Neuropsychopharmacology (2008) 33, 2546–2547

www.neuropsychopharmacology.org

Letter to the Editor

'Effects of Risperidone Augmentation in Patients with Treatment-Resistant Depression: Results of Open-Label Treatment Followed by Double-Blind Continuation.'

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Neuropsychopharmacology (2008) **33,** 2546–2547; doi:10.1038/sj.npp.1301613; published online 21 November 2007

Sir

The report of Rapaport *et al* (2006a) raises several concerns. Contrary to policy, the data were previously published *in extenso* (Nemeroff, 2005), but this previous report was not acknowledged. Next, a corrigendum (Rapaport *et al*, 2006b) belatedly disclosed the authors' financial ties to the sponsor (Janssen). No author may claim ignorance of the journal's policies on prior publication and disclosure of competing interests. Now comes a second corrigendum (Rapaport *et al*, 2007) that disowns a claim of efficacy. This retraction highlights but one of several unexplained differences in statistical reporting and conclusions between this report and Janssen's 2005 report on ClinicalTrials.gov.

In a subgroup analysis, Rapaport *et al* (2006a) claimed significant efficacy for risperidone on two measures of relapse prevention. The second corrigendum disowned one of these claims (proportions relapsing) as an 'error.' Janssen (2005) never made this claim. The result never approached significance ($p = 0.4$) (Rapaport *et al*, 2007), yet the authors stated $p = 0.05$ in the text and highlighted $p \leqslant 0.05$ in Abstract.

The second corrigendum further implied that the efficacy result based on time to relapse remained significant. That claim also differs from Janssen's 2005 report. Janssen reported $p = 0.0512$, calling the result of 'borderline statistical significance.' The present authors reported this analysis as $p = 0.05$ and characterized it as 'statistically and potentially clinically meaningful' (Rapaport *et al*, 2006a). Elsewhere, the authors characterized this result as 'significant' (Nemeroff, 2005) and 'significantly delayed (relapse)' (Nemeroff *et al*, 2004). These characterizations differ from Janssen's candid statement.

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Received 5 August 2007; revised 12 August 2007; accepted 14 August 2007

An additional discrepancy involves the toxicity data. Janssen (2005) reported that mean weight gain in the maintenance treatment phase was significantly greater with risperidone than with placebo. Rapaport *et al* (2006a) reported the same data but without providing the statistical analysis. This omission was not explained. Likewise, they presented no statistical analysis of the proportions who gained 7% or more body weight during long-term treatment. These proportions appear to be 8.3% or 10 of 122 patients on risperidone, 2.6% or 3 of 119 patients on placebo. For this distribution, the Pearson's χ^2 result is borderline significant ($p = 0.0512$), as is the Fisher's exact probability test result ($p = 0.046$, one-tailed).

Thus, the risk–benefit profile of long-term risperidone use in refractory depression may not be as favorable as depicted by Rapaport *et al* (2006a)—higher risk, lower benefit. The only remaining efficacy claim—temporary improvement with short-term risperidone augmentation—rests on uncontrolled data, the weakest level of evidence. The claim that risperidone significantly prevented relapse in a subgroup should be retracted.

DISCLOSURE/CONFLICT OF INTEREST

The author receives consulting compensation from Lundbeck, a manufacturer of antidepressant drugs, and from Astra Zeneca, a manufacturer of antidepressant and antipsychotic drugs.

Current consulting, etc (past 3 years)

Consultant: Astra Zeneca, GlaxoSmithKline, Lundbeck; Stanford University, St Louis University, the University of Michigan; the University of Washington.

Royalty: Multi-Health Systems, Toronto, Canada (Carroll Depression Scales).

Travel support: Cyberonics Inc. (direct travel support to Cyberonics workshop). Lundbeck, Copenhagen (indirect travel support to melancholia symposium)

Stock ownership over $10 000: none.

Advisory boards: none.

Patents: none.

Speaker bureaus: Wyeth.

Past consulting, etc.

In the past 35 years, Dr Carroll has given consultations to Astra (Sweden), Astra Zeneca, Becton Dickinson, Bristol Myers Squibb, Cato Research, Cyberonics, Dupont, GlaxoSmithKline, Ives Laboratories, Janssen, Lilly, National Medical Laboratories, Novartis, Parke-Davis, Pfizer, Roche, Servier, Shire, Skila, and Wyeth. He has received research support from Janssen, Pfizer, Upjohn, Warner Lambert—Parke-Davis, and Wyeth. He has received speaker honoraria from Abbott, Janssen, Lilly, Pfizer, and Wyeth.

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