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Reply to Carroll and Rubin

Reply: Clinical and Biological Effects of Mifepristone Treatment for Psychotic Treatment

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Sir

We are responding to the letter from Bernard Carroll and Robert Rubin regarding our paper 'Clinical and Biological Effects of Mifepristone Treatment for Psychotic Depression', which was published in your journal in March 2006 (Flores *et al*, 2006). Although Rubin and Carroll make some interesting points, they have overlooked the larger picture. Our study was an NIH-funded, exploratory study begun in 1999 to examine whether there was a signal that would support further investigation into the mechanism and efficacy of mifepristone as a treatment for major depressive disorder with psychotic features (PMD). A medication trial of only 30 patients is obviously not a definitive study on any treatment. Below we respond to their specific points.

(1) Carroll and Rubin state that we 'used an uncorrected chi-square to test to obtain this result, even though the frequency is less than 5 in one of the cells of the 2×2 distribution… .' It is true that the *p*-value computed is an approximation, as is the *p*-value using the Yates' correction, as is the *p*-value that Carroll and Rubin report using the Fisher's Exact test, based on the assumption that all four marginals are kept constant in resampling. The issue here is not the exact *p*-value but the indication that the treatment effect may have an effect size of clinical significance for future studies.

Incidentally, a Yates correction should be used when an expected cell size is less than 5 and is not based on the actual cell size found. The expected cell sizes in this study were not less than 5 given the high placebo response rates observed in a recent PMD in-patient, add-on trial (DeBattista *et al*, 2003). Moreover, in a previous criticism of the Belanoff case series (Rubin and Carroll, 2004), they themselves applied an uncorrected χ^2 to even smaller cell sizes. The inconsistency is striking.

Rubin and Carroll further state, 'However, similar to our concerns about earlier trials of mifepristone for this disorder (Rubin and Carroll, 2004), we have reservations about the authors' interpretations of their data.' Again, their interpretation concerns appear to be linked with statistical significance, for which this pilot study is not powered. We did, however, observe an effect size of 0.7 for psychotic symptoms at 1 week over placebo, which is a moderate effect. We believe this is particularly striking when one considers it was above and beyond the background effects of stable treatment and hospitalization. In the Belanoff *et al* (2002) study, the effect size for psychotic symptoms for the 600 mg/day dose at the end of 1 week was 0.9. These are dramatic when one considers that antidepressants and atypical antipsychotics have effect sizes of 0.2–0.3 after 6–8 weeks of treatment (eg Faries *et al*, 2000). Further, large effect sizes have been observed in all of the other small studies published to date on mifepristone in psychotic depression (Belanoff *et al*, 2001a, 2002).

(2) Carroll and Rubin criticize the study for utilizing multiple outcome measures (the BPRS total, the BPRS-positive symptom scale, and the Hamilton Depression Rating Scale). Our hypothesis, first stated in 1985, was that glucocorticoid overactivity played a role in PMD in the pathogenesis of psychotic symptoms and not in depressive symptoms: 'This hypothesis is not intended primarily to account for why patients become depressed but rather why some depressed patients become psychotic' (Schatzberg *et al*, 1985). Depression scores were never intended to be the primary outcome for this research. The authors note we did not observe an antidepressant effect at 1 week but that was exactly what was to be expected from our hypothesis. In our report, we found little effect on depressive symptoms, Cohen's $d = 0.20$, although the Simpson (Simpson *et al*, 2005) report found marked antidepressant effects at 4 and 8 weeks post 6 days of mifepristone monotherapy. Further studies are needed to determine the effect sizes on both depressive and psychotic symptoms.

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(3) The authors criticize the generalizability of these results to clinical practice and that '…many patients had relatively mild or transient symptoms and that they were generally not in clinical crisis.' We are not sure how they drew this conclusion. Was it based on our recruiting some patients via online advertisements? Most, if not all, of the sample, were in fact significantly incapacitated by their illness. They were unable to stop their standing medications. The PMD patients were recruited via online advertisements, including Center Watch, which is the listing of NIMH-supported clinical trials. These patients were often in acute distress and were looking for any new possible treatment for their illness. Patients were recruited widely. All were in treatment with a psychiatrist with whom we consulted. If their treating psychiatrist agreed that other avenues had been tried and failed, then they were considered for our study. Patients who were not actively psychotic at the time of initiation were not included. Importantly, it should be noted that in patients with psychotic depression, depressive symptoms do not need to be severe to have co-occurring psychotic symptoms. Ohayon and Schatzberg (2002) previously reported that psychotic symptoms can and do occur in patients with less severe depressive symptoms. Thus, depression severity is not a trump card for psychotic symptoms.

(4) Carroll and Rubin stated that we 'did not examine clinical utility. Rather they examined a surrogate psychometric measure of psychotic symptom severity.' They then suggest that 'Straightforward and easily understood measures of clinical utility would include: How many patients achieved remission of depression with mifepristone compared to placebo.'

They seem to indicate that as our patients still had psychotic and depressive symptoms, the treatment was not effective. However, we only reported at the end of 1 week of treatment; results from DeBattista (DeBattista and Belanoff, 2004) and Simpson (Simpson *et al*, 2005) point to progressive response over the 4–8 weeks following 1 week of therapy. Moreover, the observed effect size even at the end of 1 week in our study points to clinical utility. If one accepted their arguments, no new antidepressants or antipsychotics would ever be approved given the low remission rates seen at 6–8 weeks with their use. In addition, symptoms have been measured in drug trials of psychotic depression and schizophrenia using the BPRS and its Positive Symptom Subscale for decades (Rothschild *et al*, 2004; Kane *et al*, 2001).

Carroll and Rubin further suggest that 'Demonstration of clinical utility also will require comparison of mifepristone with standard treatments for psychotic depression, such as antidepressant–antipsychotic drug combinations and ECT.' This baffles us. If they truly do not believe the drug is more effective than placebo, how could one ethically go on to compare the drug to other active treatments? Indeed, we reiterate that this was a pilot study, and that once the effectiveness against placebo is established, the natural course would be to challenge the drug against other active treatments, whichever are, at that time, considered 'standard practice.'

In recent studies, the efficacy of the standard treatments has been questioned in this population. Rothschild *et al* (2004) examined the efficacy of an antipsychotic, placebo, or the combination of antidepressant and antipsychotic medication in the treatment of PMD in two separate trials. In one trial, they found that after 8 weeks of treatment, the group given combination therapy had greater improvement than the group given placebo. In a second study, there were no significant differences in clinical outcome between the three treatment groups. Furthermore, Prudic *et al* (2004) found that in a community setting remission rates for full courses of ECT were 30.3–46.7%, and that relapse was more frequent in patients with PMD, occurring at a rate of 4%/day for 10 days after stopping the treatment. That study was an open-label treatment, which almost certainly overstates the treatment response one might see in a blinded study. Thus, current treatment options for psychotic major depression appear to be less effective than Carroll and Rubin imply.

(5) 'As well, the authors failed to demonstrate baseline overactivity or dysregulation of the hypothalamo-pituitary-adrenal (HPA) axis, a salient feature of PMD that provides the rationale for trials of a glucocorticoid receptor blocker like mifepristone.' In the Flores study, no comparisons were made to healthy controls. Their statement is misleading to those who have not read our paper. In a recently published paper (Keller *et al*, 2006), we did report overactivity of the HPA axis as compared to nonpsychotic depressed patients and healthy controls in the same patients described in the Flores paper. This information was not included in their letter.

Similarly, in their 2004 poster (Rubin and Carroll, 2004), Rubin and Carroll stated that in the Belanoff *et al* paper (Belanoff *et al*, 2002) '…most subjects did not show increased HPA activity' and then inappropriately cited controls from another laboratory carried out 20 years ago with a different assay method to validate the statements. The Belanoff study did not even have a normal control group for comparison, so no conclusions relative to normals should be drawn. In fact, examination of the cortisol data in PMD patients in the Belanoff mifepristone study point to much higher cortisol levels than were seen in healthy controls he has studied, using the same methods for analyzing cortisol (Belanoff *et al*, 2001b, 2002).

(6) In their letter they state '…the claim of HPA axis 're-regulation' by reference to 'steepened ascending slopes' of cortisol and ACTH reflects nothing more than the drug confound.' This is a distortion of what we said regarding the biological effects of mifepristone. As we stated in our abstract, 'These results suggest that short-term use of mifepristone may be effective in the treatment of PMD and may reregulate the HPA axis.' Their assertion that we claimed 're-regulation of the HPA axis' is misleading. We continue to believe that it *may* occur and that further investigation with a different design is warranted. The authors point out that our short-term treatment does not provide evidence of what happens weeks or months post-treatment. We agree. Longer-term follow-up studies would be needed to investigate the distant effects of treatment with this compound. Although as noted above, two studies have reported continued benefit at 4 and 8 weeks. We must reiterate that this was a pilot study, not a definitive study designed to answer all possible questions about mifepristone. What would constitute a definitive study to investigate

the mechanisms of drug action or to investigate the long-term effects of the drug would be very different.

On a related note, they state that 'cortisol responses seen with mifepristone were merely expected.' This is also incorrect. We observed an increase in cortisol levels both before and after the nighttime nadir. Previous studies in healthy controls have reported that evening cortisol is not increased with mifepristone (Wiedemann *et al*, 1992).

Their current criticisms echo their erroneous assertions regarding our previous findings in their ACNP poster (Rubin and Carroll, 2004) in which they said: 'Many (of the patients in the Belanoff study (Belanoff *et al*, 2002)) failed to show the expected HPA response to mifepristone.' That statement was also misleading. Of the 18 patients, 17 in the 600 and 1200 mg dose groups showed the expected rise in afternoon cortisol. Indeed, 14/18 showed a 100% rise in cortisol. As indicated in that paper (Belanoff *et al*, 2002), the changes from baseline were statistically significant in both groups.

It is clear that only larger-scale trials will allow us to truly determine whether the medication is useful and whether it improves both psychosis and depression. Two companies are currently examining glucocorticoid antagonists compounds in large, multi-center trials and the results should be known in the next year. DeBattista and Belanoff (2004) have already reported significant differences between mifepristone and placebo in 200 patients studied over a 4- to 8-week period post 7 days of therapy.

Overall, the purpose and the conclusions of our study appear to have been ignored by Rubin and Carroll, and we are concerned that their letter will confuse others. Ongoing trials hopefully will help clarify the range of efficacy of GR antagonists in patients with this severe disorder.

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REFERENCES

Belanoff JK, Flores BH, Kalezhan M, Sund B, Schatzberg AF (2001a). Rapid reversal of psychotic depression using mifepristone. *J Clin Psychopharmacol* **21**: 516–521.

Belanoff JK, Kalehzan M, Sund B, Fleming Ficek SK, Schatzberg AF (2001b). Cortisol activity and cognitive changes in psychotic major depression. *Am J Psychiatry* **158**: 1612–1616.

Belanoff JK, Rothschild AJ, Cassidy F, DeBattista C, Baulieu EE, Schold C *et al* (2002). An open label trial of C-1073 (mifepristone) for psychotic major depression. *Biol Psychiatry* **52**: 386–392.

Carroll BJ (2004a). Sertraline and the Cheshire cat in geriatric depression. *Am J Psychiatry* **161**: 759 (author reply 759).

Carroll BJ (2004b). Untreated depression and hippocampal volume loss. *Am J Psychiatry* **161**: 1309.

DeBattista C, Belanoff JK, Schatzberg AF (2003). C-1073 (mifepristone) *vs* placebo add on to usual treatment of psychotic major depression. *Presented at the 42nd Annual Meeting of the American College of Neuropsychopharmacology*. San Juan, Puerto Rico.

DeBattista C, Belanoff J (2004). A double-blind, placebo controlled trial of C-1073 (Mifepristone) in the treatment of psychotic major depression. *Presented at the 43rd Annual Meeting of the American College of Neuropsychopharmacology*, San Juan, Peurto Rico.

Faries D, Herrera J, Rayamajhi J, DeBrota D, Demitrack M, Potter WZ (2000). The responsiveness of the Hamilton Depression Rating Scale. *J Psychiatr Res* **34**: 3–10.

Flores B, Kenna H, Keller J, Solvason HB, Schatzberg AF (2006). Clinical and biological effects of mifepristone treatment for psychotic depression. *Neuropsychopharmacology* **31**: 628–636.

Kane JM, Marder SR, Schooler NR, Wirshing WC, Umbricht D, Baker RW *et al* (2001). Clozapine and haloperidol in moderately refractory schizophrenia: a 6-month randomized and double-blind comparison. *Arch Gen Psychiatry* **58**: 965.

Keller J, Flores B, Gomez RG, Solvason HB, Kenna H, Williams G *et al* (2006). Cortisol circadian rhythm alterations in psychotic major depression. *Biol Psychiatry* **60**: 275–281.

NY Times Editorial Desk (2003). Disclosure at the Medical Journals, September 30.

Ohayon MM, Schatzberg AF (2002). Prevalence of depressive episodes with psychotic features in the general population. *Am J Psychiatry* **159**: 1855–1861.

Prudic J, Olfson M, Marcus SC, Fuller RB, Sackeim HA (2004). Effectiveness of electroconvulsive therapy in community settings. *Biol Psychiatry* **55**: 301–312.

Rothschild AJ, Williamson DJ, Tohen MF, Schatzberg A, Anderson SW, Van Camper LE *et al* (2004). A double-blind, randomized study of olanzapine and olanzapine/fluoxetine combination for major depression with psychotic features. *J Clin Psychopharmacol* **24**: 365–373.

Rubin RT, Carroll BJ (2004). Mifepristone (RU486) in the treatment of psychotic depression: re-evaluation of published data. *Neuropsychopharmacology* **29**(Suppl 1): S203–S204.

Schatzberg AF, Rothschild AJ, Langlais PJ, Bird ED, Cole JO (1985). A corticosteroid/dopamine hypothesis for psychotic depression and related states. *J Psychiatr Res* **19**: 57–64.

Schneider LS, Nelson JC, Clary CM, Newhouse P, Rama KRR, Krishnan Shiovitz T *et al* (2004). Dr Schneider and colleagues reply. *Am J Psychiatry* **161**: 759–761.

Simpson GM, El Sheshai A, Loza N, Kingsbury SJ, Fayek M, Fawzy W (2005). An 8-week open-label trial of a 6-day course of mifepristone for the treatment of psychotic depression. *J Clin Psychiatry* **66**: 598–602.

Wiedemann K, Lauer C, Loycke A, Pollmacher T, Durst P, Macher JP *et al* (1992). Antiglucocorticoid treatment disrupts endocrine cycle and nocturnal sleep pattern. *Eur Arch Psychiatry Clin Neurosci* **241**: 372–375.