Whither the Ingelfinger rule? An editor's perspective

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The problem

The Food and Drug Amendments Act 2007 requires pharmaceutical companies to register nearly all trials and to disclose their results publicly within a timeframe dictated by the new legislation or pay penalties of $10K a time

Will this infringe the Ingelfinger rule and make it impossible to publish trials in medical journals?

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What results have to be disclosed for FDA?

Four tables:

- demographic and baseline data collected overall and for each arm of the trial, including patients dropped out and excluded from analysis
- raw data and stats tests for each of the primary and secondary outcome measures for each arm of the trial
- anticipated and unanticipated serious adverse events grouped by organ system, with number and frequency of such event in each arm of the clinical trial
- anticipated and unanticipated adverse events exceeding 5% frequency in any arm of the trial, grouped by organ system

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What I aim to cover

- International Committee of Medical Journal Editors (ICMJE) policy
- BMJ policy
- what investigators and authors need to know to continue publishing clinical trial results in top-tier journals and comply with the new law

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ICMJE policy

ICMJE said in June 2007 that member journals * will not consider results posted in a clinical trials register as previous publications if presented in the form of a brief, structured (<500 words) abstract or table.

ICMJE meets next in May: will this policy change to cover FDAA's required four tables?

* Annals of Internal Medicine, BMJ, Canadian Medical Association Journal, Croatian Medical Journal, JAMA, Nederlands Tijdschrift voor Geneeskunde, New England Journal of Medicine, New Zealand Medical Journal, The Lancet, The Medical Journal of Australia,Tidsskrift for Den Norske Llegeforening, and Ugeskrift for Laeger

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ICMJE left door open

".. We recognise that **the climate for results registration will probably change dramatically and unpredictably over coming years. For the present**, the ICMJE will not consider results posted in the same primary clinical trials register in which the initial registration resides as previous publications if the results are presented in the form of a brief, structured (<500 words) abstract or table…"

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BMJ policy - history

- 1997 – BMJ was one of 100 journals offering amnesty for unreported trials (but only165 trials in first year)
- 1999 – BMJ called for registration in any of the many burgeoning registers
- 2004 – BMJ supported ICMJE rules on compulsory trial registration but disagreed with criterion that registers had to be not for profit, which only clinicaltrials.gov then met
- 2006 – BMJ supported WHO's International Clinical Trials Registry Platform (ICTRP)

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Precedents at BMJ

BMJ believes the Ingelfinger rule is outdated, and does not consider these to preclude journal publication:

- research presented at scientific meetings
- research published in non-English languages and/or for limited audiences
- systematic reviews and meta-analyses conducted for and posted by:
  - Cochrane Library
  - UK Health Technology Assessment Agency

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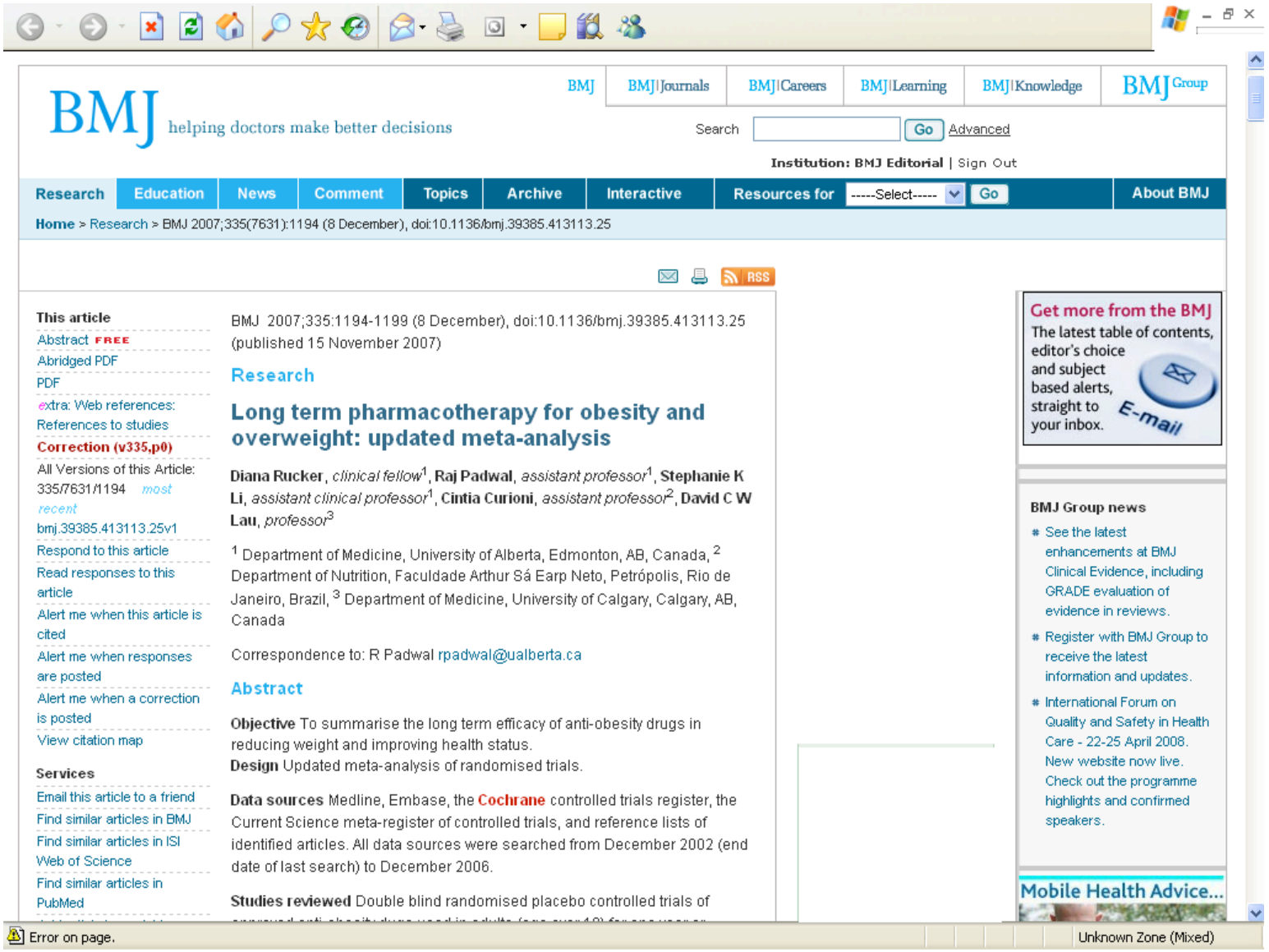
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BMJ 2007;335:1194-1199 (8 December), doi:10.1136/bmj.39385.413113.25 (published 15 November 2007)
Research
Long term pharmacotherapy for obesity and overweight: updated meta-analysis
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Abstract
Objective To summarise the long term efficacy of anti-obesity drugs in reducing weight and improving health status.
Design Updated meta-analysis of randomised trials.
Data sources Medline, Embase, the Cochrane controlled trials register, the Current Science meta-register of controlled trials, and reference lists of identified articles. All data sources were searched from December 2002 (end date of last search) to December 2006.
Studies reviewed Double blind randomised placebo controlled trials of
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Obesity

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Conclusions Orlistat, sibutramine, and rimonabant modestly reduce weight, have differing effects on cardiovascular risk profiles, and have specific adverse effects.

Introduction

Obesity and overweight are highly and increasingly prevalent chronic conditions currently affecting over 1.1 billion individuals worldwide and are associated with premature mortality, chronic morbidity, and increased healthcare use.[1 2] Recently published guidelines recommend lifestyle modification as the initial treatment for obesity and suggest that adjunctive drug treatment is considered in patients with a body mass index ≥30 or 27-29.9 with medically complicated obesity.[2] Orlistat, a gastrointestinal lipase inhibitor, sibutramine, a centrally acting monoamine reuptake inhibitor, and rimonabant, an endocannabinoid receptor antagonist, are approved for long term treatment of obesity (one year or more).[3]
Treatment with anti-obesity drugs is common, with global sales in 2005 estimated at $1.2bn.[4] As weight losses achieved with lifestyle intervention are modest and limited by high rates of recidivism and compensatory slowing of metabolism,[5 6] there is potential for even greater use of drug treatment. Furthermore, as the prevalence and incidence of obesity grow and as newer agents are developed, use of these drugs will probably increase further.

We carried out an updated systematic review and meta-analysis to quantify the efficacy of and adverse effects associated with the long term use of anti-obesity drugs. This paper is a summary of a recently updated **Cochrane** collaboration systematic review.[7]

Methods

Inclusion and exclusion criteria and outcomes

With the help of a medical librarian we searched Medline, Embase, the **Cochrane** controlled trials register, and the metaregister of controlled trials (www.controlled-trials.com) from December 2002 to December 2006 and examined reference lists of identified articles. In the original version of this review, the search covered the period from the inception of each database to December 2002.[8] We searched for placebo controlled clinical trials of at least one year in duration that evaluated the effects of anti-obesity drugs on weight, cardiovascular risk factors, cardiovascular morbidity and mortality, and overall mortality. A subgroup analysis examined weight loss and glycaemic control in patients with type 2 diabetes. All trials had to be double blind (patient and care provider) randomised controlled trials examining overweight or obese adults

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Abstract
Background
Worldwide prevalence rates of obesity and overweight are rising and safe and effective treatment strategies are urgently needed. A number of anti-obesity agents have been studied in short-term clinical trials, but long-term efficacy and safety need to be established.
Objectives
To assess/compare the effects and safety of approved anti-obesity medications in clinical trials of at least one-year duration.
Search strategy
MEDLINE, EMBASE, the Cochrane Controlled Trials Register (CENTRAL), the Current Science Meta-register of Controlled Trials, and reference lists of original studies and reviews were searched. Date of last search was December 2002. Drug
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  - explain what the work adds to knowledge
  - say when results will be/were disclosed for FDA
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But…

BMJ gives priority to articles that help doctors make better decisions. So we're interested in trials:

- where intervention goes head to head against best current treatment, rather than placebo
- of new indications and drugs rather than me-toos
- with adequate doses of intervention and control drugs
- with clinically important outcomes including harms
- that show no benefit as long as there's sufficient power and important/relevant outcomes
- that are relevant enough to a wide range of doctors

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Thank you

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