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BMJ (5 May 2018, Vol. 361, No. 8151)

Emollient bath additives for the treatment of childhood eczema (BATHE): Multicentre pragmatic parallel group randomised controlled trial of clinical and cost effectiveness

Miriam Santer, Matthew J Ridd, Nick A Francis, et al.
BMJ 2018; 361 (Published 03 May 2018)
https://www.bmj.com/content/361/bmj.k1332

Abstract
Objectives To determine the clinical effectiveness and cost effectiveness of including emollient bath additives in the management of eczema in children.
Design Pragmatic randomised open label superiority trial with two parallel groups.
Setting 96 general practices in Wales and western and southern England.
Participants 483 children aged 1 to 11 years, fulfilling UK diagnostic criteria for atopic dermatitis. Children with very mild eczema and children who bathed less than once weekly were excluded.
Interventions Participants in the intervention group were prescribed emollient bath additives by their usual clinical team to be used regularly for 12 months. The control group were asked to use no bath additives for 12 months. Both groups continued with standard eczema management, including leave-on emollients, and caregivers were given standardised advice on how to wash participants.
Main outcome measures The primary outcome was eczema control measured by the patient oriented eczema measure (POEM, scores 0-7 mild, 8-16 moderate, 17-28 severe) weekly for 16 weeks. Secondary outcomes were eczema severity over one year (monthly POEM score from baseline to 52 weeks), number of eczema exacerbations resulting in primary healthcare consultation, disease specific quality of life (dermatitis family impact), generic quality of life (child health utility-9D), utilisation of resources, and type and quantity of topical corticosteroid or topical calcineurin inhibitors prescribed.
Results 483 children were randomised and one child was withdrawn, leaving 482 children in the trial: 51% were girls (244/482), 84% were of white ethnicity (447/470), and the mean age was 5 years. 96% (461/482) of participants completed at least one post-baseline POEM, so were included in the analysis, and 77% (370/482) completed questionnaires for more than 80% of the time points for the primary outcome (12/16 weekly questionnaires to 16 weeks). The mean baseline POEM score was 9.5 (SD 5.7) in the bath additives group and 10.1 (SD 5.8) in the no bath additives group. The mean POEM score over the 16

week period was 7.5 (SD. 6.0) in the bath additives group and 8.4 (SD 6.0) in the no bath additives group. No statistically significant difference was found in weekly POEM scores between groups over 16 weeks. After controlling for baseline severity and confounders (ethnicity, topical corticosteroid use, soap substitute use) and allowing for clustering of participants within centres and responses within participants over time, POEM scores in the no bath additives group were 0.41 points higher than in the bath additives group (95% confidence interval −0.27 to 1.10), below the published minimal clinically important difference for POEM of 3 points. The groups did not differ in secondary outcomes, economic outcomes, or adverse effects.
Conclusions This trial found no evidence of clinical benefit from including emollient bath additives in the standard management of eczema in children. Further research is needed into optimal regimens for leave-on emollient and soap substitutes.

Biases in electronic health record data due to processes within the healthcare system: Retrospective observational study
Denis Agniel, Isaac S Kohane, Griffin M Weber
BMJ 2018; 361 (Published 30 April 2018)
https://www.bmj.com/content/361/bmj.k1479

Abstract
Objective To evaluate on a large scale, across 272 common types of laboratory tests, the impact of healthcare processes on the predictive value of electronic health record (EHR) data.
Design Retrospective observational study.
Setting Two large hospitals in Boston, Massachusetts, with inpatient, emergency, and ambulatory care.
Participants All 669 452 patients treated at the two hospitals over one year between 2005 and 2006.
Main outcome measures The relative predictive accuracy of each laboratory test for three year survival, using the time of the day, day of the week, and ordering frequency of the test, compared to the value of the test result.
Results The presence of a laboratory test order, regardless of any other information about the test result, has a significant association (P<0.001) with the odds of survival in 233 of 272 (86%) tests. Data about the timing of when laboratory tests were ordered were more accurate than the test results in predicting survival in 118 of 174 tests (68%).
Conclusions Healthcare processes must be addressed and accounted for in analysis of observational health data. Without careful consideration to context, EHR data are unsuitable for many research questions. However, if explicitly modeled, the same processes that make EHR data complex can be leveraged to gain insight into patients' state of health.

Effect of public reporting of surgeons' outcomes on patient selection, "gaming," and mortality in colorectal cancer surgery in England: Population based cohort study
Abigail E Vallance, Nicola S Fearnhead, Angela Kuryba, et al.
BMJ 2018; 361 (Published 02 May 2018)
https://www.bmj.com/content/361/bmj.k1581

Abstract
Objective To determine the effect of surgeon specific outcome reporting in colorectal cancer surgery on risk averse clinical practice, “gaming” of clinical data, and 90 day postoperative mortality.
Design National cohort study.
Setting English National Health Service hospital trusts.
Population 111 431 patients diagnosed as having colorectal cancer from 1 April 2011 to 31 March 2015 included in the National Bowel Cancer Audit.
Intervention Public reporting of surgeon specific 90 day mortality in elective colorectal cancer surgery in England introduced in June 2013.
Main outcome measures Proportion of patients with colorectal cancer who had an elective major resection, predicted 90 day mortality based on characteristics of patients and tumours, and observed 90 day mortality adjusted for differences in characteristics of patients and tumours, comparing patients who had surgery between April 2011 and June 2013 and between July 2013 and March 2015.
Results The proportion of patients with colorectal cancer undergoing major resection did not change after the introduction of surgeon specific public outcome reporting (39 792/62 854 (63.3%) before versus 30 706/48 577 (63.2%) after; P=0.8). The proportion of these major resections categorised as elective or scheduled also did not change (33 638/39 792 (84.5%) before versus 25 905/30 706 (84.4%) after; P=0.5). The predicted 90 day mortality remained the same (2.7% *v* 2.7%; P=0.3), but the observed 90 day mortality fell (952/33 638 (2.8%) *v* 552/25 905 (2.1%)). Change point analysis showed that this reduction was over and above the existing downward trend in mortality before the introduction of public outcome reporting (P=0.03).
Conclusions This study did not find evidence that the introduction of public reporting of surgeon specific 90 day postoperative mortality in elective colorectal cancer surgery has led to risk averse clinical practice behaviour or “gaming” of data. However, its introduction coincided with a significant reduction in 90 day mortality.

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JAMA: Journal of the American Medical Association (8 May 2018, Vol. 319, No. 18)

Effect of Coaching to Increase Water Intake on Kidney Function Decline in Adults with Chronic Kidney Disease: The CKD WIT Randomized Clinical Trial

William F. Clark, Jessica M. Sontrop, Shih-Han Huang, et al

JAMA. 2018; 319 (18): 1870-1879.
https://jamanetwork.com/journals/jama/fullarticle/2680548

Abstract
Importance In observational studies, increased water intake is associated with better kidney function.
Objective To determine the effect of coaching to increase water intake on kidney function in adults with chronic kidney disease.
Design, Setting, and Participants The CKD WIT (Chronic Kidney Disease Water Intake Trial) randomized clinical trial was conducted in 9 centers in Ontario, Canada, from 2013 until 2017 (last day of follow-up, May 25, 2017). Patients had stage 3 chronic kidney disease (estimated glomerular filtration rate [eGFR] 30-60 mL/min/1.73 m ^{2}and microalbuminuria or macroalbuminuria) and a 24-hour urine volume of less than 3 0.L.
Interventions Patients in the hydration group (n = 316) were coached to drink more water, and those in the control group (n = 315) were coached to maintain usual intake.

Main Outcomes and Measures The primary outcome was change in kidney function (eGFR from baseline to 12 months). Secondary outcomes included 1-year change in plasma copeptin concentration, creatinine clearance, 24-hour urine albumin, and patient-reported overall quality of health (0 [worst possible] to 10 [best possible.([

Results Of 631 randomized patients (mean age, 65.0 years; men, 63.4%; mean eGFR, 43 mL/min/1.73 m ;^{2}median urine albumin, 123 mg/d), 12 died (hydration group [n = 5]; control group [n = 7]). Among 590 survivors with 1-year follow-up measurements (95% of 619), the mean change in 24-hour urine volume was 0.6 L per day higher in the hydration group (95% CI, 0.5 to 0.7 ;*P* .(001. > The mean change in eGFR was −2.2 mL/min/1.73 m ^{2} in the hydration group and −1.9 mL/min/1.73 m ^{2}in the control group (adjusted between-group difference, −0.3 mL/min/1.73 m %95] ^{2}CI, −1.8 to 1.2 ;*P* .([74. = The mean between-group differences (hydration vs control) in secondary outcomes were as follows: plasma copeptin, −2.2 pmol/L (95% CI, −3.9 to −0.5 ;*P* ;(01. = creatinine clearance, 3.6 mL/min/1.73 m %95) ^{2}CI, 0.8 to 6.4 ;*P* ;(01. = urine albumin, 7 mg per day (95% CI, −4 to 51 ;*P* ;(11. = and quality of health, 0.2 points (95% CI, −0.3 to 0.3 ;*P*.(22. =

Conclusions and Relevance Among adults with chronic kidney disease, coaching to increase water intake compared with coaching to maintain the same water intake did not significantly slow the decline in kidney function after 1 year. However, the study may have been underpowered to detect a clinically important difference.

Effect of Intravesical Instillation of Gemcitabine vs Saline Immediately Following Resection of Suspected Low-Grade Non–Muscle-Invasive Bladder Cancer on Tumor Recurrence: SWOG S0337 Randomized Clinical Trial

Edward M. Messing; Catherine M. Tangen; Seth P. Lerner; et al

JAMA. 2018; 319 (18): 1880-1888.
https://jamanetwork.com/journals/jama/article-abstract/2680547?redirect=true

Abstract

Importance Low-grade non–muscle-invasive urothelial cancer frequently recurs after excision by transurethral resection of bladder tumor (TURBT).

Objective To determine whether immediate post-TURBT intravesical instillation of gemcitabine reduces recurrence of suspected low-grade non–muscle-invasive urothelial cancer compared with saline.

Design, Setting, and Participants Randomized double-blind clinical trial conducted at 23 US centers. Patients with suspected low-grade non–muscle-invasive urothelial cancer based on cystoscopic appearance without any high-grade or without more than 2 low-grade urothelial cancer episodes within 18 months before index TURBT were enrolled between January 23, 2008, and August 14, 2012, and followed up every 3 months with cystoscopy and cytology for 2 years and then semiannually for 2 years. Patients were monitored for tumor recurrence, progression to muscle invasion, survival, and toxic effects. The final date of follow-up was August 14, 2016.

Interventions Participants were randomly assigned to receive intravesical instillation of gemcitabine (2 g in 100 mL of saline) (n = 201) or saline (100 mL) (n = 205) for 1 hour immediately following TURBT.

Main Outcomes and Measures The primary outcome was time to recurrence of cancer. Secondary end points were time to muscle invasion and death due to any cause.

Results Among 406 randomized eligible patients (median age, 66 years; 84.7% men), 383 completed the trial. In the intention-to-treat analysis, 67 of 201 patients (4-year estimate, 35%) in the gemcitabine group and 91 of 205 patients (4-year estimate, 47%) in the saline group had cancer recurrence within 4.0 years (hazard ratio, 0.66; 95% CI, 0.48-0.90;

P<.001 by 1-sided log-rank test for time to recurrence). Among the 215 patients with low-grade non–muscle-invasive urothelial cancer who underwent TURBT and drug instillation, 34 of 102 patients (4-year estimate, 34%) in the gemcitabine group and 59 of 113 patients (4-year estimate, 54%) in the saline group had cancer recurrence (hazard ratio, 0.53; 95% CI, 0.35-0.81; *P* = .001 by 1-sided log-rank test for time to recurrence). Fifteen patients had tumors that progressed to muscle invasion (5 in the gemcitabine group and 10 in the saline group; *P* = .22 by 1-sided log-rank test) and 42 died of any cause (17 in the gemcitabine group and 25 in the saline group; *P* = .12 by 1-sided log-rank test). There were no grade 4 or 5 adverse events and no significant differences in adverse events of grade 3 or lower.
Conclusions and Relevance Among patients with suspected low-grade non–muscle-invasive urothelial cancer, immediate postresection intravesical instillation of gemcitabine, compared with instillation of saline, significantly reduced the risk of recurrence over a median of 4.0 years. These findings support using this therapy, but further research is needed to compare gemcitabine with other intravesical agents.

Association of Vasopressin Plus Catecholamine Vasopressors vs Catecholamines Alone With Atrial Fibrillation in Patients With Distributive Shock: A Systematic Review and Meta-analysis

William F. McIntyre, Kevin J. Um, Waleed Alhazzani, et al
JAMA. 2018; 319 (18): 1889-1900.
https://jamanetwork.com/journals/jama/article-abstract/2680546?redirect=true

Abstract
Importance Vasopressin is an alternative to catecholamine vasopressors for patients with distributive shock—a condition due to excessive vasodilation, most frequently from severe infection. Blood pressure support with a noncatecholamine vasopressor may reduce stimulation of adrenergic receptors and decrease myocardial oxygen demand. Atrial fibrillation is common with catecholamines and is associated with adverse events, including mortality and increased length of stay (LOS).
Objectives To determine whether treatment with vasopressin + catecholamine vasopressors compared with catecholamine vasopressors alone was associated with reductions in the risk of adverse events.
Data Sources MEDLINE, EMBASE, and CENTRAL were searched from inception to February 2018. Experts were asked and meta-registries searched to identify ongoing trials.
Study Selection Pairs of reviewers identified randomized clinical trials comparing vasopressin in combination with catecholamine vasopressors to catecholamines alone for patients with distributive shock.
Data Extraction and Synthesis Two reviewers abstracted data independently. A random-effects model was used to combine data.
Main Outcomes and Measures The primary outcome was atrial fibrillation. Other outcomes included mortality, requirement for renal replacement therapy (RRT), myocardial injury, ventricular arrhythmia, stroke, and LOS in the intensive care unit and hospital. Measures of association are reported as risk ratios (RRs) for clinical outcomes and mean differences for LOS.
Results Twenty-three randomized clinical trials were identified (3088 patients; mean age, 61.1 years [14.2]; women, 45.3%). High-quality evidence supported a lower risk of atrial fibrillation associated with vasopressin treatment (RR, 0.77 [95% CI, 0.67 to 0.88]; risk difference [RD], −0.06 [95% CI, −0.13 to 0.01]). For mortality, the overall RR estimate was 0.89 (95% CI, 0.82 to 0.97; RD, −0.04 [95% CI, −0.07 to 0.00]); however, when limited to trials at low risk of bias, the RR estimate was 0.96 (95% CI, 0.84 to 1.11). The overall RR

estimate for RRT was 0.74 (95% CI, 0.51 to 1.08; RD, −0.07 [95% CI, −0.12 to −0.01]). However, in an analysis limited to trials at low risk of bias, RR was 0.70 (95% CI, 0.53 to 0.92, *P* for interaction = .77). There were no significant differences in the pooled risks for other outcomes.

Conclusions and Relevance In this systematic review and meta-analysis, the addition of vasopressin to catecholamine vasopressors compared with catecholamines alone was associated with a lower risk of atrial fibrillation. Findings for secondary outcomes varied.

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The Lancet (5 May 2018, Vol. 391, No. 10132)

Development and validation of a Hospital Frailty Risk Score focusing on older people in acute care settings using electronic hospital records: An observational study

Thomas Gilbert, Jenny Neuburger, Joshua Kraindler, et al.

The Lancet: Volume 391, No. 10132, p1775–1782, 5 May 2018
https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(18)30668-8/fulltext

Summary

Background

Older people are increasing users of health care globally. We aimed to establish whether older people with characteristics of frailty and who are at risk of adverse health-care outcomes could be identified using routinely collected data.

Methods

A three-step approach was used to develop and validate a Hospital Frailty Risk Score from International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10) diagnostic codes. First, we carried out a cluster analysis to identify a group of older people (≥75 years) admitted to hospital who had high resource use and diagnoses associated with frailty. Second, we created a Hospital Frailty Risk Score based on ICD-10 codes that characterised this group. Third, in separate cohorts, we tested how well the score predicted adverse outcomes and whether it identified similar groups as other frailty tools.

Findings

In the development cohort (n=22 139), older people with frailty diagnoses formed a distinct group and had higher non-elective hospital use (33·6 bed-days over 2 years compared with 23·0 bed-days for the group with the next highest number of bed-days). In the national validation cohort (n=1 013 590), compared with the 429 762 (42·4%) patients with the lowest risk scores, the 202 718 (20·0%) patients with the highest Hospital Frailty Risk Scores had increased odds of 30-day mortality (odds ratio 1·71, 95% CI 1·68–1·75), long hospital stay (6·03, 5·92–6·10), and 30-day readmission (1·48, 1·46–1·50). The c statistics (ie, model discrimination) between individuals for these three outcomes were 0·60, 0·68, and 0·56, respectively. The Hospital Frailty Risk Score showed fair overlap with dichotomised Fried and Rockwood scales (kappa scores 0·22, 95% CI 0·15–0·30 and 0·30, 0·22–0·38, respectively) and moderate agreement with the Rockwood Frailty Index (Pearson's correlation coefficient 0·41, 95% CI 0·38–0·47).

Interpretation

The Hospital Frailty Risk Score provides hospitals and health systems with a low-cost, systematic way to screen for frailty and identify a group of patients who are at greater risk of adverse outcomes and for whom a frailty-attuned approach might be useful.

Trends in future health financing and coverage: Future health spending and universal health coverage in 188 countries, 2016–40

Global Burden of Disease Health Financing Collaborator Network
The Lancet: Volume 391, No. 10132, p1783–1798, 5 May 2018
https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(18)30697-4/fulltext

Summary

Background

Achieving universal health coverage (UHC) requires health financing systems that provide prepaid pooled resources for key health services without placing undue financial stress on households. Understanding current and future trajectories of health financing is vital for progress towards UHC. We used historical health financing data for 188 countries from 1995 to 2015 to estimate future scenarios of health spending and pooled health spending through to 2040.

Methods

We extracted historical data on gross domestic product (GDP) and health spending for 188 countries from 1995 to 2015, and projected annual GDP, development assistance for health, and government, out-of-pocket, and prepaid private health spending from 2015 through to 2040 as a reference scenario. These estimates were generated using an ensemble of models that varied key demographic and socioeconomic determinants. We generated better and worse alternative future scenarios based on the global distribution of historic health spending growth rates. Last, we used stochastic frontier analysis to investigate the association between pooled health resources and UHC index, a measure of a country's UHC service coverage. Finally, we estimated future UHC performance and the number of people covered under the three future scenarios.

Findings

In the reference scenario, global health spending was projected to increase from US$10 trillion (95% uncertainty interval 10 trillion to 10 trillion) in 2015 to $20 trillion (18 trillion to 22 trillion) in 2040. Per capita health spending was projected to increase fastest in upper-middle-income countries, at 4·2% (3·4–5·1) per year, followed by lower-middle-income countries (4·0%, 3·6–4·5) and low-income countries (2·2%, 1·7–2·8). Despite global growth, per capita health spending was projected to range from only $40 (24–65) to $413 (263–668) in 2040 in low-income countries, and from $140 (90–200) to $1699 (711–3423) in lower-middle-income countries. Globally, the share of health spending covered by pooled resources would range widely, from 19·8% (10·3–38·6) in Nigeria to 97·9% (96·4–98·5) in Seychelles. Historical performance on the UHC index was significantly associated with pooled resources per capita. Across the alternative scenarios, we estimate UHC reaching between 5·1 billion (4·9 billion to 5·3 billion) and 5·6 billion (5·3 billion to 5·8 billion) lives in 2030.

Interpretation

We chart future scenarios for health spending and its relationship with UHC. Ensuring that all countries have sustainable pooled health resources is crucial to the achievement of UHC.

Spending on health and HIV/AIDS: Domestic health spending and development assistance in 188 countries, 1995–2015

Global Burden of Disease Health Financing Collaborator Network

The Lancet: Volume 391, No. 10132, p1799–1829, 5 May 2018
https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(18)30698-6/fulltext

Summary

Background

Comparable estimates of health spending are crucial for the assessment of health systems and to optimally deploy health resources. The methods used to track health spending continue to evolve, but little is known about the distribution of spending across diseases. We developed improved estimates of health spending by source, including development assistance for health, and, for the first time, estimated HIV/AIDS spending on prevention and treatment and by source of funding, for 188 countries.

Methods

We collected published data on domestic health spending, from 1995 to 2015, from a diverse set of international agencies. We tracked development assistance for health from 1990 to 2017. We also extracted 5385 datapoints about HIV/AIDS spending, between 2000 and 2015, from online databases, country reports, and proposals submitted to multilateral organisations. We used spatiotemporal Gaussian process regression to generate complete and comparable estimates for health and HIV/AIDS spending. We report most estimates in 2017 purchasing-power parity-adjusted dollars and adjust all estimates for the effect of inflation.

Findings

Between 1995 and 2015, global health spending per capita grew at an annualised rate of 3·1% (95% uncertainty interval [UI] 3·1 to 3·2), with growth being largest in upper-middle-income countries (5·4% per capita [UI 5·3–5·5]) and lower-middle-income countries (4·2% per capita [4·2–4·3]). In 2015, $9·7 trillion (9·7 trillion to 9·8 trillion) was spent on health worldwide. High-income countries spent $6·5 trillion (6·4 trillion to 6·5 trillion) or 66·3% (66·0 to 66·5) of the total in 2015, whereas low-income countries spent $70·3 billion (69·3 billion to 71·3 billion) or 0·7% (0·7 to 0·7). Between 1990 and 2017, development assistance for health increased by 394·7% ($29·9 billion), with an estimated $37·4 billion of development assistance being disbursed for health in 2017, of which $9·1 billion (24·2%) targeted HIV/AIDS. Between 2000 and 2015, $562·6 billion (531·1 billion to 621·9 billion) was spent on HIV/AIDS worldwide. Governments financed 57·6% (52·0 to 60·8) of that total. Global HIV/AIDS spending peaked at 49·7 billion (46·2–54·7) in 2013, decreasing to $48·9 billion (45·2 billion to 54·2 billion) in 2015. That year, low-income and lower-middle-income countries represented 74·6% of all HIV/AIDS disability-adjusted life-years, but just 36·6% (34·4 to 38·7) of total HIV/AIDS spending. In 2015, $9·3 billion (8·5 billion to 10·4 billion) or 19·0% (17·6 to 20·6) of HIV/AIDS financing was spent on prevention, and $27·3 billion (24·5 billion to 31·1 billion) or 55·8% (53·3 to 57·9) was dedicated to care and treatment.

Interpretation

From 1995 to 2015, total health spending increased worldwide, with the fastest per capita growth in middle-income countries. While these national disparities are relatively well known, low-income countries spent less per person on health and HIV/AIDS than did high-income and middle-income countries. Furthermore, declines in development assistance for health continue, including for HIV/AIDS. Additional cuts to development assistance could hasten this decline, and risk slowing progress towards global and national goals.

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The New England Journal of Medicine (3 May 2018, Vol. 378, No. 18)

Once-Daily Single-Inhaler Triple versus Dual Therapy in Patients with COPD
David A. Lipson, Frank Barnhart, Noushin Brealey, et al. for the IMPACT Investigators
N Engl J Med 2018; 378:1671-1680 May 3, 2018
https://www.nejm.org/doi/full/10.1056/NEJMoa1713901

Abstract

Background

The benefits of triple therapy for chronic obstructive pulmonary disease (COPD) with an inhaled glucocorticoid, a long-acting muscarinic antagonist (LAMA), and a long-acting β2-agonist (LABA), as compared with dual therapy (either inhaled glucocorticoid–LABA or LAMA–LABA), are uncertain.

Methods

In this randomized trial involving 10,355 patients with COPD, we compared 52 weeks of a once-daily combination of fluticasone furoate (an inhaled glucocorticoid) at a dose of 100 µg, umeclidinium (a LAMA) at a dose of 62.5 µg, and vilanterol (a LABA) at a dose of 25 µg (triple therapy) with fluticasone furoate–vilanterol (at doses of 100 µg and 25 µg, respectively) and umeclidinium–vilanterol (at doses of 62.5 µg and 25 µg, respectively). Each regimen was administered in a single Ellipta inhaler. The primary outcome was the annual rate of moderate or severe COPD exacerbations during treatment.

Results

The rate of moderate or severe exacerbations in the triple-therapy group was 0.91 per year, as compared with 1.07 per year in the fluticasone furoate–vilanterol group (rate ratio with triple therapy, 0.85; 95% confidence interval [CI], 0.80 to 0.90; 15% difference; P<0.001) and 1.21 per year in the umeclidinium–vilanterol group (rate ratio with triple therapy, 0.75; 95% CI, 0.70 to 0.81; 25% difference; P<0.001). The annual rate of severe exacerbations resulting in hospitalization in the triple-therapy group was 0.13, as compared with 0.19 in the umeclidinium–vilanterol group (rate ratio, 0.66; 95% CI, 0.56 to 0.78; 34% difference; P<0.001). There was a higher incidence of pneumonia in the inhaled-glucocorticoid groups than in the umeclidinium–vilanterol group, and the risk of clinician-diagnosed pneumonia was significantly higher with triple therapy than with umeclidinium–vilanterol, as assessed in a time-to-first-event analysis (hazard ratio, 1.53; 95% CI, 1.22 to 1.92; P<0.001).

Conclusions

Triple therapy with fluticasone furoate, umeclidinium, and vilanterol resulted in a lower rate of moderate or severe COPD exacerbations than fluticasone furoate–vilanterol or umeclidinium–vilanterol in this population. Triple therapy also resulted in a lower rate of hospitalization due to COPD than umeclidinium–vilanterol.

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n−3 Fatty Acid Supplementation for the Treatment of Dry Eye Disease
The Dry Eye Assessment and Management Study Research Group
N Engl J Med 2018; 378:1681-1690 May 3, 2018
https://www.nejm.org/doi/full/10.1056/NEJMoa1709691

Abstract

Background

Dry eye disease is a common chronic condition that is characterized by ocular discomfort and visual disturbances that decrease quality of life. Many clinicians recommend the use of supplements of n−3 fatty acids (often called omega-3 fatty acids) to relieve symptoms.

Methods

In a multicenter, double-blind clinical trial, we randomly assigned patients with moderate-to-severe dry eye disease to receive a daily oral dose of 3000 mg of fish-derived n−3 eicosapentaenoic and docosahexaenoic acids (active supplement group) or an olive oil placebo (placebo group). The primary outcome was the mean change from baseline in the score on the Ocular Surface Disease Index (OSDI; scores range from 0 to 100, with higher scores indicating greater symptom severity), which was based on the mean of scores obtained at 6 and 12 months. Secondary outcomes included mean changes per eye in the conjunctival staining score (ranging from 0 to 6) and the corneal staining score (ranging from 0 to 15), with higher scores indicating more severe damage to the ocular surface, as well as mean changes in the tear break-up time (seconds between a blink and gaps in the tear film) and the result on Schirmer's test (length of wetting of paper strips placed on the lower eyelid), with lower values indicating more severe signs.

Results

A total of 349 patients were assigned to the active supplement group and 186 to the placebo group; the primary analysis included 329 and 170 patients, respectively. The mean change in the OSDI score was not significantly different between the active supplement group and the placebo group (−13.9 points and −12.5 points, respectively; mean difference in change after imputation of missing data, −1.9 points; 95% confidence interval [CI], −5.0 to 1.1; P=0.21). This result was consistent across prespecified subgroups. There were no significant differences between the active supplement group and the placebo group in mean changes from baseline in the conjunctival staining score (mean difference in change, 0.0 points; 95% CI, −0.2 to 0.1), corneal staining score (0.1 point; 95% CI, −0.2 to 0.4), tear break-up time (0.2 seconds; 95% CI, −0.1 to 0.5), and result on Schirmer's test (0.0 mm; 95% CI, −0.8 to 0.9). At 12 months, the rate of adherence to treatment in the active supplement group was 85.2%, according to the level of n−3 fatty acids in red cells. Rates of adverse events were similar in the two trial groups.

Conclusions

Among patients with dry eye disease, those who were randomly assigned to receive supplements containing 3000 mg of n−3 fatty acids for 12 months did not have significantly better outcomes than those who were assigned to receive placebo.

Randomized Trial of Verubecestat for Mild-to-Moderate Alzheimer's Disease

Michael F. Egan, James Kost, Pierre N. Tariot, et al.

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Abstract

Background

Alzheimer's disease is characterized by the deposition of amyloid-beta (Aβ) plaques in the brain. Aβ is produced from the sequential cleavage of amyloid precursor protein by β-site amyloid precursor protein–cleaving enzyme 1 (BACE-1) followed by γ-secretase. Verubecestat is an oral BACE-1 inhibitor that reduces the Aβ level in the cerebrospinal fluid of patients with Alzheimer's disease.

Methods

We conducted a randomized, double-blind, placebo-controlled, 78-week trial to evaluate verubecestat at doses of 12 mg and 40 mg per day, as compared with placebo, in patients who had a clinical diagnosis of mild-to-moderate Alzheimer's disease. The coprimary outcomes were the change from baseline to week 78 in the score on the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog; scores range from 0 to 70, with higher scores indicating worse dementia) and in the score on the Alzheimer's

Disease Cooperative Study Activities of Daily Living Inventory scale (ADCS-ADL; scores range from 0 to 78, with lower scores indicating worse function).

Results

A total of 1958 patients underwent randomization; 653 were randomly assigned to receive verubecestat at a dose of 12 mg per day (the 12-mg group), 652 to receive verubecestat at a dose of 40 mg per day (the 40-mg group), and 653 to receive matching placebo. The trial was terminated early for futility 50 months after onset, which was within 5 months before its scheduled completion, and after enrollment of the planned 1958 patients was complete. The estimated mean change from baseline to week 78 in the ADAS-cog score was 7.9 in the 12-mg group, 8.0 in the 40-mg group, and 7.7 in the placebo group (P=0.63 for the comparison between the 12-mg group and the placebo group and P=0.46 for the comparison between the 40-mg group and the placebo group). The estimated mean change from baseline to week 78 in the ADCS-ADL score was −8.4 in the 12-mg group, −8.2 in the 40-mg group, and −8.9 in the placebo group (P=0.49 for the comparison between the 12-mg group and the placebo group and P=0.32 for the comparison between the 40-mg group and the placebo group). Adverse events, including rash, falls and injuries, sleep disturbance, suicidal ideation, weight loss, and hair-color change, were more common in the verubecestat groups than in the placebo group.

Conclusions

Verubecestat did not reduce cognitive or functional decline in patients with mild-to-moderate Alzheimer's disease and was associated with treatment-related adverse events.

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Sources

BMJ: British Medical Journal	http://www.bmj.com/theBMJ
JAMA: The Journal of the American Medical Association	http://jama.ama-assn.org/
The Lancet	www.thelancet.com
The New England Journal of Medicine	http://content.nejm.org/
The British Medical Journal (BMJ), JAMA and the New England Journal of Medicine (NEJM) can be accessed in full-text through your NHS Athens account. Unfortunately the national subscription to The Lancet has been cancelled.	https://www.evidence.nhs.uk/nhs-evidence-content/journals-and-databases or http://www.openathens.net/
If you have not already registered for an NHS Athens Account, please register at: NB: It is recommended that you register on a Trust (NHS) PC for speedy confirmation of your username and password. Once registered, your account can be accessed from any device with online access.	https://openathens.nice.org.uk/

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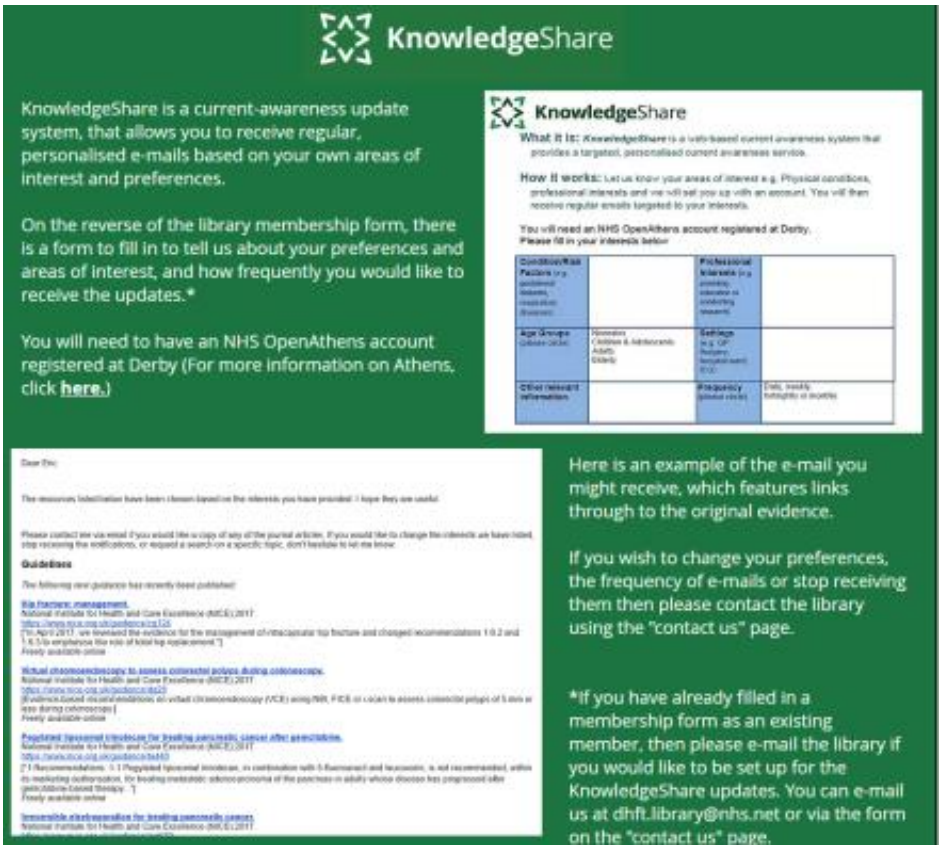

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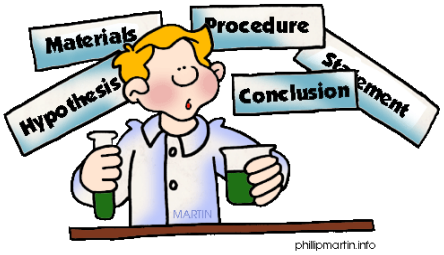

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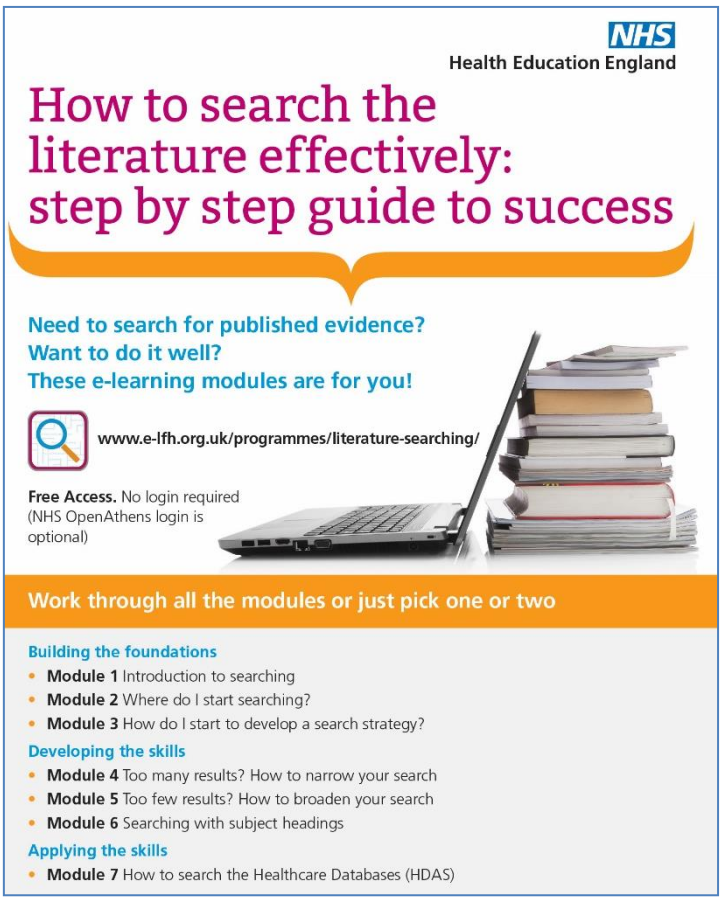

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