV prevention and care. *HIV Med* (doi: 10.1111/hiv.12420)

Updated European guidelines for diagnosing *Clostridium difficile* infection

The European Society of Clinical Microbiology and Infectious Diseases has released new guidelines outlining best practice methods to diagnose *Clostridium difficile* infection (Crobach et al, 2016). The latest document updates the original 2009 guidelines produced by the society, and includes recommendations concerning the use of new diagnostic technology such as nucleic acid amplification tests.

Despite the development of new tests for *C. difficile* infection, the authors strongly recommend against the routine use of any single test, irrespective on the technology on which it is based.

The new guidelines also make recommendations on repeated testing of both positive and negative samples, as well as on the selection of samples to be tested.

The strongest recommendations based on the evidence from all 41 studies included in the meta-analysis are:

- Samples to be tested for *C. difficile* infection should not be limited to cases in which a physician has specifically recommended a test
- A rectal swab can be used for testing by (toxigenic) culture, nucleic acid amplification test or glutamate dehydrogenase enzyme immunoassay in patients with apparent ileus (inactive bowel with no discernible bowel sounds)

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- Single, standalone tests are not reliable and should not be used: a two-step algorithm is necessary.

This two-step algorithm involves a combination of fast assays with follow-up tests:

- Route one – the two-stage procedure should begin with either a nucleic acid amplification test or a glutamate dehydrogenase enzyme immunoassay test. Negative tests should be treated as *C. difficile* infection-negative, while positive tests should be followed up with a toxin A/B enzyme immunoassay test to confirm the result
- Route two – the two-stage procedure should begin with both the glutamate dehydrogenase enzyme immunoassay test and the toxin A/B enzyme immunoassay test. If both are positive, *C. difficile* infection is likely to be present. If both are negative, *C. difficile* infection is unlikely to be present; however, if glutamate dehydrogenase is positive and toxin A/B is negative, then the tests may optionally be followed up with a nucleic acid amplification test or toxigenic culture test.

In endemic situations, repeat testing is not recommended after a positive result has been obtained but is advised after an initial negative sample from a patient with persistent high clinical suspicion.

‘The new guidelines are intended for use among medical microbiologists, gastroenterologists, infectious disease specialists and infection control practitioners,’ explains Professor Ed Kuijper of the Leiden University Medical Center, The Netherlands, whose research group has published the guidelines.

Discussing the role of the guidelines, he emphasized: ‘Our aim is to not only improve diagnosis of *C. difficile* infection, but also to standardise the diagnostic process across Europe to allow for improved surveillance of the disease.’

Crobach MJT, Planche T, Eckert C et al (2016) European Society of Clinical Microbiology and Infectious Diseases: update of the diagnostic guidance document for *Clostridium difficile* infection. *Clin Microbiol Infect* **22**(Suppl 4): S63–S81 (doi: 10.1016/j.cmi.2016.03.010)

Artery ligation and rubber band ligation compared for treatment of symptomatic haemorrhoids

Optimum surgical intervention for low-grade haemorrhoids is unknown. Haemorrhoidal artery ligation has been proposed as an effective, safe therapy while rubber band ligation is a commonly used outpatient treatment.

A multicentre, open-label, parallel group, randomized controlled trial (Brown et al, 2016) compared recurrence after haemorrhoidal artery ligation *vs* rubber band ligation in patients with grade II–III haemorrhoids. Eligible patients were randomly assigned to either rubber band ligation or haemorrhoidal artery ligation with Doppler. The primary outcome was recurrence at 1 year, derived from the patient's self-reported assessment in combination with resource use from their GP and hospital records.

Of 969 patients screened, 185 were randomly assigned to the haemorrhoidal artery ligation group and 187 to the rubber band ligation group. Of these, 337 had primary outcome data (176 in the rubber band ligation group and 161 in the haemorrhoidal artery ligation group). At 1 year post-procedure, 87 (49%) of 176 patients in the rubber

band ligation group and 48 (30%) of 161 patients in the haemorrhoidal artery ligation group had haemorrhoid recurrence (adjusted odds ratio 2.23, 95% confidence interval 1.42–3.51, $P=0.0005$). The main reason for this difference was the number of extra procedures required to achieve improvement (57 [32%] participants in the rubber band ligation group and 23 [14%] participants in the haemorrhoidal artery ligation group had a subsequent procedure for haemorrhoids).

Although recurrence after haemorrhoidal artery ligation was lower than a single rubber band ligation, because of the need for repeat bandings in this group, haemorrhoidal artery ligation was more painful than rubber band ligation. Patients (and health commissioners) might prefer rubber band ligation to the more invasive haemorrhoidal artery ligation.

Brown SR, Tiernan JP, Watson AJ et al; HubBLE Study team (2016) Haemorrhoidal artery ligation versus rubber band ligation for the management of symptomatic second-degree and third-degree haemorrhoids (HubBLE): a multicentre, open-label, randomised controlled trial. *Lancet* **388**(10042): 356–64 (doi: 10.1016/S0140-6736(16)30584-0)

Weight loss surgery in severely obese patients associated with increased fracture risk

Severely obese patients undergoing weight loss surgery are more likely to have increased fracture risks both before and after the surgical procedure compared to obese and non-obese people who do not need surgery (Rousseau et al, 2016).

A study examined the incidence and sites of fracture in severely obese patients who had undergone weight loss surgery, and compared them to obese and non-obese controls matched for sex and age.

Data were analysed from the Quebec Integrated Chronic Diseases Surveillance System (QICDSS) on 12 676 patients, and 38 028 obese and 126 760 non-obese people in the control groups between 2001–14.



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Before surgery, 10.5% of patients in the weight loss surgery group had at least one fracture compared with 8.1% of obese and 6.6% of non-obese people in the control groups.

After a mean follow up of 4.4 years, 4.1% of weight loss surgery patients had at least one fracture compared with 2.7% of obese and 2.4% of non-obese groups. The median time to first fracture was 3.9 years.

The increased risk remained even after adjusting for fracture history, number of comorbidities, material and social deprivation, and area of residence.

Rousseau C, Jean S, Gamache P et al (2016) Change in fracture risk and fracture pattern after bariatric surgery: nested case-control study. *BMJ* **354**: i3794 (doi: 10.1136/bmj.i3794)

Gender-specific differences important in type 2 diabetes

Type 2 diabetes is more frequently diagnosed at lower age and body mass index in men, but obesity, the most prominent risk factor, is more common in women. Both biological and psychosocial factors are responsible for sex and gender differences in diabetes risk and outcome (doi: 10.1210/er.2015-1137).

Women more likely to die within 30 days from *S. aureus* bacteraemia

Researchers from Denmark and Spain analysed data from population-based medical registers on 2638 patients diagnosed with bacteraemia caused by *Staphylococcus aureus*. When they assessed deaths within the first 30 days, they found that 29% of the women died compared to 22% of the men (adjusted hazard ratio = 1.30, 95% confidence interval 1.11–1.53) (doi: 10.1016/j.cmi.2016.06.002).

Four-strain influenza vaccine approved in the UK

The Medicines and Healthcare products Regulatory Agency has approved a quadrivalent influenza vaccine (split virion, inactivated) from Sanofi Pasteur MSD UK, which contains two A strains and two B strains of the influenza virus. The vaccine is licensed for use from 36 months of age.

Cancer overtakes heart disease as the main cause of death in 12 European countries

Although cardiovascular disease kills more people worldwide than anything else, with 17.3 million deaths globally, cancer has now overtaken cardiovascular disease as the main cause of death in 12 European countries, including the UK (Townsend et al, 2016).

Dr Nick Townsend, senior researcher at the BHF Centre on Population Approaches for Non-Communicable Disease Prevention at the University of Oxford, who led the research, said: 'These figures highlight the wide inequalities between European countries in deaths from cardiovascular disease.'

He continued: 'The 12 countries in which cancer has overtaken cardiovascular disease as the main cause of death are all found in western Europe... The highest numbers of deaths from cardiovascular disease tend to be seen in eastern European countries.'

Townsend N, Wilson L, Bhatnagar P, Wickramasinghe K, Rayner M, Nichols M (2016) Cardiovascular disease in Europe: epidemiological update 2016. *Eur Heart J* (doi: 10.1093/eurheartj/ehw334)

Delirium in patients with advanced cancer often goes undetected in the emergency department

A new study indicates that delirium is relatively frequent and underdiagnosed by physicians in patients with advanced cancer visiting the emergency department (Elsayem et al, 2016). Delirium was similarly common among older and younger patients, which suggests that in the setting of advanced cancer, all patients should be considered at higher risk for delirium.

To investigate the frequency of delirium among patients with cancer presenting to the emergency department, a team led by Dr Knox Todd, of The University of Texas MD Anderson Cancer Center in Houston, assessed a random sample of English-speaking advanced cancer patients who presented to the emergency department. All patients were assessed with two methods: the Confusion Assessment Method (CAM) to screen for delirium and the Memorial Delirium Assessment Scale (MDAS) to measure delirium severity.

Of 243 enrolled patients with an age range of 19–89 years, 22 (9%) had CAM-positive delirium and a median MDAS score of 14. Delirium was mild in 18 (82%) CAM-positive



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patients and moderate in four (18%) according to the MDAS.

Of 99 patients aged 65 years and older, ten (10%) had CAM-positive delirium, compared with 12 (8%) of the 144 patients younger than 65 years. When asked whether their patients were delirious, emergency department physicians failed to detect delirium in nine (41%) CAM-positive delirious patients.

'We found evidence of delirium in one of every ten patients with advanced cancer who are treated in the emergency department. Given that we

could only study patients who were able to give consent to enter our study, even 10% is likely to be a low estimate,' said Dr Todd.

He added: 'We also identified many psychoactive medications that could have contributed to delirium, and sharing this information with treating oncologists may help them avoid such complications in the next patient they treat.'

Elsayem AF, Bruera E, Valentine AD et al (2016) Delirium frequency among advanced cancer patients presenting to an emergency department: A prospective, randomized, observational study. *Cancer* (doi: 10.1002/cncr.30133)

Genetic variant in glucose transporter gene alters effects of metformin

The Metformin Genetics Consortium, funded by Wellcome, Diabetes UK and the National Institutes of Health in the USA, has identified a genetic variant in the gene encoding the glucose transporter GLUT2, a protein that plays an important role in transporting glucose inside the body (Zhou et al, 2016).

Metformin, a drug used by hundreds of millions of people with type 2 diabetes worldwide, has been in use for over 50 years. It protects against heart disease, and eye and kidney disease in people with type 2 diabetes, has been shown to have benefits against cancer, and is undergoing new clinical trials to determine if it can promote healthy ageing.

It has been known for some time that metformin works better in some people than others but the reasons for this have not been understood. The Consortium, led by the University of Dundee and University of California, San Francisco, investigated how well metformin worked in 13 123 participants of different ethnicity.

They showed that people who carried this variant had reduced levels of GLUT2 in the liver and other tissues resulting in a defect in how the body handles glucose. Metformin acted to specifically reverse this deficiency, resulting in a better response to metformin in people with this gene variant.

'The genetic effect was greatest in more overweight people,' said Dr Kaixin

Zhou from the School of Medicine at the University of Dundee. 'The normal dose of metformin used to treat patients with diabetes is between 500 mg and 2000 mg. We have found that overweight people who carry two copies of the genetic variant respond much better to metformin, equivalent to receiving an extra 550 mg of the drug.'

The researchers believe that their findings represent a significant step towards personalised, targeted therapy in the treatment of type 2 diabetes.

Zhou K, Yee SW, Seiser EL et al (2016) Variation in the glucose transporter gene SLC2A2 is associated with glycemic response to metformin. *Nat Genet* (doi: 10.1038/ng.3632)

Composition of IVF culture media affects the outcomes of embryos and babies

The first randomized controlled trial to look at the effect on perinatal outcomes of different in vitro fertilization (IVF) culture media found that they affected the numbers of viable embryos created, the rates of successful implantation in the womb, the pregnancy rates and the babies' birthweights (Kleijkers et al, 2016).

Dr John Dumoulin, IVF laboratory director in the department of obstetrics and gynaecology at Maastricht University Medical Centre,

The Netherlands, and his colleagues recruited 836 couples who were scheduled for IVF or intracytoplasmic sperm injection treatment at one of ten IVF centres in The Netherlands between July 2010 and May 2012. They randomized them to have their embryos cultured in one of two culture media: human tubal fluid or G5. The researchers followed the progress of the couples for a year after randomization or, where there were ongoing pregnancies, until birth.

A total of 383 babies were born alive, of which 300 were singletons and 80 were twins.



Dr John Dumoulin, Director, Department of Obstetrics and Gynaecology, Maastricht University Medical Centre, The Netherlands

The researchers found that birthweight was lower in the G5 group compared with the human tubal fluid group, with an average difference of 158g. More singleton babies were born prematurely in the G5 group (8.6% vs 2.2%), and even when the researchers adjusted for gestational age at birth and gender, the average birthweight was still lower in the G5 group.

Dr Dumoulin said:

'For the first time, a large randomized controlled trial [has] shown that human embryos that are cultured

in vivo are sensitive to their environment and that something is programmed into these embryos during those few days before transfer to the womb that still has an effect 9 months later. ...we should no longer blindly accept new culture media, or other alterations in laboratory or clinical procedures, without first rigorously studying effectiveness and safety.'

Kleijkers SH, Mantikou E, Slappendel E et al (2016) Influence of embryo culture medium (G5 and HTF) on pregnancy and perinatal outcome after IVF: a multicenter RCT. *Hum Reprod* (doi: 10.1093/humrep/dew156)

Prescription drug abuse assessed in EU countries

A study has investigated non-medical prescription drug use in Denmark, Germany, Spain, Sweden and the UK (Novak et al, 2016). Examining opioids, sedatives and stimulants the researchers found that out of the five countries examined, Germany had the lowest levels of non-medical prescription drug use, while the UK, Spain and Sweden had the highest levels. Lifetime and past-year prevalence of non-medical prescription drug use was estimated for opioids (13.5 and 5.0%), sedatives (10.9 and 5.8%), and stimulants (7.0 and 2.8%).

The most common sources of prescription drugs for non-medical use were family and friends – 44% for opioids and 62% for sedatives. Non-medical prescription drug

use was more common among men relative to women, among white relative to non-white people, and among those who were unemployed compared with other levels of employment. Young people aged 12–17 years were at lower risk of non-medical prescription drug use than people aged 18 years or older.

Having been prescribed a pain reliever was associated with an eight times higher risk of subsequent non-medical use of prescription pain relievers. The risk was ten times higher for sedatives and seven times higher for stimulants.

Novak SP, Håkansson A, Martinez-Raga J, Reimer J, Krotki K, Varughese S (2016) Nonmedical use of prescription drugs in the European Union. *BMC Psychiatry* 16: 274 (doi: 10.1186/s12888-016-0909-3)

CT scanning protocol for patients with severe trauma

An international, multicentre, randomized controlled trial was carried out at four hospitals in the Netherlands and one in Switzerland (Sierink et al, 2016). Patients with trauma with compromised vital parameters, clinical suspicion of life-threatening injuries, or severe injury were randomly assigned to immediate total-body computed tomography (CT) scanning or a standard work-up with conventional imaging supplemented with selective CT scanning.

Diagnosing patients with an immediate total-body CT scan did not reduce in-hospital mortality compared with the standard radiological work-up. Future research should focus on the selection of patients who will benefit from immediate total-body CT.

Sierink JC, Treskes K, Edwards MJ et al; REACT-2 study group (2016) Immediate total-body CT scanning versus conventional imaging and selective CT scanning in patients with severe trauma (REACT-2): a randomised controlled trial. *Lancet* 388(10045): 673–83 (doi: 10.1016/S0140-6736(16)30932-1)

Chondroitin sulfate and glucosamine sulfate may have no benefit for patients with knee osteoarthritis

Chondroitin sulfate plus glucosamine sulfate was no better than placebo for reducing pain and functional impairment, according to a multicentre, randomized, double-blinded, placebo-controlled study of 164 patients with knee osteoarthritis (doi: 10.1002/art.39819).

Patients were randomized to receive either chondroitin sulfate (1200 mg) plus glucosamine sulfate (1500 mg) or placebo in a single oral daily dose for 6 months.

Additional research may provide insights on the possible role of chondroitin sulfate and glucosamine sulfate therapy in the management of osteoarthritis.