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RESEARCH

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# 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]

[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

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## Abstract

**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).

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

## 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.

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# Table

**Table 1| 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 |
|---|---|---|---|---|---|---|---|
| | CSR | Keller | RIAT | CSR | Keller | RIAT | RIAT reanalysis |
| 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.