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**Reply: A dangerous bias**

Sir,

We appreciate Drs Broudy and Payne’s interest in our paper and their letter. They disagree with our statement ‘there is little evidence of benefit from the antidepressants prescribed for the majority of women of childbearing age—and there is ample evidence of risk’. We stand by this statement as being accurate. Several meta-analyses have been performed on the subject of antidepressant efficacy: the drug–placebo differences are remarkably reliable in these analyses and they do not meet the standard criterion for clinical significance, as the table below demonstrates (table courtesy of I. Kirsch, personal communication):

<table>
<thead>
<tr>
<th>Effect sizes (NICE criterion for clinical significance = 0.50)</th>
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<tbody>
<tr>
<td>Kirsch et al. (2008)</td>
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<tr>
<td>Fountoulakis and Möller (2011)</td>
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<td>Turner et al. (2008)</td>
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<td>NICE (2004)</td>
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<td>Fournier et al. (2010)</td>
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<th>Hamilton improvement (NICE criterion = 3)</th>
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<td>Kirsch et al. (2008)</td>
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<td>Fournier et al. (2010)</td>
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<td>Khin et al. (2011)</td>
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<tr>
<td>Vilazodone (Vibryd) (FDA, 2011)</td>
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To support their claim that antidepressants work in non-severe depression, Broudy and Payne refer to Stewart’s 2012 study (Stewart et al., 2012). This study used an HRSD cut-off of 23 to determine severity. This is not the cut-off used by the APA or NICE (NICE, 2004). These groups use 19–22 for severely depressed, which means that a study using a cut-off of 23 (as Stewart et al. did) would include severely depressed patients. Stewart et al. concluded the paper by noting: ‘We agree with Fournier et al. that more predictably effective treatments are needed for all depressed subjects’.

Broudy and Payne also cite Isacsson et al. (2012) to argue that Fournier’s results (Fournier et al., 2010) are based on unreliable data. The conclusions drawn by Isacsson et al. are that ‘the HDRS Scale provides unreliable primary data’ and that ‘the clinical value of antidepressants cannot be evaluated from unreliable data’. In that case, one should
conclude that there is no evidence for the effectiveness of antidepressants because the data, including that cited, are unreliable. Broudy and Payne go on to argue that ‘drugs [antidepressants] shown to work in the general population would also work in specific populations [pregnant women].’ However as detailed above, the antidepressants do not appear to provide clinically significant benefit for most patients with depression in the general population.

To demonstrate their effectiveness in pregnancy, Broudy and Payne cite the Cohen et al., 2006 study (Cohen et al., 2006). This study, however, had significant flaws (Urato, 2006). For example, one major shortcoming was the lack of any mention of the issue of withdrawal. It is now well established that patients who stop antidepressants can have severe symptoms. The Cohen et al. (2006) paper was about pregnant women stopping antidepressants, but nowhere does the word ‘withdrawal’ appear and the issue is never addressed in the paper. The Yonkers (2011) study did not find increased relapse amongst women who discontinued their medications in pregnancy (Yonkers et al., 2011).

In their letter, Broudy and Payne also wish to make clear their belief that depression itself increases pregnancy complications. However, this association is not clear from the studies on the topic (Yonkers et al., 2009). We understand that this belief is strong among many and it is what prompted two editorialists recently to comment: ‘Although this belief is strong among some investigators, the evidence to support the independent association of depression with these outcomes is weak (Palmsten and Hernandez-Diaz, 2012).’

For those who consider that depression is clearly associated with worsened pregnancy outcomes, and that antidepressants clearly provide clinically meaningful benefit, then the question remains: why do none of the hundreds of studies in this area show improved pregnancy outcomes in the antidepressant-treated group? With a truly effective drug (e.g. insulin) and a disease that clearly causes pregnancy complications (e.g. diabetes) it is not at all difficult to show benefit in the treated group.

Overall, in their letter, Broudy and Payne attempt to make the argument that depression is clearly linked to pregnancy complications and that antidepressants are effective in treating depression. In 25 years of study in this area, not a single study shows improved pregnancy outcomes in the group being treated with the antidepressants. The available scientific evidence suggests that any link between depression and pregnancy complications is unclear, that antidepressants do not provide clinically significant benefit for most depressed patients and that antidepressant treatment itself leads to pregnancy complications. With a proper understanding of what the evidence shows, it then becomes clear why the antidepressant-treated pregnancies have the poorer outcomes in study after study.

We certainly agree that depressed women need good care and treatment, and an essential part of that is providing them with the correct information so that they can make informed choices. This is what our paper sought to do and we stand by the scientific evidence and our conclusions.

References


Urato AC. Antidepressant treatment and relapse of depression during pregnancy. JAMA 2006;296:166.


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