

THERAPEUTICS INITIATIVE

Evidence Based Drug Therapy

Study 329: Why is it so important?

Study 329 is a GlaxoSmithKline (GSK) sponsored trial with 22 academic authors that compared paroxetine, imipramine, and placebo for adolescent depression. In this trial 275 adolescents with major depression were randomized in a double-blind fashion to paroxetine (93), imipramine (95) or placebo (87) for 8 weeks. Those who completed 8 weeks were studied in a 6-month continuation phase.

Published 8-week results (2001)¹: Compared with placebo, paroxetine demonstrated significantly greater improvement in 3 **selected** depression rating scales and a Clinical Global Improvement score of 1 or 2. The response to imipramine was not significantly different from placebo for any measure.

Authors' conclusions: "Paroxetine is generally well tolerated and effective for major depression in adolescents."¹

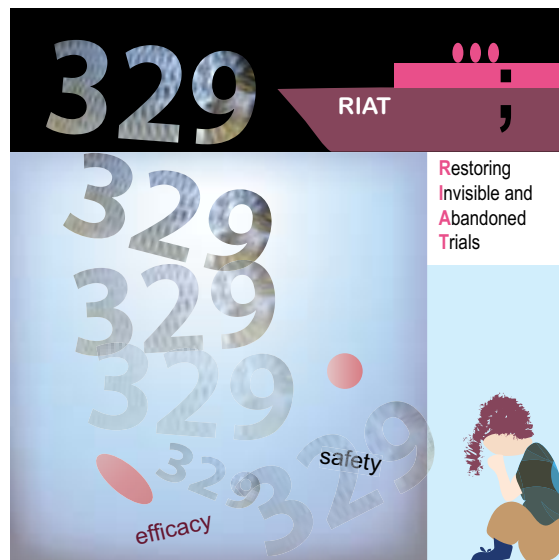
This trial has been cited over 600 times and was very influential in increasing prescribing of paroxetine in this clinical setting.²

Did these published conclusions reflect "reality"?

Critical appraisal of the 2001 publication would have led to questions about the authors' conclusions. The differences between paroxetine and placebo were small, and the authors noted that neither paroxetine nor imipramine differed significantly from placebo for parent- or self-rating measures of depression. Furthermore, serious adverse events occurred in 11 patients in the paroxetine group, 5 in the imipramine group, and 2 in the placebo group. Ten of the 11 serious adverse events in the paroxetine group were psychiatric, e.g. depression, suicidality, hostility or euphoria.¹ In 2004, Garland called attention to the "weak or nonexistent evidence of efficacy" of SSRIs in this setting and the "serious psychiatric adverse effects" of paroxetine.³

A solution: Restoring Invisible and Abandoned Trials (RIAT) initiative

The RIAT initiative is an attempt by independent researchers to analyze and publish misreported or unpublished trials.⁴ The RIAT researchers identified Study 329 as an example of a potentially misreported acute phase trial in need of restoration and an unpublished continuation phase trial that had been abandoned. **The restored trial⁵ and the abandoned trial⁶ are now published.**



The publications report in detail the methods used to re-analyze Study 329. Notably, they followed the protocol (and amendments) established by GSK⁷ and used all appropriate procedural steps to avoid bias. They have also made the original anonymous patient data available for others to analyze.

RIAT analysis of Study 329 (acute phase)

The trial protocol⁷ specified two primary efficacy variables: change in total score on a Hamilton depression rating scale (HAM-D) from baseline to endpoint, and the proportion of responders at the end of 8 weeks. Responders were defined as achieving a reduction of $\geq 50\%$ in HAM-D score, or a score of ≤ 8 . It also specified seven secondary efficacy variables.

Results: Paroxetine and imipramine were not statistically or clinically significantly different from placebo for any of the 9 pre-specified primary or secondary efficacy outcomes. The four statistically significant outcomes in the 2001 publication¹ were neither specified in the original protocol nor in any amendment. Withdrawals due to adverse effects occurred in 15% of subjects taking paroxetine, 32.6% taking imipramine and 6.9% taking placebo. This was predominantly due to 12% of subjects experiencing adverse psychiatric effects with paroxetine and 16% of subjects experiencing adverse cardiovascular effects with imipramine. More paroxetine adverse events were rated as severe.

RIAT authors' conclusions: "Neither paroxetine nor high dose imipramine were efficacious for major depression in adolescents, whereas both drugs increased harms."⁵



Mailing Address: Therapeutics Initiative
The University of British Columbia
Department of Anesthesiology, Pharmacology & Therapeutics
2176 Health Sciences Mall
Vancouver, BC Canada V6T 1Z3

Tel.: 604 822 0700
Fax: 604 822 0701
E-mail: info@ti.ubc.ca
www.ti.ubc.ca

This example demonstrates and emphasizes the importance of independent access to data, and the value of reanalysis of trials. **The implications for clinical practice are enormous and apply beyond this setting to the use of antidepressants in adult depression and to other drugs and indications.**⁸

RIAT analysis of Study 329 (continuation phase)

The continuation phase of Study 329 was designed to assess relapse rates in the longer term and to assess safety while patients were on drug or placebo and during a tapering discontinuation phase.⁶ Tapering was recommended for all patients, whether they left either phase of the study early, completed the acute phase but did not continue, or completed the six-month continuation phase. If the patient accepted a taper phase, the protocol recommended tapering medication or placebo over 7-17 days. Of 190 adolescents who completed the eight-week acute phase, 119 entered the 6-month continuation phase (paroxetine n = 49; imipramine n = 39; placebo n = 31).

Results: In these 119 subjects the response rate at 6 months was the same for all 3 treatments: 31% on paroxetine, 31% on imipramine and 39% on placebo. In the continuation phase, adverse event rates were similar for the 3 groups. During tapering, severe adverse events were much higher for the drugs: paroxetine 16, imipramine 14 and placebo 1. Suicidality and suicide-related events were of particular concern during acute treatment, 6 month continuation, and taper: paroxetine 23 events in 15 patients, imipramine 11 events in 9 patients and placebo 5 events in 5 patients. With paroxetine, 5 of the suicide-related events occurred in 5 patients during the taper phase.

References

- Keller MB, Ryan ND, Strober M, et al. *Efficacy of paroxetine in the treatment of adolescent major depression: a randomized, controlled trial.* J Am Acad Child Adolesc Psychiatry. 2001; 40(7):762-72. DOI:10.1097/00004583-200107000-00010
- Doshi P. *No correction, no retraction, no apology, no comment: paroxetine trial reanalysis raises questions about institutional responsibility.* BMJ. 2015; 351:h4629. DOI:10.1136/bmj.h4629
- Garland EJ. *Facing the evidence: antidepressant treatment in children and adolescents.* CMAJ. 2004; 170(4):489-91.
- Doshi P, Dickersin K, Healy D, et al. *Restoring invisible and abandoned trials: a call for people to publish the findings.* BMJ. 2013; 346:f2865. DOI:10.1136/bmj.f2865
- Le Noury JC, Nardo JM, Healy D, et al. *Restoring Study 329: efficacy and harms of paroxetine and imipramine in treatment of major depression in adolescence.* BMJ. 2015; 351:h4320. DOI:10.1136/bmj.h4320
- Le Noury JC, Nardo JM, Healy D, et al. *Study 329 continuation phase: Safety and efficacy of paroxetine and imipramine in extended treatment of adolescent major depression.* International Journal of Risk & Safety in Medicine. 2016; 28(3):143-61. DOI:10.3233/JRS-160728
- SmithKline Beecham. *A multi-center, double-blind, placebo controlled study of paroxetine and imipramine in adolescents with unipolar major depression.* Protocol number 29060/329. 1993, amended 1994, 1996. [Internet]. Available from: www.gsk.com/media/360485/329-AppA.PDF [Accessed 29 February 2016].
- Maund E, Guski LS, Göttsche PC. *Considering benefits and harms of duloxetine for treatment of stress urinary incontinence: a meta-analysis of clinical study reports.* CMAJ 2016; November 14. DOI:10.1503/cmaj.151104
- Ioannidis JP. *Why most clinical research is not useful.* PLoS Med. 2016; 13(6):e1002049. DOI:10.1371/journal.pmed.1002049

Conclusions: The continuation phase did not offer support for longer-term efficacy of either paroxetine or imipramine but demonstrated additional safety concerns for both drugs in the taper phase and particularly adverse psychiatric events with paroxetine.⁶

What has happened as a result of these revelations?

Nothing. A British Medical Journal editorial² documents that there has been no correction, no retraction, no apology and mostly no comment from the authors, journal editor, or from the universities where authors worked in 2001.

The RIAT analyses of Study 329 and **the lack of any correction of the original flawed paper** have major implications for clinical practice decisions being made on the basis of published clinical trials. Leading experts on clinical trials now believe that we must question the validity of the data and conclusions of all published clinical trials that have not been subject to independent analysis.⁹

Conclusions

- Independent analysis of Study 329 demonstrated serious harms and a lack of efficacy for acute and longer-term use of paroxetine and imipramine for adolescents with major depression.**
- This example of the RIAT initiative reveals that the current methods of trial conduct, analysis and publication are unacceptable.
- Published conclusions about efficacy and safety of drugs without independent analysis cannot be accepted as trustworthy.**
- It is essential that primary trial data and protocols for all clinical trials be made available for independent analysis.