Paxil Reversal: Was Safe for Teen Depression, But Now It's Not

By Gil Ross — September 18, 2015

[1] In 2001, a multi-center group of psychiatric researchers published a study [2] of SmithKline Beecham's antidepressant drug, paroxetine, in the *Journal of the American Academy of Child and Adolescent Psychiatry*. SKB referred to this as "Study 329." The authors concluded that their study of 275 teens with major depression, treated with either paroxetine (Paxil), imipramine (an older antidepressant drug), or placebo, over an eight-week course, found a beneficial effect of Paxil and a tolerable degree of adverse effects. The lead author was Dr. Martin Keller of Brown University; funding was supplied by SKB, and two of the co-authors were SKB employees.

When the successor to SKB, GlaxoSmithKline, submitted this study to the FDA the drug was approved for adolescent depression. Subsequent studies cast some doubt on its validity, and the concerns over an actual predilection to suicidal thoughts provoked the FDA to add a "black box" warning to its label in 2003. Nevertheless, sales of Paxil increased markedly between 2001-03.

In 2013, in the face of the selective reporting of outcomes of randomized controlled trials, an international group of researchers called on funders and investigators of abandoned (unpublished) or misreported trials to publish undisclosed outcomes [3] or correct misleading publications. This initiative was called restoring invisible and abandoned trials (RIAT).

The researchers identified many trials requiring restoration and emailed the funders, asking them to signal their intention to publish the unpublished trials or publish corrected versions of misreported trials. If funders and investigators failed to undertake to correct a trial that had been identified as unpublished or misreported, independent groups were encouraged to publish an accurate representation of the clinical trial based on the relevant regulatory information.

The current article [4] represents a RIAT re-assessment of SKB's Study 329. The reanalysis under the RIAT initiative was done to see whether access to, and reanalysis of, a full dataset from a randomized controlled trial would have clinically relevant implications for evidence based medicine. And so it did. From the new publication's conclusion:

"The efficacy of paroxetine and imipramine was not statistically or clinically significantly different
from placebo for any prespecified primary or secondary efficacy outcome. ... There were clinically
significant increases in harms, including suicidal ideation and behaviour and other serious adverse
events in the paroxetine group and cardiovascular problems in the imipramine group. ... Neither
paroxetine nor high dose imipramine showed efficacy for major depression in adolescents, and
there was an increase in harms with both drugs.

"Access to primary data from trials has important implications for both clinical practice and
research, including that published conclusions about efficacy and safety should not be read as
authoritative. The reanalysis of Study 329 illustrates the necessity of making primary trial data and
protocols available to increase the rigour of the evidence base."

With scientific methods and reporting currently under fire from all sides, it seems which studies
yield valid, reliable information important for use in clinical medicine, and which (like the SKB/GSK
Paxil study) are evaluated from a slanted perspective (whether intentionally or not) it makes for a
ball of confusion and uncertainty for doctors, patients, and scientists alike.

A blizzard of retracted and irreproducible studies in various fields creates an atmosphere of fear
and mistrust regarding previously respected icons of science and public health. One respected
academic [5] (Dr. John Ioannidis, M.D., Ph.D.) has made a career out of reporting the scary fact
that well over half of "important" medical "gold standard" results have never been confirmed or
have been shown to be unsupported. One can only conclude that the appropriate response to
even the most solid appearing studies is a healthy dose of skepticism, and await repeated
successful efforts at validation.

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