develops enhanced colonic inflammatory responses in adulthood (3). This would set the stage so that when the perinatally BPA-exposed female rat becomes pregnant, the pregnancy may be marked by enhanced inflammation. Paradoxically, estrogenic exposure may have anti-inflammatory effects in the exposed adult, but inappropriate estrogen exposure may have pro-inflammatory effects in the perinatally exposed offspring. These effects were observed at levels of BPA exposure previously believed to be too low for observed adverse effects in humans (3).

I have proposed elsewhere an estrogenic endocrine disruption theory of schizophrenia, in which inappropriate dosage, timing, or duration of prenatal estrogen exposure causes schizophrenia (4, 5). Within this theoretical framework, inappropriate estrogen exposure occurring in the brain could also be occurring in the colon so that an association of celiac disease or some other inflammation and schizophrenia may be observable not from a genetic link per se but rather a transgenerational effect of prenatal estrogen exposure.

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JAMES S. BROWN, JR., M.D., M.P.H.
*Richmond, Va.*

*The author reports no financial relationships with commercial interests.*

*This letter (doi: 10.1176/appi.ajp.2012.12060735) was accepted for publication in June 2012.*

## Alternative Interpretation for the Early Detection of Psychosis Study

To the Editor: In the April issue, the Treatment and Intervention in Psychosis (TIPS) early-detection study reports 10-year results in a manner that overstates the impact of reducing the duration of untreated psychosis (1). The authors dismissed a 50% increase in hospitalization in the treatment group after 5 years as the result of regional policy differences. They did not describe the policy differences or analyze the effects of this impressive confound on the small difference in symptoms, instead claiming to have demonstrated "positive effects on clinical and functional status" (2, 3). They omit hospitalization results altogether at 10 years, despite this being by far the most impressive result at 5 years (1).

Perhaps because at 5 years the researchers reported a nonsignificant advantage in remission for the control group (2), at 10 years they introduce a new recovery metric, based largely on work function, which showed a significant advantage for the treatment group (1). Although they acknowledge a significant attrition bias by 10 years, they do not report that at 5 years there was no difference in work function, or suggest how reducing the duration of untreated psychosis at baseline would not improve work function at 5 years but double work function at 10 years.

The authors reported that the control group achieved independent living significantly more often at the 10-year mark, but dismiss this evidence of worse function in the treatment group, suggesting that independent living is not evidence of recovery because it is not included in the new metric. They do not analyze the possibility that failure to achieve independent living is evidence of poor function (1).

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ANDREW AMOS, B.ARTS (HONS), M.B.B.S.
*Brisbane, Australia*

*The author reports no financial relationships with commercial interests.*

*This letter (doi: 10.1176/appi.ajp.2012.12050578) was accepted for publication in June 2012.*

## Response to Amos Letter

To the Editor: Dr. Amos raises several points of criticism regarding the TIPS study and our interpretation of the data, as he did previously (1) in response to abstracts from our group. We thank the *Journal* for the opportunity to respond.

First, Dr. Amos points out that patients from the health care area practicing early detection had significantly higher rates of hospitalization at the 5-year follow-up, and he is critical of the fact that we did not thoroughly investigate this possible confounder. This is a valid concern; however, he seems to miss the point that it is the group of patients *not* in symptom remission (a prerequisite of recovery) who received more inpatient care in the early-detection area. For recovered patients, there was no difference between early and usual detection. Knowing that more hospital time did not lead to better recovery, hospitalization cannot be a confounder.

Second, Dr. Amos questions the finding that while there apparently were no differences in work function at the 5-year follow-up, the early-detection patients had double the chance of full-time employment at 10 years. He goes on to imply that we might have chosen a new measure of "recovery" out of convenience, having made sure that this measure would yield us more favorable results. At 5 years, we used "working at least

20 hours per week" as the employment outcome (2). At the 10-year follow-up, using a new measure of recovery chosen before data collection and on the basis of recent developments in the field, we looked only at full-time employment. This is a stricter measure and was significantly higher for early detection patients. However, nonrecovered patients had poor working capacity both in early and usual-detection areas, both at 5 and 10 years.

Third, Dr. Amos addresses the finding that more patients from the usual-detection area were living independently. However, living independently is a necessary but not sufficient element in recovery. In fact, as reported in our 10-year follow-up in the April issue, only 17.9% of the patients living independently in the usual-detection area were fully recovered with both symptom remission and full-time employment, compared with 48.4% for early-detection patients. This seems to indicate that living independently does not automatically imply better health and function.

All in all, as we have noted elsewhere (3), we agree that early detection cannot and should not be presented as a "cure for all." Nevertheless, our data show that early detection does seem to have long-standing positive associations with outcome measures for a large group of patients, and it improves the chances of recovery. However, for a considerable group of patients, we were not able to demonstrate a long-term effect.

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WENCHE TEN VELDEN HEGELSTAD, M.Sc.
TOR K. LARSEN, M.D. Ph.D.
JAN O. JOHANNESEN, M.D. Ph.D.
*Stavanger, Norway*

INGRID MELLE, M.D. Ph.D.
*Oslo, Norway*

ERIK SIMONSEN, M.D. Ph.D.
*Roskilde, Denmark*

SVEIN FRIIS, M.D. Ph.D.
*Oslo, Norway*

THOMAS McGLASHAN, M.D.
*New Haven, Conn.*


*The authors' disclosures accompany the original article.*

*This reply (doi: 10.1176/appi.ajp.2012.12050578r) was accepted for publication in June 2012.*

## Bilateral Pallidal Necrosis and Cardiac Toxicity in a Patient With Venlafaxine and Bupropion Overdose

To the Editor: The new generation of antidepressants is generally thought to be safer than traditional antidepressants. Although combining antidepressants is recommended for the treatment of refractory depression, the toxicity of drug overdose from more than one antidepressant is seldom addressed.

### *Case Report*

**A 30-year-old woman was sent to the emergency department 1 hour after ingesting venlafaxine and bupropion in a suicide attempt. The exact dose was uncertain, but according to the metabolites of venlafaxine, bupropion, and benzodiazepine found in her urine, it is probable that she consumed a 1-month prescription of 150 mg venlafaxine, 300 mg bupropion, and 3 mg lorazepam that was prescribed 3 days earlier.**

**She had clear consciousness initially, but generalized myoclonus soon occurred. A fever (40.6°C) and tachycardia (100–170 bpm) developed with normal blood pressure (122/91 mmHg), respiratory rate (16/min), and $O_2$ saturation ($SpO_2$=95%). An ECG demonstrated prolonged QRS complex with a deep, slurred S wave on lead I and an R wave on lead aVR. Sodium bicarbonate was then administrated.**

**One hour later, the patient became drowsy and confused and she suffered respiratory distress. Her blood pressure decreased (94/36 mmHg), tachycardia increased (200 bpm), and $SpO_2$ decreased (49%). Endotracheal intubation was performed within 5 minutes, and her $SpO_2$ and blood pressure returned to normal. After sodium bicarbonate treatment, the patient recovered from the changes seen on the ECG. However, leukocytosis ($10.27\times10^9$/L), elevated creatine kinase (520 U/L) and creatinin (1.5 mg/dL) levels, and changes in vital signs suggested serotonin syndrome. Cyprohepadine was provided with supportive treatment; intravenous lorazepam was also given continuously for agitated behavior. Fever and disturbed consciousness ameliorated within 2 days, but creatine kinase and alanine transaminase levels continued to increase, peaking at 107,895 U/L and 2,453 U/L around 43 and 102 hours, respectively, after overdose. The patient was extubated 7 days later.**

**One week after extubation, purposeful involuntary movement and akathisia were noted after discontinuing lorazepam. Suspecting benzodiazepine withdrawal, lorazepam was resumed with pramipexole, 0.75mg/day, until the akathisia subsided 2 weeks later. The choreoathetosis remained, with frontal releasing signs (i.e., Luria test, glabellar reflex) and impaired recent memory, language, and executive function. An MRI scan revealed bilateral pallidal necrosis 7 weeks after admission (Figure 1 and Figure 2).**

### *Discussion*

A limited number of reports of antidepressant overdose-related bilateral pallidal necrosis have been published. Szólics et al. (1) reported similar pallidal necrosis with multiple functional changes and extrapyramidal symptoms after fluoxetine overdose, implying a complex relationship between serotonin and the nigrastriatal dopaminergic system. The bilateral pallidal necrosis in our patient could have been caused by transient hypoxia, but the toxicity of venlafaxine and/or bupropion could not be excluded. It is therefore worth being cautious when prescribing venlafaxine concomitantly with bupropion for patients at high risk of deliberate