Restoring Study 329: efficacy and harms of paroxetine and imipramine in treatment of major depression in adolescence

Joanna Le Noury,[1] John M Nardo,[2] David Healy,[1] Jon Jureidini,[3] Melissa Raven,[3] Catalin Tufanaru,[4] Elia Abi-Jaoude[5]

EDITORIAL by Henry and Fitzpatrick

FEATURE, p 14

[1]School of Medical Sciences, Bangor University, Bangor, Wales, UK

[2]Emory University, Atlanta, Georgia, USA

[3]Critical and Ethical Mental Health Research Group, Robinson Research Institute, University of Adelaide, Adelaide, South Australia, Australia

[4]Joanna Briggs Institute, Faculty of Health Sciences, University of Adelaide, Adelaide, South Australia, Australia

[5]Department of Psychiatry, The Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada

Correspondence to: J Jureidini
Jon.Jureidini@adelaide.edu.au

Cite this as: *BMJ* 2015;351:h4320
doi: 10.1136/bmj.h4320

This is a summary of a paper that was published on thebmj.com as *BMJ* 2015;351:h4320

STUDY QUESTION

What does reanalysis of SmithKline Beecham's Study 329 (a multicentre double blind, placebo controlled study of paroxetine and imipramine in adolescents with unipolar major depression) show about the need for access to clinical trial data sources?

SUMMARY ANSWER

Access to the full individual patient level dataset, backed up by the case report forms (CRFs) and the a priori protocol, is required to judge the validity of published reports of clinical trials. Reanalysis based on these documents showed that, contrary to the original trial report, efficacy was not established for either paroxetine or imipramine, which both increased harms.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

In the absence of access to primary data, misleading conclusions in publications of trials can seem definitive. This paper makes it clear that it is not possible to adequately scrutinise trial outcomes simply on the basis of what is reported in the body of clinical study reports (CSRs), which can contain important errors. This has important implications for clinical practice, research, regulation of trials, and licensing of drugs.

Design

Access was gained to the data from a double blinded randomised controlled trial of paroxetine, imipramine, and placebo, under the restoring invisible and abandoned trials (RIAT) initiative. Those data were reanalysed according to the a priori study protocol.

Participants and setting

275 adolescents with major depression of at least eight weeks in duration, treated at 12 North American academic psychiatry centres, in a study previously published in 2001.

Primary outcomes

Change from baseline to the end of the eight week acute treatment phase in total Hamilton depression scale (HAM-D) score; and the proportion of responders (HAM-D score ≤8 or ≥50% reduction in baseline score) at acute endpoint (eight weeks).

Main results and the role of chance

Access to data, adherence to the a priori protocol, and transparent reporting of outcomes led to different conclusions about the efficacy and safety of paroxetine for adolescents from those in the original CSR and journal article. In our reanalysis, the efficacy of paroxetine and imipramine was neither statistically nor clinically significantly different from placebo for any pre-specified efficacy outcome. HAM-D scores decreased by 10.7 (least squares mean, 95% confidence interval 9.1 to 12.3), 9.0 (7.4 to 10.5), and 9.1 (7.5 to 10.7) points, respectively, for the paroxetine, imipramine, and placebo groups (P=0.204).

Harms

Clinically significant increases in harms were observed, including suicidal ideation and behaviour and other serious adverse events in the paroxetine group and cardiovascular problems in the imipramine group. Many of these harms went unreported in the CSR and the published paper. Increased harms in the taper phase were consistent with withdrawal effects from ceasing antidepressants.

Bias, confounding, and other reasons for caution

Access to case report forms was difficult, and coding of adverse events required judgment. Several members of the RIAT team had previously challenged the original trial report and might be regarded as biased. To our knowledge, this kind of reanalysis has never been published before.

Generalisability

This reanalysis provides a clear message about the necessity of access to data and protocols, particularly in relation to harms. Increasing data transparency will allow other trials to be scrutinised. If other CSRs are found to contain similar analytical errors, whether intentional or inadvertent, this could inform changes in the requirements for submissions to the regulatory agencies tasked with evaluating the safety and efficacy of our pharmacopeia and to the editors and reviewers whose role it is to oversee the integrity of our literature.

Study funding/potential competing interests

No funding received. DH has been and is an expert witness for plaintiffs in legal cases involving paroxetine and other antidepressants. JJ has provided expert analysis and opinion for plaintiffs about Study 329 and Forest's paediatric citalopram randomised controlled trials.

Adverse events (AE) for paroxetine and placebo groups in Study 329 according to clinical study report (CSR), paper by Keller and colleagues (ADECS coded), and RIAT reanalysis (MedDRA coded)

	Paroxetine (n=93)			Placebo (n=87)			AE ratio paroxetine:placebo RIAT reanalysis
	CSR	Keller	RIAT	CSR	Keller	RIAT	
Total AEs	338	265	481	277	207	330	1.4
Severe AEs	70	—	70	25	—	25	2.6
Psychiatric AEs	—	—	103	—	—	24	4.0
AEs in taper phase*	45	—	47	10	—	10	2.2
Severe AEs in taper phase*	13	—	13	1	—	1	6.2
Suicidal and self injurious patients (acute/taper)	7	5	11	1	1	1	10.3

*Paroxetine n=19, placebo n=9.

Potential of trans fats policies to reduce socioeconomic inequalities in mortality from coronary heart disease in England: cost effectiveness modelling study

Kirk Allen,[1 2] Jonathan Pearson-Stuttard,[3] William Hooton,[4] Peter Diggle,[1] Simon Capewell,[2] Martin O'Flaherty[2]

EDITORIAL by Veerman

[1]Lancaster Medical School, Lancaster University, Lancaster LA1 4YW, UK
[2]Department of Public Health and Policy, Liverpool University, Liverpool L69 3GB, UK
[3]Division of Medical Sciences, University of Oxford, Oxford OX3 9DU, UK
[4]Pembroke College Alumni, University of Oxford, Oxford OX1 1DW, UK
Correspondence to: K Allen
allenk@liverpool.ac.uk

Cite this as: *BMJ* 2105;351:h4583
doi: 10.1136/bmj.h4583

This is a summary of a paper that was published on thebmj.com as *BMJ* 2015;351:h4583

thebmj.com
Editorial: Learning from soft power (*BMJ* 2015;351: h4645)

STUDY QUESTION

How might policies to reduce or eliminate industrial trans fatty acids from processed foods in England differ in their population level effect on coronary heart disease, effect on socioeconomic differences in coronary heart disease, and societal economic costs?

SUMMARY ANSWER

A regulatory policy to eliminate trans fatty acids from processed foods in England would be the most effective, equitable, and cost saving policy option.
Policies with limited reach (enhanced labelling of content or bans at restaurant/fast food establishments) might be a third to a half as effective, equitable, and cost saving.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Trans fatty acids increase incidence of coronary heart disease by 23% for each 2% of food energy they account for, and other countries have taken stronger action than the UK to reduce or eliminate them from processed foods. A total ban on industrial trans fatty acids in processed foods in England might potentially prevent or postpone about 7200 deaths from coronary heart disease (2.6%) from 2015-20 and reduce inequality in mortality by about 3000 deaths (15%).

Participants and setting

This study models the effect on mortality from, and incidence of, coronary heart disease among adults aged ≥25 in England, stratified by fifths of socioeconomic class.

Design

This epidemiological modelling study used data sources that included dietary surveys, effect sizes from meta-analysis, projections of mortality from, and incidence of, coronary heart disease, population projections, and published health economic parameters.

Primary outcomes

Reduction in mortality from, and incidence of, coronary heart disease associated with different policy options and associated cost outcomes (policy savings from reductions in direct healthcare, informal care, and productivity loss; policy costs to government only in the optimistic scenario and also to industry in the pessimistic scenario). Negative net costs represent savings.

Main results and the role of chance

A total ban on trans fatty acids in processed foods might prevent or postpone about 7200 deaths from coronary heart disease (2.6%) from 2015-20 and reduce inequality in related mortality by about 3000 deaths (15%). Policies to improve labelling or simply remove trans fatty acids from restaurants/fast food could prevent between 1800 (0.7%) and 3500 (1.3%) deaths from coronary heart disease and reduce inequalities by 600 (3%) to 1500 (7%) deaths, thus making them at best half as effective. A total ban would have the greatest net cost savings of about £265m excluding reformulation costs or £64m if substantial reformulation costs are incurred outside the normal cycle.

Bias, confounding, and other reasons for caution

We used an area based measure of socioeconomic status (IMDQ). Within an area there naturally will be mixing of individuals with higher and lower status. Therefore, we cannot make firm conclusions about individuals.

Generalisability to other populations

Modelling was restricted to England because we can reliably link mortality from coronary heart disease to an indicator of socioeconomic class. Any policy that applied to the whole UK would also benefit Scotland, Wales, and Northern Ireland. Internationally, a ban on trans fatty acids in the UK would put the country in line with WHO recommendations and contribute to recent progress against trans fatty acids at the EU level and in the United States.

Study funding

The study was funded by the National Institute for Health Research's School for Public Health Research (NIHR SPHR).

Overall reduction in deaths from coronary heart disease (CHD), reduction in absolute inequality of such deaths, and optimistic and pessimistic net costs for 2015-20 for each policy option

	CHD deaths (95% CI); % reduction		Net costs (£m) (95% CI)	
Policy option	Reduction	Reduction in absolute inequality	Optimistic	Pessimistic
Total ban	7200 (3200 to 12 500); 2.6%	3000 (1300 to 5200), 14.7%	−264.1 (−433.3 to −98.0)	−64.1 (−233.3 to 102.0)
Label (no SEC gradient)	3500 (1500 to 6200); 1.3%	1500 (600 to 2600); 7.4%	−114.8 (−198.8 to −32.2)	−21.9 (−105.9 to 60.6)
Fast food	2600 (1200 to 4600); 1.0%	1200 (600 to 2200); 5.9%	−75.1 (−136.5 to −14.8)	−12.5 (−73.9 to 47.8)
Label (SEC gradient)	2200 (1000 to 3800); 0.8%	700 (200 to 1200); 3.4%	−58.9 (−111.0 to −7.6)	−2.8 (−54.9 to 48.4)
Restaurant	1800 (700 to 3400); 0.7%	600 (300 to 1100); 2.9%	−47.4 (−93.0 to −2.6)	0.0 (−45.5 to 44.8)

SEC=socioeconomic circumstance.

Exercise capacity and muscle strength and risk of vascular disease and arrhythmia in 1.1 million young Swedish men: cohort study

Kasper Andersen,[1] Finn Rasmussen,[2] Claes Held,[1] Martin Neovius,[3] Per Tynelius,[2] Johan Sundström[1]

[1]Department of Medical Sciences and Uppsala Clinical Research Center, Uppsala University Hospital, Uppsala, SE-751 85, Sweden
[2]Child and Adolescent Public Health Epidemiology Unit, Department of Public Health Sciences, Karolinska Institutet, Stockholm, Sweden
[3]Clinical Epidemiology Unit, Department of Medicine, Karolinska Institutet, Stockholm, Sweden
Correspondence to: K Andersen
kasper.andersen@medsci.uu.se

Cite this as: *BMJ* 2015;351:h4543
doi: 10.1136/bmj.h4543

This is a summary of a paper that was published on thebmj.com as *BMJ* 2015;351:h4543

thebmj.com
Clinical Review; Sudden cardiac arrest in athletes (*BMJ* 2015;350: h1218)

STUDY QUESTION

Is exercise capacity and muscle strength at age 18 years related to an increased risk of vascular disease and arrhythmia?

SUMMARY ANSWER

Higher exercise capacity and muscle strength in late adolescence were independently and jointly associated with lower long term risk of vascular disease.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

High exercise capacity and muscle strength have been associated with lower risk of vascular disease and mortality, but exercise could increase the risk of arrhythmia. In this study, higher exercise capacity and muscle strength in late adolescence were independently and jointly associated with lower risk of vascular disease, but exercise capacity had a U shaped association with arrhythmia.

Participants and setting

All Swedish men participating in mandatory military conscription between 1 August 1972 and 31 December 1995, at a median age of 18.2 years.

Design, size, and duration

The cohort comprised 1.1 million men. Exposures and outcomes were obtained from the military service conscription register in combination with other official Swedish registries. Participants were followed until 31 December 2010. Maximum exercise capacity was estimated by the ergometer bicycle test, and muscle strength was measured as handgrip strength by a hand dynamometer. We used Cox proportional hazards models to examine associations, and adjusted for age, conscription date, region, education level, height and muscle strength or exercise capacity; and systolic and diastolic blood pressure, weight, and interim ischaemic heart disease (for arrhythmia outcomes only).

Main results and the role of chance

During a median follow-up of 26.3 years, 26 088 vascular disease events and 17 312 arrhythmia events were recorded. Exercise capacity (measured in watts) was inversely associated with risk of vascular disease and its subgroups (ischaemic heart disease, heart failure, stroke, and cardiovascular death). Muscle strength (measured in newtons) was also inversely associated with vascular disease risk, driven by associations of higher muscle strength with lower risk of heart failure and cardiovascular death. Exercise capacity had a U shaped association with the risk of arrhythmia, driven by a direct association with risk of atrial fibrillation and a U shaped association with bradyarrhythmia. Higher muscle strength was associated with lower risk of arrhythmia (specifically, lower risk of bradyarrhythmia and ventricular arrhythmia). High (above median) exercise capacity and high muscle strength were jointly associated with a hazard ratio of 0.67 (95% confidence interval 0.65 to 0.70) for vascular events and 0.92 (0.88 to 0.97) for arrhythmias compared with low exercise capacity and low muscle strength combined.

Bias, confounding, and other reasons for caution

Exercise capacity and muscle strength were only measured at the time of conscription, and the applicability of those measures to exposures before and after the conscription is uncertain. Other factors linked to the exposure (such as genetic factors or exercise factors in childhood) could have contributed to the associations, rather than the amount of exercise in later life. With an observational design, this study was subject to potential confounding; in particular, information on lifestyle factors such as smoking and diet was lacking.

Generalisability to other populations

The cohort only included 18 year old men who were mainly white. Generalisability to women, other ethnic groups, or age groups is unknown.

Study funding/potential competing interests

All researchers are independent of the study funders, the Swedish Research Council and Geriatric Fund Sweden. JS is part of the advisory board for Itrim and AstraZeneca, and MN is part of the advisory board for Itrim.

Exercise capacity and muscle strength and risk of vascular disease and arrhythmia