

Study 329 and the use of paroxetine in child and adolescent unipolar depression

JUAN CARLOS MARTÍNEZ-AGUAYO¹, MARCELO ARANCIBIA², SEBASTIÁN CONCHA³, EVA MADRID⁴

¹ Department of Pediatrics, School of Medicine, Faculty of Medicine, Universidad de Valparaíso, Valparaíso, Chile.

² Department of Psychiatry, Faculty of Medicine, Universidad de Valparaíso, Valparaíso, Chile.

³ School of Medicine, Faculty of Medicine, Universidad de Valparaíso, Valparaíso, Chile.

⁴ Department of Public Health, School of Medicine, Faculty of Medicine, Universidad de Valparaíso, Valparaíso, Chile. Biomedical Research Centre, School of Medicine, Faculty of Medicine, Universidad de Valparaíso, Valparaíso, Chile.

Martínez-Aguayo JC et al. / *Arch Clin Psychiatry*. 2016;43(4):93

Received: 4/8/2016 – **Accepted:** 12/9/2016

DOI: 10.1590/0101-60830000000092

Dear Editor,

We have recently published the article “Ten years after the FDA black box warning for antidepressant drugs: a critical narrative review” regarding the warning issued in 2003 by the United States Food and Drug Administration (FDA) about the use of serotonin reuptake inhibitors and venlafaxine for the treatment of child and adolescent depression, and its association to an increased suicidality risk¹. However, considering the new evidence emerged on the topic, we would like to update our article using new available information regarding paroxetine use, a serotonin reuptake inhibitor involved in FDA's warning as well.

In 2001, Keller *et al.* published the study “Efficacy of paroxetine in the treatment of adolescent major depression: a randomized, controlled trial”² (Study 329), sponsored and conducted by SmithKline Beecham (which later became Glaxo SmithKline), concluding that paroxetine is generally well tolerated and effective for unipolar major depression in adolescents when compared with placebo. The “ghostwritten” published results of Study 329 were used for a marketing campaign characterizing paroxetine as remarkably effective and safe. After the campaign, over 2 million off-label prescriptions were written. In 2012, Glaxo SmithKline was fined a record \$3 billion for dishonest encouragement of paroxetine use³. Additionally, the manuscript was made by a medical writer hired by the laboratory, and all the 22 authors in the manuscript denied having participated in writing the draft³.

Recently, the British Medical Journal has published the reanalysis of Study 329, carried out by independent researchers⁴, using Clinical Data Records, in the context of the RIAT initiative “Restoring Invisible and Abandoned Trials,” and in order to check whether access to and reanalysis of a full dataset from a randomized controlled trial would have clinically relevant implications for evidence based medicine. The authors demonstrated that the antidepressant is neither

safe nor effective in adolescent depression. Indeed, the effect of paroxetine was not significantly different from placebo for primary or secondary outcome measure. There were significant increases in harms, suicidal ideation and behavior in paroxetine group, while imipramine group displayed cardiovascular problems. The authors highlighted the need of making primary trial data and protocols available to increase the thoroughness of the evidence. In our study, Study 329 was not included, and neither was its reanalysis¹.

We consider of utmost relevance to take this case into account, especially when considering that the outcome of a clinical intervention is directly related to suicide spectrum. Although in our article we showed some criticism about the ambiguity of the FDA warning, we do not support, in whatever way, these type of practices, which discredit the medical community and science in general.

References

1. Martínez-Aguayo JC, Arancibia M, Concha S, Madrid E. Ten years after the FDA black box warning for antidepressant drugs: a critical narrative review. *Arch Clin Psychiatry*. 2016;43(3):60-6.
2. Keller MB, Ryan ND, Strober M, Klein RG, Kutcher SP, Birmaher B, 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.
3. Doshi P. No correction, no retraction, no apology, no comment: paroxetine trial reanalysis raises questions about institutional responsibility. *BMJ*. 2015;351:h4629.
4. Le Noury J, Nardo JM, Healy D, Jureidini J, Raven M, Tufanaru C, et al. Restoring Study 329: efficacy and harms of paroxetine and imipramine in treatment of major depression in adolescence. *BMJ*. 2015;351:h4320.