clozapine (an average dose of 293 mg/day), there was also no significant clinical improvement.

We then decided to administer amisulpride additionally to these patients. Treatment success was monitored with the Clinical Global Impression Scale (CGI) and the Brief Psychiatric Rating Scale (BPRS). The average dose of amisulpride was 543 mg/day (SD=223, range=200–800); comedication included lithium in two cases and lorazepam in three. The addition of amisulpride to clozapine was followed by a decrease in the mean BPRS total score from 50.1 (SD=3.9) to 45.9 (SD=4.6) after a 17-day period (Wilcoxon test: $z=-2.02$, $p<0.05$) and to 33.7 (SD=9.3) after an average of 9.7 months (Wilcoxon test: $z=-2.20$, $p<0.03$). Global severity of the disease (CGI score) decreased from 6.7 (SD=0.5) to 4.6 (SD=1.1) points (Wilcoxon test: $z=-2.20$, $p<0.03$). Treatment response was rated as at least good (CGI score ≥3) in six of seven cases.

A 12-channel ECG was carried out before initiation of amisulpride (baseline) and 17 days later, on average. QTc times were evaluated as described elsewhere (2). There were no significant changes in ECG time intervals after the addition of amisulpride to clozapine; the mean resting heart rate and mean QTc time both remained unchanged (heart rate: 95.9 bpm versus 93.6 bpm; QTc: 339 msec versus 331 msec). The maximal QTc time was 410 msec. Mean clozapine plasma levels did not differ significantly compared to baseline (the average difference was –28.3 ng/ml).

Even though we could not definitively dismiss that monotherapy with clozapine might otherwise have led in some cases to an improvement in psychosis over long-term treatment (3), our preliminary data suggest that combined clozapine and amisulpride significantly improves schizophrenia symptoms after a relatively short time. The mechanisms underlying this remain unclear. The dopamine D_2 and D_3 receptor-blocking effects of amisulpride might complement the receptor binding profile of clozapine effectively, and such a combined receptor interaction might trigger an improvement in psychotic symptoms.

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Antidepressants and Premature Labor

TO THE EDITOR: Gregory E. Simon, M.D., M.P.H., and colleagues (1) neglected to include important issues in their report. The risk factors for premature labor include low socioeconomic status, previous occurrence of premature labor, gestational bleeding, and uterocervical anomalies (2). Failure to consider obstetrical health presents the possibility that these factors occurred more commonly in the group exposed to selective serotonin reuptake inhibitors (SSRIs) and were responsible for the higher rate of prematurity.

The study included women who delivered between January 1986 and December 1998. The rates of preterm delivery over the interval 1975 to 1995 increased by 3.6% among blacks and by 22.3% among whites, which indicates the presence of period effects (3). SSRI use was more common than tricyclic antidepressant use in the latter years of the study by Dr. Simon et al. (1986–1998). Therefore, a twofold increase in the rates of preterm labor cannot be specifically attributed to SSRI exposure.

Depressive symptoms were not assessed directly. Some women in both antidepressant treatment groups and the control group will remain depressed or have subthreshold symptoms. Either the active (state) effects of depression or the residual (trait) effects (changes in maternal physiology that remain even when the mother is asymptomatic) could affect pregnancy outcome negatively. Negative outcomes attributed to an SSRI may be related to either unremitting depression or the interaction of depression with SSRI exposure. To propose that negative outcomes are not due to depression because they occurred differentially across the two antidepressant-treated groups is valid only if symptom levels in both groups were equivalent.

Potentially toxic exposures have specific considerations during pregnancy that are not reported: the dose, the timing of the dose during gestation, and the changes in dose across the pregnancy. Malformations are unrelated to second- and third-trimester exposures. The likelihood that exposure to an SSRI at any time during pregnancy affects outcomes at birth is biologically implausible and conflicts with the findings of Chambers et al. (4) and Cohen et al. (5), who found that only third-trimester SSRI exposure affected birth outcomes. Pastuszak et al. (6) also found no relationship between first-trimester exposure to fluoxetine or a tricyclic antidepressant and gestational age or birth weight, contrary to such a statement by Dr. Simon et al. (p. 2060).

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Dr. Simon and Colleagues Reply

TO THE EDITOR: Drs. Sunder and Wisner raise several questions regarding our study's methods. We have clear answers for some of them but not for all. Regarding time trends in the rates of premature birth, this would be a potential confounder had our sampling not matched for year of delivery. Given the matching procedure, confounding by time effects is not a concern.

The writers mention several other potential confounding factors: socioeconomic status, history of premature labor, gestational bleeding, and uterocervical abnormalities. One of these risk factors would act as a confounder, however, only if it increased the risk of both premature delivery and the use of antidepressants. Given that we observed a specific effect of SSRI exposure, such a confounding factor would also have to increase the risk of SSRI exposure without increasing exposure to tricyclic drugs. We are not aware of any evidence that these risk factors for premature delivery are specifically associated with the use of one class of antidepressant.

Regarding the effects of early pregnancy exposure on premature delivery, we agree that the mechanism for such an effect is not clear. But we reported what we observed. Whether our finding is a chance error or a true effect will be decided by replication in other studies rather than by argument. We agree that the study by Pastuszak et al. (1993) indicated a difference in the rate of miscarriage rather than the rate of premature delivery, and we appreciate that Drs. Sunder and Wisner corrected our error.

We agree that confounding due to differences in the severity of depression is the greatest threat to the validity of our findings or those of any observational study. Depression clearly satisfies essential criteria for a potential confounding factor as it increases the risk of both antidepressant exposure and premature delivery. We attempted to account for this potential confounding by matching for history of depression treatment. While this method is certainly an advance over previous studies (in which comparison groups did not suffer from depression), it is far from perfect. Even measures of depressive symptoms in the exposed and unexposed groups would not rule out confounding due to unmeasured differences. Our article clearly acknowledges the potential for residual confounding due to differences in depression severity during the index pregnancy. Once again, the specificity of the observed effect (association with SSRI exposure but not with tricyclic exposure) argues against confounding as an explanation. As we pointed out, this question could be answered definitively only if depressed pregnant women were randomly assigned to an SSRI antidepressant or placebo. We doubt that such a study will ever be conducted. Instead, we will probably have to rely on even larger observational studies to compare risk across multiple classes of antidepressant drugs.

In the end, we suspect that we differ with Drs. Sunder and Wisner regarding the value we place on different types of evidence. Our design, a population-based sample of exposed children and a systematically selected population-based comparison group, does not permit the more detailed assessments that are possible with specialty clinic-based groups. We believe, however, that systematic sample selection and careful matching offer the best protection against bias and unmeasured confounding.

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Diagnostic Stability of Personality Disorders

TO THE EDITOR: Since the article by M. Tracie Shea, Ph.D., et al. (1) is not the only recent report in the literature of rapid change in personality found with the use of semistructured DSM personality instruments (2), it is important to discuss what may be important implications. Although the article by Dr. Shea et al. discussed some of these issues, I feel it is important that they be fleshed out.

The first issue to raise is whether semistructured DSM personality instruments are as accurate as we believe. Although much has been made of the difference in outcomes between semistructured and self-report instruments, I am not aware of any reports indicating that semistructured interviews agree with each other much beyond the diagnosis of any personality disorder. These instruments may have a wide variance in their measurements.

Next, we know that personality measurements are often influenced by state affects (3, 4). The variation we may be seeing may be the result of patients coming to clinics with more severe axis I symptoms that decline over time, taking down the state-dependent personality measure with it.

Of course, the most interesting possibility is that we may have wrongly conceptualized personality disorders as long lasting and immutable; they may in reality show a considerable fluctuation of symptoms. Related to this, we may not be dealing with one set of disorders but two. One set is long lasting and the second, "stress-induced" or "state" personality disorders, may be relatively transient (5).

Finally, there is the issue of treatment. Although the article by Dr. Shea et al. did not report such a finding, there are many reports of personality traits being treated by medications (6, 7), and this should be kept in mind in the interpretation of the results. I hope that this letter furthers productive discussion in this area.

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