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Post-partum depression—a glimpse of light in the darkness?

Published Online
June 12, 2017
http://dx.doi.org/10.1016/S0140-6736(17)31546-5

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There can be little doubt about the importance of mood episodes in pregnancy and following childbirth.[1] Mood episodes are common—post-partum depression is the most common medical complication of maternity, affecting around one in ten new mothers.[2] They can also be severe—episodes of post-partum psychosis represent some of the most serious episodes of illness seen in psychiatry.[3] Perinatal mood episodes cause substantial impairment to women and have a wide ranging impact on their babies, families, and society. The total long-term cost to society of perinatal depression, anxiety, and psychosis has been estimated to be £8·1 billion for each 1-year cohort of births in the UK.[4]

Despite the clear need, there are limited options for the management of these disorders. In addition to psychological approaches such as cognitive behavioural therapy, medications, particularly for more severe episodes of illness, are a mainstay of treatment.[5] Because, at least in part, pregnant and breastfeeding women are excluded from clinical trials, decisions about medication for perinatal mood episodes are difficult; they must be made by extrapolating the data available for their use at other times of women's lives. It is clear, therefore, that developing new, evidence-based treatments is essential.

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In *The Lancet*, Stephen Kanes and colleagues[6] report the results of a double-blind, randomised, placebo-controlled, phase 2 study of a new treatment for post-partum depression. The compound, brexanolone, is an intravenous formulation of allopregnanolone, a positive allosteric modulator of γ-aminobutyric acid (GABA) receptors. In this small study in 21 women with severe post-partum depression, infusion of brexanolone resulted in a rapid, sustained, statistically significant, and clinically meaningful response compared with placebo (at 60 h, mean reduction in Hamilton Rating Scale for Depression [HAM-D] total score from baseline 21·0 points [SE 2·9] in the brexanolone group *vs* 8·8 points [SE 2·8] in the placebo group; difference −12·2, 95% CI −3·67 to −20·77; p=0·0075; effect size 1·2). There were significant differences between groups from 24 h; by 60 h, seven (70%) women in the brexanolone group had achieved remission compared with one (9%) woman in the placebo group (p=0·0364). These results, while based on a small sample, are very impressive; indeed, some readers might feel that they are too good to be true. For women with post-partum depression and the professionals who treat them, however, these findings are promising.

The investigators are to be applauded for targeting women with severe episodes of post-partum depression, and for showing that a clinical trial in women with this condition is feasible.

The current study, it must be noted, involved only ten women treated with brexanolone. The pressing

need is therefore for replication of these results in larger phase 3 trials. Further questions may then need to be addressed that are raised but not answered by this study. It does not tell us, for example, if this is a treatment for post-partum episodes specifically, or for depression more generally? Is the treatment effective in other psychiatric conditions triggered by childbirth such as post-partum psychosis or in a wider group of reproductive and endocrine-related mood disorders such as those related to menstruation and menopause?

The findings have potentially important implications for our understanding of the pathophysiology of post-partum mood disorders and, given what is known about the action of brexanolone, provide further evidence implicating neuroactive steroids in general, and the GABA type A ($GABA_A$) receptor δ subunit in particular. Other research disciplines, such as neuroimaging and genetics, can further explore this promising avenue of research.

The need for a 60 h intravenous infusion with brexanolone, although possibly not an issue for women with severe post-partum depression, could be problematic if the treatment is found to be effective in less severe forms of the disorder. To this end, it will be interesting to see if it will be possible to develop $GABA_A$ positive allosteric modulators that can be administered orally with similar efficacy. Finally, in addition to the treatment of women who are currently symptomatic, will this or similar treatments be suitable for the prevention of episodes in women at high risk?

Those of us hoping for the development of effective pharmacological treatments that specifically target post-partum depression have, like our patients, felt in a dark place. With the very encouraging results of this trial, perhaps we can begin to see the first glimpses of light.

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I declare no competing interests.

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Preventing major gastrointestinal bleeding in elderly patients

Published Online June 13, 2017 http://dx.doi.org/10.1016/S0140-6736(17)31507-6

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Antiplatelet therapy is the most frequently recommended treatment to prevent recurrent ischaemic events in patients who have had an ischaemic stroke, an acute coronary syndrome, or symptomatic peripheral arterial disease. The most frequently used drugs are aspirin or clopidogrel. Most guidelines recommend lifelong intake of antiplatelet therapy. However, randomised trials that have investigated the benefit of antiplatelet therapy had an observation period of between 2 years and 4 years.[1] Therefore, we lack data on the long-term benefit and risk of antiplatelet therapy across long time periods, particularly in elderly patients.

In *The Lancet*, Linxin Li and colleagues[2] report bleeding events and outcomes in 3166 patients with first transient ischaemic attack, ischaemic stroke, or myocardial infarction who were treated with antiplatelet drugs (mainly aspirin) and were followed prospectively for 10 years. Half of the patients (n=1582) were aged 75 years or older.

Major bleeding and fatal bleeding were significantly related to age and showed a steep increase in incidence above the age of 75 years. The hazard ratio for major upper gastrointestinal bleeds was 4·13 for age 75 years or older and 10·26 for those bleeds that were disabling or fatal. The proportion of gastrointestinal bleeding events that were disabling or fatal was higher than the proportion of ischaemic stroke or intracerebral haemorrhage. At age 75 years or older, most major upper gastrointestinal