**Restoring Study 329: Efficacy and harms of paroxetine and imipramine in the treatment of adolescent major depression: restoration of a randomised controlled trial**

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**Study question:** Does reanalysis of the data from GSK's Study 329 (*A Multi-center, Double-blind, Placebo Controlled Study of Paroxetine and Imipramine in Adolescents with Unipolar Major Depression*) have clinically relevant implications for evidence based medicine?

**Summary answer:** Reanalysis of Study 329 showed that, contrary to the original trial report, efficacy was not established for either paroxetine or imipramine, while both increased harms; and it demonstrated that access to trial data challenges the authority of authorship.

**What is known and what this paper adds:** In the absence of access to primary data, misleading conclusions in publications of trials can appear definitive. Reanalysis of primary data from Study 329 demonstrated that published conclusions about efficacy and safety should not be read as authoritative.

**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 329 protocol.

**Participants and setting:** 275 adolescents with major depression of at least 8 weeks in duration, treated at 12 North American academic psychiatry centres, in a study previously published in 2001.

**Primary outcome(s):** Change from baseline to the end of the 8-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 HAM-D) at acute endpoint (8 weeks).

**Main results and the role of chance:** Access to data, compliance with the *a priori* protocol, and transparent reporting of outcomes led to conclusions about the efficacy and safety of paroxetine for adolescents that differed from the original trial report.

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 10.73 [9.134 to 12.328], 8.95 [7.356, to 10.541] and 9.08 [7.450 to 10.708] points, LS MEAN [95% Confidence Interval], respectively, for the paroxetine, imipramine and placebo groups (p = 0.204).

**Harms:** Clinically significant increases in harms, including suicidal ideation and behaviour and other serious adverse events, were observed in the paroxetine group (see table), and cardiovascular problems in the imipramine group. Increased harms in the taper phase were consistent with withdrawal effects from ceasing antidepressants.

Table: Summary of harms outcomes for paroxetine and placebo groups in Study 329

|  |  |  |  |
| --- | --- | --- | --- |
|  | Paroxetine N=93 | Placebo N=87 | AE per patient Paroxetine:placebo |
| Total AEs | 479 | 330 | 1.4 |
| Severe AEs | 70 (15%) | 25 (8%) | 2.6 |
| AEs in taper phase | 47 | 10 | 4.4 |
| Severe AEs in taper | 12 (26%) | 1 (10%) | 11 |
| Psychiatric AEs | 55 | 17 | 3.0 |
| Suicidal ideation/gesture /attempt | 13 | 1 | 13 |

**Bias, confounding and other reasons for caution:** So far as we know, this kind of reanalysis has never been attempted before. Access to case reports was difficult, and coding of adverse events required judgement. Several members of the RIAT team had previously challenged the original trial report.

**Generalisability to other populations:** This study left an uncertain message re generalisability of efficacy findings, a clearer message regarding harms, and a very clear message about access to data.

**Study funding/potential competing interests:** No funding received. DH has been an expert witness for plaintiffs in legal cases involving paroxetine and other antidepressants. JJ has been paid by Baum, Hedlund, Aristei & Goldman to provide expert analysis and opinion related to GSK's Study 329 and Forest's paediatric citalopram RCTs.

**Trial registration number:** SmithKline Beecham study 29060/329