research update

FROM THE JOURNALS Edited highlights of Richard Lehman's blog on http://bmj.co/Lehman

Cost and BENEFIT

BENEFIT is the name of a trial of belatacept for long term immunosuppression after renal transplantation. Given it was known that the drug would cost a lot (£17 000 first year, £5000 subsequently) this was quite a witty choice. Efficacy is how good a thing is at doing its job. Belatacept has good efficacy: "A 43% reduction in the risk of death or graft loss was observed for both the more-intensive and the less-intensive belatacept regimens as compared with the cyclosporine regimen." What matters for the patient is efficacy divided by cost difference (in principle), and ciclosporin costs 10-20 times less than belatacept. Here we get into NICE territory, and this takes us into the region of QALYs and absolute differences. Look at the Kaplan-Meier chart and you find that this impressive sounding 43% relative difference is actually quite tiny, because ciclosporin is already a pretty efficacious drug. So what's the real numerator and denominator, and how do you make the choice? Leave it to the patient, I would say; but this is difficult terrain.

N Engl J Med 2016, doi:10.1056/NEJMoa1506027

Maternal vitamin D and wheezy kids

Vitamin D could be the secret of so many things. But as we test each plausible hypothesis, expectations shrink. In this week's *JAMA*, two trials tested the idea that vitamin D supplementation during pregnancy might reduce wheezing in young children. The first trial was conducted in Copenhagen, where it seems that normal practice is to give all pregnant women 400 IU/day of vitamin D3. The interventions were either placebo or an additional 2400 IU/day. "The use of 2800 IU/d of vitamin D3 during the third trimester of pregnancy compared with 400 IU/d did not result in a statistically significant reduced risk of persistent wheeze in the offspring through age 3 years. However, interpretation of the study is limited by a wide CI [confidence interval] that includes a clinically important protective effect."

JAMA 2016, doi:10.1001/jama.2015.18318

The second trial was based in the United States and compared a dose 4400 IU daily with 400 IU. Numbers were similar but the period of administration was a little longer. Again, the effect size was too small to reach statistical significance by three years.

JAMA 2016, doi:10.1001/jama.2015.18589

Mighty mitral surgery

I'm still in awe of people who open up the heart and mess with its valves. As a child I remember seeing headlines about the first successes of open heart surgery, which were regarded as a miracle at the time. When I was a medical student, a single chest surgeon was doing it in Oxford, mostly on people with severe disease as a legacy of rheumatic fever. The work was still regarded as "heroic," with all that implied for patient outcomes. In this trial, 251 patients had severe mitral regurgitation as a result of ischaemic damage, and their mean age was 68 (you have to go to the supplement to find their baseline characteristics—naughty). In the two years following either full mitral valve replacement or mitral valve repair, 20% of the patients died, in both groups. The main difference between groups was that over half of those with repair instead of replacement had regurgitation, which led to a greater incidence of acute heart failure and hospital admission.

N Engl J Med 2016, doi:10.1056/NEJMoa1512913

"Intensive" NRT no better

Nicotine satisfies the craving for nicotine by binding to brain nicotine receptors. Varenicline reduces the craving for nicotine by binding to brain nicotine receptors. In this trial the researchers compared single mode nicotine administration (patch), dual mode nicotine (patch+lozenges, called C-NRT), and varenicline. "Among adults motivated to quit smoking, 12 weeks of open-label treatment with nicotine patch, varenicline, or C-NRT produced no significant differences in biochemically confirmed rates of smoking abstinence at 26 weeks."

JAMA 2016, doi:10.1001/jama.2015.19284

Patchy postal service

In a research setting, provision of nicotine patches in reducing doses, together with behavioural support, seems to help people stop smoking. But observational studies suggest that this may not happen in real life. A Canadian trial tested the value of posting the patches to 500 people who smoked more than 10 cigarettes a day and wanted help in giving up, while leaving another 500 to fend for themselves. Self reported abstinence rates were significantly higher among participants who were sent nicotine patches compared with the control group (30 day abstinence: 38 of 500 *v* 15 of 499; odds ratio 2.65). The researchers had hoped to confirm cessation with biochemical proof from saliva, but only half the participants submitted usable samples. It was half and half between spitting for the study and spitting on it. Not very grateful, considering how much nicotine patches cost in North America.

JAMA Intern Med 2016, doi:10.1001/jamainternmed.2015.7792

CORDELIA MOLLOY/SPL

ORIGINAL RESEARCH Randomised clinical trial (LIFE Study)

Effect of structured physical activity on prevention of serious fall injuries in adults aged 70-89

Gill TM, Pahor M, Guralnik JM, et al

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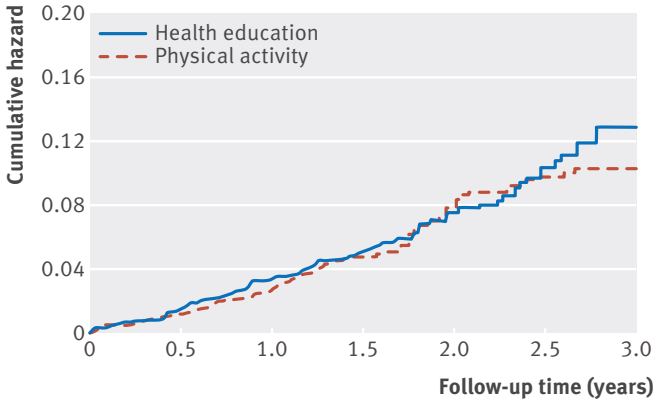
Find this at: http://dx.doi.org/10.1136/bmj.i245



Effect of a moderate physical activity intervention on time to first serious fall injury. Outcomes represent cumulative number of participants with a serious fall injury

Study question Does a long term, structured physical activity programme reduce the risk of serious fall injuries in sedentary older people with functional limitations?

Methods This randomised trial (LIFE Study) enrolled 1635 sedentary people (70-89 years) at eight centres throughout the US between February 2010 and December 2011. Participants had functional limitations (short physical performance battery score ≤9) but could walk 400 m. Participants were randomised to a structured, moderate intensity physical activity programme (n=818) conducted in a centre (twice/week) and at home (3-4 times/week), which included aerobic, strength, flexibility, and balance training activities, or to a health education programme (n=817) consisting of workshops on topics relevant to older people and upper extremity stretching exercises. Serious fall injuries (a fall resulting in a clinical, non-vertebral fracture or leading to hospital admission for another serious injury) was a prespecified secondary outcome in the study. Staff masked to intervention assignment assessed outcomes every six months for 42 months.

Study answer and limitations Over a median follow-up of 2.6 years, 75 (9.2%) participants in the physical activity group and 84 (10.3%) in the health education group experienced a serious fall injury (hazard ratio 0.90, 95% confidence interval 0.66 to 1.23; P=0.52). The trial was underpowered to detect small, but possibly important reductions in serious injuries.

What this study adds A structured physical activity programme, compared with a health education programme, did not reduce the risk of serious fall injuries among sedentary older people. These null results were accompanied by suggestive evidence that the physical activity programme may reduce the rate of fall related fractures and hospital admissions in men.

Funding, competing interests, data sharing
National Institute on Aging (cooperative agreement U01AG22376). The authors declare no competing interests. Information about data sharing is available at www.thelifestudy.org/public/index.cfm.
Study registration ClinicalsTrials.gov identifier NCT01072500.

RESEARCH METHODS AND REPORTING Use of PRISMA harms checklist

PRISMA harms checklist: improving harms reporting in systematic reviews

Zorzela L, Loke YK, Ioannidis JP, et al, and PRISMA harms group

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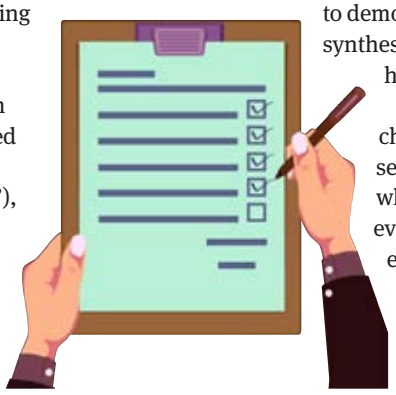
For any health intervention, accurate knowledge of both benefits and harms is needed. Systematic reviews often compound poor reporting of harms in primary studies by failing to report harms or doing so inadequately. While the PRISMA statement (Preferred Reporting Items for Systematic reviews and Meta-Analyses) helps systematic review authors ensure complete and transparent reporting, it is focused mainly on efficacy. Thus, a PRISMA harms checklist has been developed to improve harms reporting in systematic reviews, promoting a more balanced assessment of benefits and harms.

A development strategy, endorsed by the EQUATOR Network and existing reporting guidelines (including the PRISMA statement, PRISMA for abstracts, and PRISMA for protocols), was used. After the development of a draft checklist of items, a modified Delphi process was initiated. The Delphi consisted of three rounds of electronic feedback followed by an in-person meeting.

The PRISMA harms checklist contains four essential reporting elements to be added to the original PRISMA statement to improve harms reporting in reviews. These are reported in the title ("Specifically mention 'harms' or other related terms, or the harm of interest in the review"), synthesis of results ("Specify how zero events were handled, if relevant"), study characteristics ("Define each harm addressed, how it was ascertained (eg, patient report, active search), and over what time period"), and synthesis of results ("Describe any assessment of possible causality"). Additional guidance regarding existing PRISMA items was developed to demonstrate relevance when synthesising information about harms.



The PRISMA harms checklist identifies a minimal set of items to be reported when reviewing adverse events. This guideline extension is intended to improve harms reporting in systematic reviews, whether harms are a primary or secondary outcome.

> Systematic reviews often compound poor reporting of harms . . . by failing to report harms or doing so inadequately

Rheumatoid arthritis and risk of non-melanoma skin cancer

ORIGINAL RESEARCH Cohort study based on nationwide prospectively recorded data from Sweden

Rheumatoid arthritis, anti-tumour necrosis factor treatment, and risk of squamous cell and basal cell skin cancer

Raaschou P, Simard JF, Asker Hagelberg C, Askling J, for the ARTIS Study Group

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Find this at: http://dx.doi.org/10.1136/bmj.i262

Study question What is the risk of squamous cell cancer (SCC) and basal cell cancer (BCC) in patients with rheumatoid arthritis naive to biologic drugs, in patients starting tumour necrosis factor (TNF) inhibitor treatment, and in the general population?

Methods Patients with rheumatoid arthritis naive to biologics (n=46 409) or starting TNF inhibitor treatment as first biologic in 1998-2012 (n=12 558) and a matched general population comparator cohort (all identified through Swedish national quality of care and health registers) were compared with respect to incidence of first in situ or invasive SCC (1998-2012) and first BCC (2004-12), using Cox regression.

Study answer and limitations For BCC, the hazard ratio was 1.22 (95% confidence interval 1.07 to 1.41) comparing biologics-naive patients with the general population and 1.14 (0.98 to 1.33; 236 *v* 1587 events) comparing TNF inhibitor treated with biologics-naive patients. For SCC, the respective hazard ratios were 1.88 (1.74 to 2.03) and 1.30 (1.10 to 1.55; 191 *v* 847 events). Analyses were adjusted for several potential confounders, and a series of sensitivity analyses explored the robustness of the findings. However, because of the non-experimental study design, the possibility of residual or unmeasured confounding cannot be excluded.

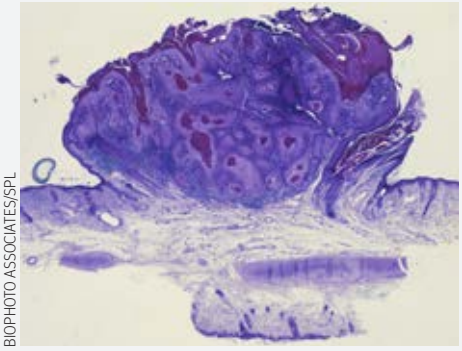
What this study adds Biologics-naive patients with rheumatoid arthritis are at a 20% increased risk of BCC and a near doubled risk of SCC compared with the general population; TNF inhibitor treatment does not have a clinically meaningful effect on the risk of BCC but may increase the risk of SCC by a further 30%. Irrespective of TNF inhibitor treatment, vigilance regarding skin malignancies may be advisable in patients with rheumatoid arthritis.

Funding, competing interests, data sharing The study was funded by Stockholm County Council, BTCure, the Swedish Cancer Society, Swedish Foundation for Strategic Research, Swedish Program on Chronic Inflammation, and Swedish Research Council. JA has received research grants from Pfizer, AstraZeneca, and Merck.

COMMENTARY Most of the excess risk is related to the disease, not the treatment

Previous studies have indicated that the incidence of non-melanoma skin cancers is higher in patients with rheumatoid arthritis than in the general population.[1 2] Immunosuppression may also contribute to an increased prevalence of these malignancies.[3 4] Tumour necrosis factor (TNF) inhibitors are the most commonly used biological immunosuppressive agents for treatment of rheumatoid arthritis. Pooled data from 74 randomised controlled trials showed that TNF inhibitors were associated with an increase in risk of non-melanoma skin cancer beyond the risk associated with rheumatoid arthritis alone.[5] Several large observational studies have supported this finding,[6 7] but others have not.[8-10] Most of these studies grouped patients with SCC and BCC together or had relatively small numbers of patients with SCC.[5-10]

The study by Raaschou and colleagues reports on the risk of SCC and BCC in biologics-naive and TNF inhibitor treated patients with rheumatoid arthritis in Sweden.[11] Capitalising on the availability of high quality national registers, the authors were able to investigate the vast majority of rheumatoid arthritis patients in Sweden during the study period. Importantly, they investigated SCC (>1000 cases) and BCC (>1800 cases) separately. Incidence rates were compared with rates observed in the matched general population. The matching strategy included county of residence to account for differences in ultraviolet light exposure.



BIOPHOTO ASSOCIATES/SPL

Raaschou and colleagues found that the risk of SCC in biologics-naive patients with rheumatoid arthritis was nearly double the risk observed in the general population, and the risk of BCC was increased by 22%. Patients treated with TNF inhibitors had a 30% greater risk of SCC than biologics-naive patients, whereas a small extra risk of BCC became insignificant after adjustment for confounders. In line with data from organ transplant literature, treatment with TNF inhibitors had a greater effect on the risk of SCC than of BCC. Even the association with SCC was modest. Assuming a causal relation, there would be one extra case of SCC each year for every 1600 patients treated with TNF inhibitors.

The main methodological limitation was that the authors were unable to adjust for severity of disease. People with more severe arthritis would be more likely to receive TNF inhibitors. If severity of arthritis is related to risk of non-melanoma skin cancer, then this outcome is confounded by indication. Any excess risk could be due to increased severity of disease rather than its treatment.

This study provides further strong evidence that people with rheumatoid arthritis have an increased risk of non-melanoma skin cancer. Treatment with TNF inhibitors is associated with a modest extra risk of SCC, but most of the overall risk originates from other factors including the disease itself. All patients with rheumatoid arthritis—regardless of treatment—might benefit from increased surveillance for skin cancer and should be advised to protect themselves from the sun.[13]

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ORIGINAL RESEARCH Prospective population based study

Benzodiazepine use and risk of incident dementia or cognitive decline

Gray S L, Dublin S, Yu O, et al

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Find this at: http://dx.doi.org/10.1136/bmj.i90

Study question What is the association between benzodiazepine use and risk of dementia or cognitive decline?

Methods In this prospective population based study the authors examined whether higher benzodiazepine use was associated with poor cognitive outcomes in adults aged ≥65 (n=3434) without dementia who received care through an integrated healthcare delivery system in Seattle, Washington. Initial recruitment began between 1994-96 and follow-up continued through September 2012. The main outcome measures included dementia, Alzheimer's disease, and cognitive decline.

B. BOISSONNET/ALAIMY

Benzodiazepine exposure was defined from computerised pharmacy data and consisted of the total standardised daily doses (TSDDs) dispensed over a 10 year period (a rolling window that moved forward in time during follow-up).

Study answer and limitations Over a mean follow-up of 7.3 years, 797 participants (23.2%) developed dementia, of whom 637 developed Alzheimer's disease. For dementia, the adjusted hazard ratios associated with cumulative benzodiazepine use compared with non-use were 1.25 (95% confidence interval 1.03 to 1.51) for 1-30 TSDDs, 1.31 (1.00 to 1.71) for 31-120 TSDDs, and 1.07 (0.82 to 1.39) for ≥121 TSDDs. Results were similar for Alzheimer's disease. A slightly higher risk of dementia was found in those with the lowest benzodiazepine use but not in those with the highest level of use. A limitation was that few participants had heavy benzodiazepine use.

What this study adds Our study suggests that higher benzodiazepine use is not associated with dementia or more rapid cognitive decline.

Funding, competing interests, data sharing This work was supported by the National Institute on Aging (NIH Grants U01AG00678, R03AG042930) and by the Branta Foundation. The authors have no competing interests or additional data to share.

ORIGINAL RESEARCH Single blind randomised controlled trial

Therapist guided internet based cognitive behavioural therapy for body dysmorphic disorder

Enander J, Andersson E, Mataix-Cols D, et al

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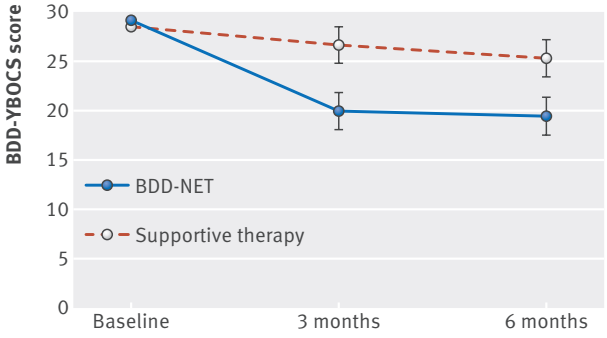
Study question To evaluate the efficacy of therapist guided internet based cognitive behavioural therapy (CBT) programme for body dysmorphic disorder (BDD-NET) compared with internet based supportive therapy.

Methods This was a single blind parallel randomised controlled trial with simple randomisation conducted in an academic medical setting. Participants were self referred adults with body dysmorphic disorder who were randomised to BDD-NET or internet based supportive therapy for 12 weeks. The primary outcome was the modified Yale-Brown obsessive compulsive scale (BDD-YBOCS) score after treatment and at six month follow-up. Responder status was defined as a reduction of ≥30% in symptoms on the BBD-YBOCS. Secondary outcomes were change in symptoms of depression (MADRS-S), clinical global improvement (CGI-I), global functioning (GAF), and quality of life (EQ5D). The six month follow-up time and all outcomes other than BDD-YBOCS and MADRS-S at three months were not pre-specified in the registration at clinicaltrials.gov because of an administrative error but were included in the original trial protocol approved by the regional ethics committee before the start of the trial.



Effect of treatment over time on Yale-Brown obsessive compulsive scale modified for body dysmorphic disorder (BDD-YBOCS) with 95% confidence intervals. Scores are shown at baseline, after treatment (3 months), and follow-up (6 months) according to treatment group

Study answer and limitations BDD-NET was superior to supportive therapy and was associated with significant improvements in severity of symptoms of body dysmorphic disorder (BDD-YBOCS group difference −7.1 points, 95% confidence interval −9.8 to −4.4) and in secondary measures of depression, global functioning, and quality of life. At follow-up, 56% of those receiving BDD-NET were responders, compared with 13% who received supportive therapy.
The number needed to treat was 2.34 (1.71 to 4.35). No serious adverse events were reported. Limitations include self referred participants who might have been particularly motivated, thereby potentially reducing the generalisability of the outcomes.

What this study adds CBT is efficacious and can be delivered safely through the internet to patients with body dysmorphic disorder. BDD-NET has the potential to increase access to evidence based psychiatric care for this mental disorder. BDD-NET could be particularly useful in a stepped care approach.

Funding, competing interests, data sharing The study was funded by the Swedish Research Council, ALF, and the Swedish Society of Medicine. The authors have no competing interest. No additional data available.
Study registration ClinicalTrials.gov NCT02010619.