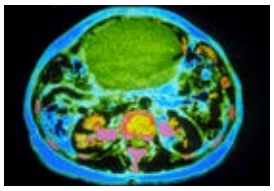
research

Total diet replacement programme leads to greater weight loss than usual care in overweight adults p 395

No apparent increase in short term overall cancer risk following use of NMDA contaminated valsartan p 396



Contemporary combined oral contraceptives associated with a reduction in ovarian cancer risk in young women p 398

Ranking of physicians' medical schools not associated with patient mortality post discharge p 398

ORIGINAL RESEARCH Pragmatic randomised controlled trial

Doctor referral of overweight people to low energy total diet replacement treatment (DROPLET)

Astbury NM, Aveyard P, Nickless A, et al

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Find this at: http://dx.doi.org/10.1136/bmj.k3760

Study question What is the effectiveness, tolerability, and safety of a total diet replacement (TDR) programme for routine treatment of obesity in a primary care setting?

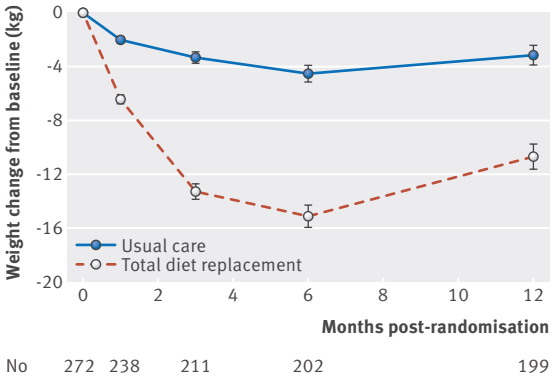
Methods The authors recruited 278 obese adults seeking support to lose weight from 10 primary care practices in Oxfordshire, to a pragmatic, two arm, parallel group, open label, individually randomised controlled trial. Participants were allocated to a TDR programme or usual care. The TDR programme comprised weekly behavioural support for 12 weeks and monthly support for three months, with formula food products providing 810 kcal/day (3389 kJ/day) as the sole food during the first eight weeks followed by reintroduction of food. Usual care comprised 12 weeks of behavioural support for weight loss from a practice nurse advising modest energy restriction. The primary outcome was weight change at 12 months analysed as intention to treat with mixed effects models. Secondary outcomes included biomarkers of cardiovascular and metabolic risk. Adverse events were recorded.

Study answer and limitations
At one year, participants in the TDR group lost more weight (−10.7 kg) than participants in the usual care group (−3.1 kg): adjusted mean difference −7.2 kg (95% confidence interval −9.4 to −4.9 kg). Improvements in markers of cardiovascular risk were commensurate with weight loss. Rates of adverse events classed as moderate severity or greater were similar in both groups, and no serious adverse events related to the intervention occurred in either group. Longer term follow-up could assess the durability of weight loss and health benefits.

What this study adds
Referral to a TDR programme with support provided by a commercial provider is an effective intervention for the treatment of obesity.

Funding, competing interests, data sharing Funding was provided by the Cambridge Weight Plan UK and the National Institute for Health Research. PA and SAJ have previously conducted studies in which weight loss interventions were provided to the NHS by WeightWatchers, Slimming World, or Rosemary Conley. Researchers may request access to data from the chief investigator.

Study registration International Standard Randomised Controlled Trials ISRCTN75092026.



Weight change over 12 months in intention to treat population. Values represent mean (standard error of the mean)

Cancer risk from contaminated valsartan

ORIGINAL RESEARCH Danish nationwide cohort study

FAST TRACK

Use of N-nitrosodimethylamine (NDMA) contaminated valsartan products and risk of cancer

Pottegård A, Kristensen KB, Ernst MT, Johansen NB, Quartarolo P, Hallas J

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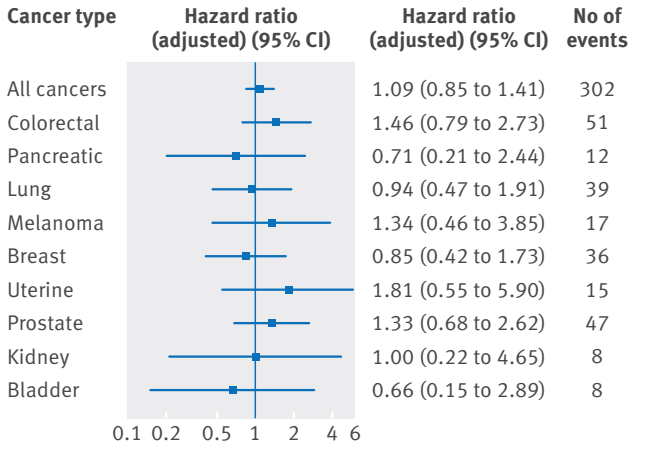
Find this at: http://dx.doi.org/10.1136/bmj.k3851

Study question What is the cancer risk associated with exposure to N-nitrosodimethylamine (NDMA) through contaminated valsartan products?

Methods This nationwide cohort study using Danish health registries included patients using valsartan at 1 January 2012 or initiating use between 1 January 2012 and 30 June 2017. Participants were followed until a cancer outcome, death, migration, or end of the study period (30 June 2018). Hazard ratios were estimated for exposure to NDMA associated with risk of all cancers except non-melanoma skin cancer.

Study answer and limitations The final cohort comprised 5150 participants followed for a median of 4.6 years. In total, 3625



Estimates for association between use of potentially N-nitrosodimethylamine (NDMA) contaminated valsartan products and risk of single cancer outcomes compared with users of non-contaminated valsartan products. Number of events are total number of events among valsartan users

COMMENTARY Regulators took rapid action, but exposed patients still require long term monitoring

Despite being limited by its short follow-up, the registry based cohort study by Pottegård and colleagues provides reassuring interim evidence about the risk of cancer in patients treated with valsartan products contaminated with a probable human carcinogen (N-nitrosodimethylamine, NDMA).[1] This study was planned, conducted, analysed, and published within three months from the notification of this quality issue to regulatory authorities.[2] It would not have been possible without linking data from four Danish nationwide registries collecting information on prescriptions, cancer diagnoses, hospital admissions, mortality, and migration. The authors report no increase in overall cancer risk among users of potentially contaminated valsartan products followed up for a median of 4.6 years.

How did regulatory agencies react to the safety concern affecting medicinal products containing valsartan? Europe, the US, Canada, and Japan rapidly started their own investigations, with some international collaboration. First, they mapped all the licensed medicines containing the active substance valsartan—an angiotensin II receptor blocker—supplied by the company that detected the impurity. They recalled the contaminated lots, amounting to more than 3000 products licensed at the national level or centrally by the European Medicines Agency.[3]

Checks and balances

Second, regulatory authorities are collecting information on the cause of this contamination; possibly related to a change in the manufacturing process in 2012. Some will wonder whether the impurity could have been detected earlier. Possibly it could. Manufacturing processes must be checked and monitored for any known impurities that imply a risk—as with NDMA, which is a recognised probable human genotoxic compound. This task is the responsibility of the manufacturers themselves, but the marketing authorisation holders are responsible for the quality of the finished medicinal products they put on the market. Public authorities are called to authorise production sites and supervise the quality of pharmaceuticals with frequent, thorough inspections.[6 7]

Regulators' relationship with industry is mainly based on trust

The European Medicines Agency has mainly a coordinating and harmonisation role, and the national drug agencies have final responsibility for inspections. However, it must be kept in mind that the relationship with industry is mainly based on trust. This applies to clinical efficacy and safety data too, not just quality. Misleading, incomplete, or delayed reporting on clinical efficacy and safety may have a much worse impact on public health than quality.[8]

Third, regulatory authorities are trying to estimate the theoretical risk of the NDMA exposure after the use of contaminated valsartan. The EMA estimated there might be one extra case of cancer for every 5000 patients using the highest valsartan dose (320 mg) every day for seven years.[9] This is based on the average levels of this impurity detected in the active substance and the possible cancer risk extrapolated from animal studies.

Similar estimates by the US Food and Drug Administration report one extra case of cancer for every 8000 patients treated for four years.[10] The Danish cohort covers about one fifth of

Rita Banzi rita.banzi@marionegri.it
Vittorio Bertele'
See bmj.com for author details

participants classified as unexposed to NDMA contributed 7344 person years and 3450 participants classified as ever exposed to NDMA contributed 11 920 person years. The adjusted hazard ratio for overall cancer was 1.09 (95% confidence interval 0.85 to 1.41). When single cancer outcomes were analysed, increases were observed in risk for colorectal cancer (hazard ratio 1.46, 95% confidence interval 0.79 to 2.73) and uterine cancer (1.81, 0.55 to 5.90), although with wide confidence intervals that included the null. The principal weakness of the study is the limited median follow-up, precluding conclusions about long term cancer risk. The limited number of outcomes made it difficult to interpret estimates for individual cancers.

What this study adds The results do not imply a marked increase in short term overall cancer risk in users of valsartan contaminated with NDMA. However, uncertainty persists about single cancer outcomes, and studies with longer follow-up are needed to assess long term cancer risk.

Funding, competing interests, data sharing This study was not funded. The authors declare no conflicts of interest. No additional data available.

the person years of exposure required to confirm the EMA estimation. Therefore, patients exposed to this impurity need continued monitoring.

Active pharmacovigilance research programmes, ideally at the European level, may be useful to clarify the potential impact on valsartan safety. Had the Danish study extended to a larger European population, we might already have a conclusive answer.

The EMA response to these safety concerns seems to have been prompt and transparent.[11] One hopes it will be effective too. Pharmaceutical companies that had used the contaminated active substance in their valsartan medicines are now required to test samples they hold to determine the actual NDMA levels in the final products. Additional checks are being done by European official control laboratories, and other manufacturers are under investigation too.

International cooperation

The outcome of the Article 31 pharmacovigilance referral procedure, dealing with safety concerns of medicinal products authorised in the European Union,[12] is expected later in September. International cooperation between regulators has become important to ensure effective oversight and to respond to the challenges of the increasingly complex global supply of medicines.

Regulatory actions coupled with the generation of robust evidence are the keys to responding promptly to emerging public health concerns.

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Find the full version with references at http://dx.doi.org/10.1136/bmj.k3855

ORIGINAL RESEARCH Prospective, nationwide cohort study

Association between contemporary hormonal contraception and ovarian cancer in women of reproductive age in Denmark

Iversen L, Fielding S, Lidegaard Ø, Mørch LS, Skovlund CW, Hannaford PC

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Find this at: http://dx.doi.org/10.1136/bmj.k3609

Study question Is the use of contemporary combined hormonal contraceptives (including progestogen types in combined preparations and all progestogen-only products) associated with the risk of ovarian cancer (overall and specific types) in women of reproductive age?

Methods This study included all women aged 15-49 in 1995-2014, excluding those who immigrated after 1995, had cancer (except non-melanoma skin cancer), had venous thrombosis, or were treated for infertility before entry. Women were categorised as never users (no record of being dispensed hormonal contraception), current or recent users (≤1 year after stopping use), or former users (>1 year after stopping use) of different hormonal contraceptives. Relative risk of ovarian cancer among users was calculated by Poisson regression. Separate analyses examined women followed until first contraception type switch and those with full contraceptive histories. Duration, time since last use, and tumour histology were examined and the population prevented fraction was calculated.

Study answer and limitations During 21.4 million person years, 1249 incident ovarian cancers occurred. Compared with never users of hormonal contraceptives, reduced risks in ovarian cancer occurred with current or recent users (relative risk 0.58, 95% confidence interval 0.49 to 0.68) and former users of any hormonal contraception (0.77, 0.66 to 0.91). Relative risks among current or recent users decreased with increasing duration of use (from 0.82 (0.59 to 1.12) with ≤1 year use to 0.26 (0.16 to 0.43) with >10 years' use; P_{trend}<0.001). Similar results were achieved among women followed up to their first switch in contraceptive type. Few women were exclusive users of progestogen-only contraceptives, so evidence regarding these contraceptives was limited; use of these products was not associated with ovarian cancer risk. Among never users of hormonal contraception, the reduction in the age standardised absolute rate of ovarian cancer was 3.2 per 100 000 person years. Based on the population prevented fraction, hormonal contraception prevented an estimated 21% of ovarian cancers in this population.

What this study adds Use of contemporary combined oral contraceptives containing newer progestogens is associated with a reduction in the risk of ovarian cancer in young women. This protective effect is related to duration of use, which diminishes after stopping use. Little evidence suggests any beneficial ovarian cancer effects among exclusive users of progestogen-only contraceptives.

Funding, competing interests, and data sharing
Supported by a grant (11645) from the Novo Nordisk Foundation. Details of competing interests are listed in full on bmj.com.

ORIGINAL RESEARCH Observational study

Association between physician *US News & World Report* medical school ranking and patient outcomes and costs of care

Tsugawa Y, Blumenthal DM, Jha AK, Orav EJ, Jena AB

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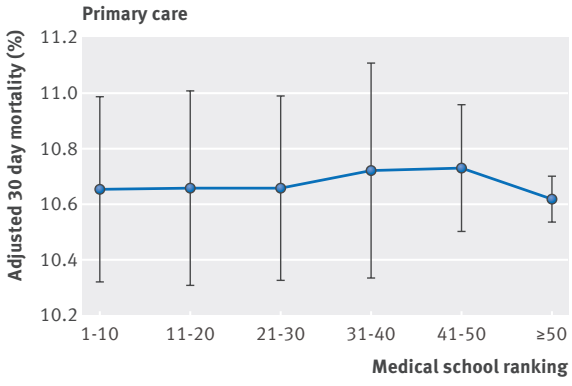
Find this at: http://dx.doi.org/10.1136/bmj.k3640

Study question Is the *US News & World Report* (USNWR) ranking of the medical school a physician attended associated with patient outcomes and healthcare spending?

Methods In this observational study the authors investigated the association between the USNWR ranking of the medical school a physician attended and the physician's patient outcomes (30 day mortality and 30 day readmission rates) and costs of care (Medicare Part B spending) adjusted for patient and physician characteristics and hospital fixed effects. The study population comprised a 20% random sample of Medicare fee-for-service beneficiaries from 2011-15 who were aged 65 years or older (n=996 212) and were admitted as an emergency to hospital with a medical condition and treated by general internists.



Association between physicians' *US News & World Report* medical school ranking for primary care and patient 30 day mortality. Adjusted for patient and physician characteristics and hospital fixed effects

Study answer and limitations Physicians who graduated from higher USNWR ranked medical schools had lower 30 day readmission rates (adjusted rate 15.7% for top 10 schools *v* 16.1% for schools ranked ≥50; adjusted risk difference 0.4%, 95% confidence interval 0.1% to 0.8%; P for trend=0.005) and slightly lower spending (adjusted spending $1029 (£790) *v* $1066; adjusted difference $36, 95% confidence interval $20 to $52; P for trend <0.001) compared with graduates of lower ranked schools, but no difference in 30 day mortality. Physicians who graduated from highly ranked medical schools had slightly lower spending compared with graduates of lower ranked schools. The analysis was limited to Medicare patients aged 65 or older, so the findings may not be generalisable to other populations.

What this study adds For physicians practising within the same hospital, the USNWR ranking of the medical school from which they graduated bears no relation to patient mortality after hospital admission and little or no relation to readmissions and costs of care.

Funding, competing interests, data sharing The authors received no specific funding for this work. See full paper on bmj.com for competing interests. Medicare data are not available for sharing.