Valproate? A Call to Action

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## It is illegal to post this copyrighted PDF on any website. SECTION CONTENTS Wishful Thinking Is Not Effective **SECTION CONTENTS Contraception: Family Planning,** 525 Should Women of Childbearing Potential Be Prescribed Contraception, and Safe Prescribing

Unplanned pregnancies account for approximately 50% of pregnancies in the United States and 40% globally.<sup>1</sup> Therefore, it is good clinical practice to treat women of reproductive potential with the idea in mind that they may become pregnant during the course of treatment, regardless of their stated intentions. In psychiatry, most of the disorders we treat are chronic or recurrent; women are often on psychotropic medications during the reproductive years, and many will require pharmacologic treatment for psychiatric illnesses during pregnancy. Therefore, the reproductive safety of medications is paramount to a major segment of the population we treat, whether or not we focus specifically on the treatment of pregnant women.

Two offerings in this month's Focus on Women's Mental Health section highlight considerations regarding the use of valproic acid, the psychotropic medication that carries the greatest risk of teratogenicity. It has up to a 10% or greater risk of major malformations, with the most noted being neural tube defects, and the exposure that leads to this devastating birth defect occurs very early in pregnancy, before most women would be aware that they are pregnant.<sup>2</sup> Additionally, long-term neurodevelopmental deficits have been noted in children exposed in utero to valproic acid.<sup>3</sup> Despite these serious considerations, many health care prescribers and patients remain unaware of the great teratogenicity of valproic acid.

Perinatal psychiatrists and guidelines on the topic of pregnancy generally consider valproic acid to be contraindicated in women of reproductive potential. A commentary in this issue by Balon and Riba highlights the dilemmas of valproic acid prescription for women of reproductive potential. Avoiding the use of valproic acid in women of reproductive potential is the safest strategy, one that has become exceedingly feasible as a growing number of medications have been introduced for treatment of bipolar disorder. The next best, but far worse, option is the avoidance of pregnancy in women taking valproic acid. The rates of unplanned pregnancy underscore the recklessness of this strategy, when there are so many other treatment choices available.

In this month's continuing medical education (CME) article, Gotlib and colleagues report the findings from a retrospective chart review of women prescribed valproic acid for psychiatric illness. In the review, they assessed whether there was chart documentation of recommended cautions for women using valproic acid, namely patient education around the risk of birth defects with valproic acid, use of contraceptives, and use of folic acid (high doses are recommended with valproic acid and other anticonvulsants, although it is not known whether such use offsets risk of neural tube defects associated with anticonvulsants). The findings are sobering: they found that "only 25 women (13.2%) on valproic acid treatment had adequate documentation regarding teratogenic risk, 15 (7.9%) were prescribed folate, and only 57 (30%) had documented contraception use." These data underscore the current gaps between prescribing guidelines and clinical practice, particularly because the consequences are so serious.

Clearly, the reproductive safety of psychiatric medications must be considered from the onset when starting medications in girls or women of reproductive potential. Also, birth control and family planning and intent for pregnancy should be regular topics of discussion between patients and their health care providers. If women do not specifically state that they intend to become pregnant, it should not be assumed that they are using birth control methods. It is clinically useful to regularly assess the use of birth control methods regularly, as one would assess current medication use.

Other important topics in women's mental health are also covered in this issue. Spinelli et al provide data to inform the study of perinatal depression and the challenges of controlled trials in its treatment research. In the primary analysis of a randomized study of interpersonal psychotherapy (IPT) versus a parenting education program (PEP) for antepartum depression, there were no significant differences on primary

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**It is illegal to post this copy** outcomes. However, in a reanalysis including those with a higher burden of depressive symptoms, the IPT group had lower depression scores at week 8 than the PEP group, showing the efficacy of IPT in those women who were at least moderately depressed. This is consistent with studies of pharmacotherapy that demonstrate more robust findings in patients with higher severity of depression compared to placebo. This research provides an important caveat for psychotherapy studies of depression, in that therapy-specific benefits may not be readily apparent in studies that include women with mild depression.

Rochon-Terry and colleagues provide new data on the topic of schizophrenia and its perinatal course. They assessed utilization of psychiatric services, including psychiatric hospitalizations, emergency department (ED) visits, and ED visits specifically related to self-harm. They found that approximately 12% of women had at least 1 psychiatric hospitalization during pregnancy, and 19% in the first year postpartum, with a peak in the immediate postpartum. While self-harm visits were low, about 10% had at least 1 psychiatric ED visit during pregnancy, and 16% had at least 1 ED visit postpartum. These data potentially inform treatment planning for women with schizophrenia during pregnancy and the postpartum.

The idea of "reproductive depressions" has been postulated, representing an expression of mood disorders among a subset of women who experience depression during times of hormonal fluctuation.<sup>4</sup> The reproductive events that are characterized by hormonal fluctuations include the menstrual cycle, pregnancy and the postpartum, and the menopausal transition. Therefore, it seems reasonable to suspect a shared vulnerability for premenstrual dysphoric disorder (PMDD), postpartum depression (PPD), and depression during the menopause transition. To look at this topic, Kepple et al assessed histories of 215 women who presented with PMDD. The PMDD diagnosis was validated by a clinical interview. Among the 137 women who had delivered at least 1 child, 11.7% had experienced past PPD. This is lower than the rates of past major depressive episodes (MDEs; 31.2%), anxiety disorders (15.3%), and substance abuse disorders (18.6%) among women with PMDD. The authors discuss and conclude that their results suggest a different pathophysiology between PMDD and PPD and note as well the high rate of past MDE among women with PPD.

Finally, Cortese et al bring us findings on gender differences in adult attention-deficit/hyperactivity disorder (ADHD) from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). The findings from this study raise important points for the screening and treatment for ADHD. While the lifetime prevalence of ADHD was higher in men than in women, persistent ADHD was similar among men and women. This appears consistent with a growing recognition that adult women may experience ADHD with associated disability in substantial numbers. It is important to note that this was an epidemiologic survey and not a sample of a treatment-seeking population. Therefore, results underscore the possibility that many women with ADHD do not receive adequate attention or treatment.

We thank the authors of this section's articles for their contributions.

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