Letters to the Editor

Risperidone-Induced Retrograde Ejaculation

TO THE EDITOR: Schizophrenic patients treated with antipsychotic drugs may suffer from a variety of sexually disabling side effects that can affect all domains of sexual activity. The most common such adverse effects in men are erectile dysfunction and retrograde ejaculation (1). Retrograde ejaculation has been mostly reported in association with typical antipsychotics, especially thioridazine (1); among the atypical antipsychotics, to our knowledge, only clozapine has been reported to cause retrograde ejaculation (2). We describe a schizophrenic patient with risperidone-induced ejaculatory failure that was compatible with retrograde ejaculation, both clinically and in the laboratory.

Mr. A was a 37-year-old man who was married with three children and who met DSM-IV criteria for paranoid schizophrenia. He was physically healthy, had no apparent concomitant general medical condition, and had never experienced ejaculatory problems. He had his first overt psychotic episode at age 29 and was successfully treated with perphenazine, 32 mg/day, without any major adverse effects. He was admitted to our psychiatric inpatient ward after a second psychotic exacerbation of the disorder and after being drug free for about 6 years. On admission, treatment with risperidone was initiated; the dose was increased to 4 mg/day by 1 mg/day increments and thereafter remained constant.

On days 6, 9, and 14 after the initiation of risperidone treatment, Mr. A engaged in sexual intercourse with his wife, after which he reported having ejaculatory difficulties compatible with retrograde ejaculation. A condom was used during all encounters. He reported a complete failure to emit semen but a normal desire, erection, and sense of orgasm. Postcoital urine was collected after days 9 and 14, and semen was evident on evaluation of the samples on both occasions. A reduction of Mr. A’s risperidone dose to 3 mg/day was associated with partial restoration of antegrade ejaculation.

Retrograde ejaculation is the consequence of surgical procedures or is associated with the use of various neuroleptic and nonneuroleptic drugs (3). These effectors are presumed to alter the sympathetic tonus of the bladder or urethral sphincter, allowing semen to pass retrogradely into the bladder during ejaculation. To date, all drugs reported to induce retrograde ejaculation share the capacity to significantly antagonize the α1-adrenergic receptor (3). We assume that risperidone, a potent α1-adrenergic receptor antagonist, induces retrograde ejaculation by means of a similar mechanism. The initial rapid escalation of the patient’s dose by 1 mg/day might have also contributed to the emergence of retrograde ejaculation, as described in other cases of neuroleptic-induced retrograde ejaculation (4). The incidence and clinical implications of risperidone-induced retrograde ejaculation and its effect on patient compliance merit further investigation.

References


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Neuroleptic Malignant Syndrome After Addition of Haloperidol to Atypical Antipsychotic

TO THE EDITOR: Patients receiving conventional antipsychotics are probably at greater risk for developing neuroleptic malignant syndrome than those taking atypical antipsychotics. It follows that patients may be at greater risk for neuroleptic malignant syndrome when conventional antipsychotics are added to an ongoing atypical antipsychotic regimen. We report such a case to call attention to the risks of restarting a conventional antipsychotic during crisis situations.

Ms. A was a 29-year-old black woman with a 10-year history of schizophrenia who was brought to the emergency room in the midst of an acute psychotic episode. Before 1997 she had received thiothixene, haloperidol, and fluphenazine decanoate. In 1997, she had started taking olanzapine, 10 mg/day, with good response for over 2 years. She relapsed in 1999, apparently from lowering her olanzapine dose from 10 to 5 mg/day. During this episode, as in previous ones, her acute symptoms were characterized by delusions and disorganization but no motor phenomena such as catatonia. In the emergency room, her olanzapine regimen was restarted at 10 mg/day, with lorazepam given as needed. When her acute symptoms did not improve within 24 hours, oral and intramuscular haloperidol was added to her regimen. Over the next 48 hours, Ms. A received a total of 23 mg of oral and intramuscular haloperidol.

The next day, there was an abrupt deterioration in Ms. A’s mental and physical status. She appeared disoriented and mute. The results of physical and laboratory tests included muscle rigidity, fever, incontinence, hypertension, leukocytosis, and an elevated creatine phosphokinas e level. She was diagnosed with neuroleptic malignant syndrome and transferred to an intensive care unit, where she had a stormy course of illness with multiple complications, including deep vein thrombosis, aspiration pneumonia, and sepsis. It took her over 3 months to recover. On follow-up, her schizophrenia was reasonably stable with 10 mg/day of olanzapine. She has not had any signs of extrapyramidal symptoms or recurrence of neuroleptic malignant syndrome.

Many practitioners believe that conventional antipsychotics are more effective than atypical antipsychotics for treating psychotic agitation. This belief was the major reason that haloperidol was added to the patient’s olanzapine regimen. It seems likely that exposure to haloperidol triggered her neu-
roleptic malignant syndrome, given that the neuroleptic malig-
nant syndrome developed immediately after haloperidol 
exposure. This case illustrates that the risks of neuroleptic 
malignant syndrome are likely higher when patients are pre-
scribed conventional antipsychotics, although this has not 
been definitively shown. The patient’s subsequent medical 
course is a sad reminder of the seriousness of neuroleptic 
malignant syndrome, which might have been avoided simply 
by continuing the atypical antipsychotic during her relapse. 
Clinicians should consider the risk of inducing neuroleptic 
malignant syndrome as they weigh the risks and benefits of 
adding conventional antipsychotics for agitated patients 
who historically have done well while taking atypical anti-
psychotics.

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Granulocytopenia With Clozapine 
and Quetiapine

To the Editor: We report the following case to call attention to 
latent hematological effects, presumably induced by cloza-
pine, when a patient’s treatment is switched from clozapine to 
another atypical neuroleptic.

Ms. A, a 53-year-old woman with a history of schizo-
phrenia that was refractory to treatment for more than 20 
years, had been treated with several typical antipsychot-
ics. Subsequent trials of both risperidone and olanzapine 
for at least 8 weeks, respectively, had little effect on her 
mental status. Trials of mood stabilizers targeted unpre-
dictable aggressiveness and were discontinued after dem-
onstrating no further improvement.

Ms. A had a baseline neutrophil level of 1,800/mm$^3$ 
before she began clozapine treatment. Clozapine was ti-
trated up to 400 mg/day and maintained at that dose for 
a year, which effected a partial treatment response. Ms. 
A’s neutrophil levels fluctuated between 1,800/mm$^3$ and 
2,200/mm$^3$ during this period. Her partial response to 
clozapine over 12 months and persistently low neutrophil 
count suggested a trial with another atypical neuroleptic, 
and quetiapine was initiated with the intention of gradu-
ally tapering the clozapine dose.

During Ms. A’s first week of taking quetiapine, 200 mg 
b.i.d., her neutrophil count dropped to 1,400/mm$^3$, and 
clozapine was discontinued. She continued taking quetia-
pine, 250 mg b.i.d., for 4 more weeks, during which time 
significant clinical deterioration occurred. Her neutrophil 
count remained less than 1,500/mm$^3$ for the entire period 
she took quetiapine and did not return to normal (>2,000/ 
mm$^3$) until 3 days after she discontinued quetiapine.

This case joins a number of previous reports suggesting 
clozapine-induced hematological iatrogenicity associated 
with an atypical neuroleptic, whether concurrent with ris-
peridone therapy (1) or days after normalization of the abso-
lute neutrophil count and the introduction of olanzapine (2). 
A recent report (3) described the development of neutropenia 
(with erythromycin therapy) 5 years after the initiation of 
clozapine treatment and supported the in vitro findings of cy-
totoxic effects of clozapine on hemopoietic progenitor cells 
(4). Current practice increasingly involves switching between 
atypical neuroleptics and overlapping them in the process.

The case presented suggests the need for close hematological 
monitoring whenever an atypical neuroleptic is used in tem-
poral proximity to clozapine treatment.

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Abuse of Topical Analgesic

To the Editor: After reading the letter that described a case of 
delirium after oral ingestion of a Mentholatum-based prod-
uct (1), we felt compelled to report a strikingly similar case 
seen recently at Massachusetts General Hospital.

Mr. A was a 53-year-old with a 30-year history of alcohol 
dependence complicated by gastritis, esophagitis, periph-
eral neuropathy, and pancreatitis. He was brought to the 
hospital by his brother, who had found him in bed, 
tachyplein. He was drowsy and had a respiratory rate of 
40 breaths/minute, a pulse of 130 bpm, and blood pres-
sure of 95/75 mm Hg. Several physicians noted a distinct 
odor of peppermint about him. The results of laboratory 
tests showed evidence of renal failure, metabolic acidosis, 
and an anion gap of 19. In addition to empty vodka bot-
tles, his brother had found an empty canister of a topical 
menthol-containing analgesic that Mr. A had been using 
intermittently to treat a “bad shoulder.” Given the strong 
menthol odor and the empty canister found near Mr. A’s bed, 
we hypothesized that Mr. A had ingested the substance 
orally, perhaps because it contained a small amount of al-
cohol. The results of an extended toxicologic screen were 
unremarkable, but it did not test for serum menthol.

Mr. A remained tachycardic, tachypneic, and hypoten-
sive, quickly requiring mechanical ventilation. His level of 
aroal gradually declined; 48 hours later he began fluct-
uating between severe lethargy and agitation. Concerned 
about acute alcohol withdrawal, his physicians adminis-
tered 8–32 mg/day of lorazepam, in addition to fentanyl 
by continuous intravenous infusion. The psychiatric ser-
vice was consulted on hospital day 8 for the management of 
ongoing agitation.

During the examination, Mr. A’s temperature was 
103.4°F, his pulse was 130 bpm, and his blood pressure 
was 85/50 mm Hg. He was then intubated. He opened his 
eyes when spoken to and blinked when threatened, but 
extraocular movements were absent. His pupils were mid-
sized and minimally reactive to light. He made no attempt 
to communicate in any way and showed no response to 
visitors. Spontaneous movements were absent; he failed to 
follow even simple one-step midline commands. His mus-
cle tone was globally lessened. There was a pronounced 
(++) pitting edema in his peripheral extremities.
The results of further laboratory tests revealed only an elevated WBC count, a high erythrocyte sedimentation rate (thought to be secondary to aspiration pneumonia), and a serum albumin level of 1.3 mg/dl. A cranial computed tomogram revealed old bilateral putaminal hypo-densities thought to represent incidental small subcortical infarcts. Mr. A’s lorazepam and fentanyl doses were gradually tapered, and haloperidol was given as needed for intermittent agitation. He was given intramuscular injections of thiamine and intravenous antibiotics for presumed pneumonia. He showed slow, gradual cognitive and motor improvement and eventually returned to baseline cognitive functioning. He could not recall the events leading to his admission and was unable to confirm that he had ingested the menthol-containing product. He continued to have some degree of weakness in the lower extremities and was discharged to a rehabilitation facility after a hospitalization of 30-plus days.

As with the patient described by Huntimer and Bean (1), our patient had a history of longstanding alcoholism, raising the strong possibility of Wernicke’s encephalopathy as a cause of his change in mental status and ophthalmoplegia. Although he also had other sequelae of alcohol abuse (e.g., pancreatitis and hepatic insufficiency), these conditions were not contributory to his recent difficulties. Moreover, several other major causes of his acute confusional state were excluded after extensive evaluation.

The history of alcoholism in both cases is intriguing. In this case, we hypothesized that the patient ingested the topical agent because it contained a small amount of alcohol. That he was admitted on a Sunday, a day on which Massachusetts liquor stores are closed and convenience stores are prohibited from selling alcohol, may be significant.

We were unable to find any previous reports of menthol-induced encephalopathy and, in fact, had begun to doubt its role in this patient until we read the recent letter in the Journal. Although some of the features of this complex neuropsychiatric case may be unrelated to the apparent ingestion of menthol, we echo the concerns of the previous letter’s authors regarding the ingestion of over-the-counter agents as a cause of delirium.

Reference

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Hippocampus and Amygdala Pathology in Depression

To the Editor: Recently, J. Douglas Bremner, M.D., and colleagues (1) reported smaller hippocampal volumes in patients with major depression than in nondepressed comparison subjects. However, an even more striking finding was mentioned without discussion of its interesting implications: patients with major depression displayed amygdala volumes that were 25% larger than those of healthy comparison subjects. This finding was only marginally significant, which probably was because of the difficulty of measuring the amygdala, which results in a high variability of data. However, to our knowledge, this is the fourth report of amygdala hypertrophy associated with different depressive syndromes (2–4).

References

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Hippocampus and Amygdala Pathology in Depression

To the Editor: Women with bipolar disorder are at especially high risk for relapse during the postpartum period, when the risk for recurrent postpartum mood episodes has been reported to be 25%–40% (1). Because of this high risk of relapse, postpartum prophylactic treatment has been advocated for most patients (2). Our preliminary data emphasize the recurrent nature of postpartum episodes in women with bipolar disorder.

Twenty-eight consecutively selected female patients with bipolar disorder were asked to respond to a structured interview regarding the impact of reproductive events on the course of their illness. After written informed consent was ob-tained, diagnosis was determined by using the Structured Clinical Interview for DSM-IV. Patients were then systematically asked about mood symptoms and episodes after childbirth.

In our study group, 17 (61%) of the women had at least one child, and 12 (71%) of the 17 described at least one postpartum mood episode. The polarity of the group’s postpartum episodes was exclusively depressive. Notably, the risk of having a postpartum depressive episode increased with successive pregnancies. Of the women who had more than one child and experienced at least one depressive postpartum episode but did not experience depressive episodes after every delivery (N=6), there was a significant relationship between number of births and depressive episodes. Women were more likely to have postpartum depressive episodes after the birth of a second child than after their first (p=0.02, McNemar’s test). In fact, if a woman experienced postpartum depression after some but not all of her pregnancies, it was only after the first pregnancy that she was spared. In the 12 women with more than one child, of those women who experienced a postpartum episode after their first child, the postpartum recurrence rate was 100%.

Although having experienced a postpartum mood episode was predictive of future postpartum episodes, not having experienced a mood episode after the birth of a first child was not protective. Of the nine women who did not experience a depressive episode after the birth of their first child and who later had more children, six (67%) experienced subsequent postpartum depression. Our preliminary findings suggest a significant relationship between risk of development of a postpartum depressive episode and number of pregnancies in women with bipolar disorder. This higher risk may be attributed to hormonal or biochemical factors, older age or longer duration of illness, or greater psychosocial stressors after later pregnancies.

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With this observation being made by four different research groups in four different patient populations, the question arises as to what this finding of depression-related amygdala hypertrophy means. It might be a risk factor for depressive syndromes in general, or it might reflect only a state of chronically greater emotional information processing. The fact that it has been observed in patients with temporal lobe epilepsy and dysthymia supports the latter assumption. Dr. Bremner et al. could have helped answer this question by analyzing a possible relationship between amygdala volumes and the duration and severity of depressive symptoms.

Furthermore, the question arises as to how cerebral substructures might increase in volume. One might speculate that a specific dysfunctional mode of information processing results in greater focal perfusion and larger cellular size. Alternatively, dysfunctional emotional information processing might result in cell division in cerebral substructures. Recently, there have been reports in the literature demonstrating this mechanism (5).

Dr. Bremner and colleagues pointed out the possible association between hippocampal atrophy and higher glucocorticoid levels in major depression (1). The amygdala does have a direct efferent connection with the supraoptical and paraventricular nuclei. Both are the most important nuclei of corticotropin-releasing hormone secretion in the brain. One might speculate that the amygdala is involved in the control of the neuroendocrinological stress system. By analyzing a relationship between amygdala enlargement and hippocampal volume loss, Dr. Bremner et al. could possibly find some evidence for a distinctive role of these two limbic structures in the regulation of the neuroendocrinological stress system in affective disorder.

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Dr. Bremner and Colleagues Reply

TO THE EDITOR: We agree with the comments of Dr. Tebartz van Elst et al. that the finding of larger volume of the amygdala in patients with depression is worthy of comment. Our finding of a 25% larger mean amygdala volume (23% on the left and 27% on the right) in patients with treated unipolar depression seemed difficult to explain at first and was not hypothesized a priori; however, as Dr. Tebartz van Elst et al. point out, there are now four reports of enlarged amygdala volumes in patients with various affective disorders, including bipolar disorder, temporal lobe epilepsy with comorbid dysthymia, and unipolar major depression in remission (our report). Dr. Tebartz van Elst et al. mention several potential explanations for a greater amygdala volume in depression, including the possibility that this is a risk factor for depression, which certainly should be explored through genetic studies. They also indicate that a greater amygdala volume could represent a neuroanatomical correlate of depression.

Dr. Tebartz van Elst et al. suggest that greater blood flow or greater neuronal number may explain larger amygdala volume. Although a greater blood flow in depression has been reported in at least one study, there are a larger number of studies that have not shown this. In any case, it is not clear how a larger blood flow would translate into greater volume. Although the potential for neurogenesis has been reported for the hippocampus, we are not aware of any studies related to the capacity for neurogenesis in the amygdala. The role of the amygdala in emotional processing suggests the possibility that greater demands on the amygdala in patients with depression result in structural changes, possibly related to plastic changes in dendritic branching or neuronal morphology in the amygdala. Dr. Tebartz van Elst et al. mention possible functional correlates of greater amygdala volume, including regulation of corticotropin-releasing hormone (CRH) release by the amygdala.

The amygdala primarily regulates extrahypothalamic release of CRH, which may explain the findings of elevations of CRH in CSF in depression, although that would not explain hypercortisolemia per se. We found no pattern of relationship between amygdala volume and plasma cortisol level, although there was a modest but nonsignificant relationship between a higher cortisol level and a smaller left hippocampal volume (r=–0.31, df=9, p=0.38). However, our patients had treated depression, and hypercortisolemia has been reported only with current episodes of depression. Future studies should look at cortisol-amygdala relationships in untreated depression. The amygdala and hippocampus also have important interconnections, as suggested by Dr. Tebartz van Elst et al., and we found a modest but nonsignificant relationship between a greater right amygdala volume and a smaller right hippocampal volume in patients (r=–0.35, df=15, p=0.19) but no pattern of relationship in comparison subjects. Future studies are indicated to replicate and extend the finding of greater amygdala volume in depression and the relationship between amygdala volume and number of depressive episodes.

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Effectiveness of Involuntary Outpatient Commitment

TO THE EDITOR: Although the randomized controlled trial of involuntary outpatient commitment reported by Marvin S.
LETTERS TO THE EDITOR

Swartz, M.D., et al. (1) is extremely important, we were surprised that it was published in its present form. Some fundamental principles of reporting randomized controlled trials have been violated.

The primary outcome measure was rehospitalization. The result of the study was negative (as was the result of the other randomized controlled trial of these patients, in New York [2]): there was no difference between the patients in involuntary outpatient commitment and the control subjects. This key result was the only one based on an intention-to-treat analysis, and it was the only unbiased finding of the article. Despite this, it merited only three sentences in the Results section (with no presentation of data) and none in the Discussion section. Instead, the authors spent two pages reporting a complex post hoc analysis based on the duration of involuntary outpatient commitment experienced by the patients. The conclusion from this analysis was that a sustained period of involuntary outpatient commitment was effective when combined with intensive treatment. However, Figure 1 seemed to show differences in hospitalization between groups of patients in short-term and long-term involuntary outpatient commitment long before the first 6 months had elapsed. This suggests that the effect had nothing to do with the treatment received but instead reflected a bias in which involuntary outpatient commitment was selectively extended when it seemed to be helping a patient. The presentation loses all the advantages that randomization offers in abolishing selection bias and confounding (3).

The authors made much of a subgroup analysis based on diagnostic categories. This was reported without presentation of the interaction between treatment condition and diagnosis and should be seen as a spurious post hoc analysis. Also unacceptable was the absence of a CONSORT diagram (4) showing how many patients were excluded from the initial cohort of those awaiting a period of court-ordered outpatient commitment and why.

Finally, we make a suggestion concerning a clinically helpful statistic for reporting results of a randomized controlled trial, especially where the treatment is long-term, possibly has serious negative effects, and is ethically contentious. This is the “number needed to treat” (5), the number of patients who need to be given the experimental treatment to achieve one extra good outcome compared to their having received the control treatment. For example, if the results reported were an unbiased comparison, and the proportion of patients in prolonged involuntary outpatient commitment with readmission in the study year was 32% compared with 48% of those not in involuntary outpatient commitment, the number needed to treat would be about six. That is, six patients would require long-term involuntary outpatient commitment to prevent one from being admitted at least once during the year. Since the researchers found no difference between the two treatment conditions, the number needed to treat was presumably far more—or possibly a negative value, indicating potential harm associated with the intervention.

The results of this trial, conducted by an eminent group of investigators, are likely to be widely quoted and have important clinical, legal, and political implications on both sides of the Atlantic. It is disappointing that recent advances in randomized trial methodology (3, 4) have been overlooked by both the authors and your editorial board.

References


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TO THE EDITOR: Having observed patient progress during conditional release (a form of involuntary outpatient commitment) and found the policy useful in protecting some individuals with serious mental illness, I anticipated positive results from the randomized clinical trial by Dr. Swartz et al. The investigators randomly assigned patients released from a mental hospital to one of two conditions: involuntary outpatient commitment (analogous to parole) or unconditional release. All patients were followed for 12 months. The finding of no difference between the involuntary outpatient commitment and control groups in the number and duration of rehospitalizations at follow-up was instructive regarding the limitations of clinical judgment.

It was, therefore, with some chagrin that I read the authors’ attempts to move beyond comparisons of their randomized groups. They dismissed their findings of no group differences and extended their data analysis to demonstrate results supporting involuntary outpatient commitment. They split the involuntary outpatient commitment group into two subgroups: one with 180 or fewer days of involuntary outpatient commitment and the other with more than 180 days of involuntary outpatient commitment. Since a person in involuntary commitment is, by definition, out of the hospital, analyzing the data by comparing the experience of the group with more than 180 days of involuntary outpatient commitment to the experience of the control group creates a statistical artifact for a result. By definition, the group with more than 180 days of involuntary outpatient commitment could have been hospitalized only during a total of 185 days in the follow-up year. The control group had a full year in which to be hospitalized. The authors arrived at unwarranted conclusions on the basis of this artifact.

The post hoc selection of the group with more than 180 days of outpatient commitment might have been acceptable had the authors compared this group to the control group that had spent more than 180 days in the community with mental health services but without involuntary outpatient commitment. Had the authors compared the two, they would have compared groups with equal risks of hospitalization during the follow-up period. Instead, they compared the involuntary outpatient commitment group with 185 days of risk...
for hospitalization to the control group with 365 days of hospitalization risk. They found that the involuntary outpatient commitment group with 185 days of risk had approximately one-half the hospitalization experience of the control subjects with a 365-day risk. They compounded their error by attributing this group difference to the intervention of involuntary outpatient commitment.

Another way of understanding the problem with their analysis is to imagine that the authors compared control group members with more than 180 days in the community without involuntary outpatient commitment with the total experimental group’s 1-year follow-up experience. The authors might then have concluded that long-term community residence without involuntary outpatient commitment leads to less frequency and a shorter duration of rehospitalization than living with involuntary outpatient commitment. Perhaps because of having half the risk, this “extended community residence” subset of the control group would have been found to have half the hospitalization of the total involuntary outpatient commitment group.

Involuntary outpatient civil commitment is one of the most controversial issues in psychiatry today. The authors owe the Journal readership appropriate comparisons with the subgroups of the control group. Should direct comparisons between the two groups with more than 180 days of treatment sustain their findings, they will have vastly enhanced the credibility of their conclusions.

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Dr. Swartz and Colleagues Reply

To the Editor: Drs. Szmukler and Hotopf’s comments on our trial of involuntary outpatient commitment raise some important issues that we attempted to address with appropriate caveats within Journal space constraints. As they point out, the results of certain statistical tests contrasting rehospitalization outcomes for patients assigned to outpatient commitment and control subjects over the entire study period were not significant—but that is hardly the whole story. The distribution of hospital outcomes precluded analysis with conventional t tests. Hence, we examined the odds of any hospital readmission using repeated measures analyses and demonstrated that for any 30-day period, the outpatient commitment group had a significantly lower risk of readmission than the control group (odds ratio = 0.64, 95% confidence interval = 0.46–0.88, p < 0.01; p. 1972). This analysis used a rigorous test, incorporated all the data for the intention-to-treat group, and considered only the initial randomized group membership—ignoring the duration of the outpatient commitment order. In short, our evidence for a significantly lower risk of readmission in the outpatient commitment group overall did not depend on postrandomization analyses.

As we showed, the lower risk of readmission was much stronger among subjects receiving longer outpatient commitment orders. In our view, failure to report the significant association between the duration of outpatient commitment and the reduced risk of readmission would have neglected an important clinical and policy-relevant finding: that sustained periods of outpatient commitment are more effective. Furthermore, we argue not that more than 180 days of outpatient commitment is a meaningful threshold per se but, rather, that more days of outpatient commitment combined with more intensive treatment improve hospital outcomes. Differences between the subjects in long-term and short-term outpatient commitment began to show up early—long before 6 months—because outpatient commitment orders can expire (or be renewed) within days or weeks after discharge.

We recognize the potential for selection bias in that subjects at highest risk for relapse might be selected differentially for extended outpatient commitment. Indeed, unpublished data have suggested that subjects at higher baseline risk for hospitalization were more likely to receive prolonged outpatient commitment. Therefore, if our results are biased, they are quite probably biased against finding an effect for extended outpatient commitment.

Drs. Szmukler and Hotopf did not see that we did test the interaction between treatment condition and diagnosis in staged, multivariable, repeated measures analyses. The addition of this interaction term resulted in significant improvement in model fit (–2 log likelihood increment in fit = 4.83, p < 0.05; p. 1972). Finally, they suggest that we should have reported the “number needed to treat,” which we believe could be misleading because it does not account for other nonhospital outcomes associated with outpatient commitment.

The premise of Dr. Segal’s critique of our analysis is that time at risk for hospitalization is an inverse function of the duration of outpatient commitment. According to this premise, subjects who received 6 months of outpatient commitment were only at risk for hospitalization during the remaining 6 months of the study year, i.e., when they were not in outpatient commitment. In fact, our research subjects remained at risk for hospitalization each day of their outpatient commitment. Unlike in Dr. Segal’s parole analogy, the outpatient commitment days did not have to be consecutive; the total period in outpatient commitment could have been interrupted by hospitalizations, and hospital readmission did not have to curtail the total period of outpatient commitment. Indeed, early hospital readmission was, for some patients, an occasion for receiving a renewal of outpatient commitment for an extended period, thereby placing them on the path to eventually spending more than 180 days in outpatient commitment

Perhaps it would have been clearer to present our finding as a comparison of subjects who received a renewal of their initial outpatient commitment order and subjects who did not. The resulting analysis would have been the same, because the clinical decision to renew the initial outpatient commitment order almost always occurred before 6 months. Therefore, the subjects who did not receive a renewed outpatient commitment order spent 180 or fewer days in outpatient commitment, whereas the subjects who did get a renewed order spent more than 180 days. The decision for renewal might have been biased for other reasons, but it did not affect time at risk for hospitalization.

Hypothetically, if a patient were to have spent a large number of days in the hospital during the year—adding up to more than 6 months—this would have precluded the same patient from spending more than 6 months in outpatient commitment, which would have introduced a selection bias in receiving brief versus extended outpatient commitment. Empirically, however, the hospital stays of short dura-
tion, with control subjects spending a mean of 27.9 days hospitalized during the year. Dr. Segal’s suggested reanalysis would not change our findings.

Outpatient commitment is a highly controversial policy, and, clearly, the data from any study on this topic will be interpreted in a highly politicized atmosphere. We believe that a careful and dispassionate reading of our published findings will help inform this important policy debate.

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Trauma and Depersonalization During Panic Attacks

To the Editor: Randall D. Marshall, M.D., and colleagues (1) failed to find support for their hypothesized association between the symptoms of depersonalization during panic attacks and a history of childhood trauma. They cautioned that the generalizability of their null findings was limited by the use of a convenience group of patients participating in a pharmacological trial for panic disorder and by the exclusion of patients with comorbid disorders. To address these limitations, we reexamined the relationship between childhood trauma and the presence of depersonalization symptoms during panic attacks using the National Comorbidity Survey (2) public use database. The National Comorbidity Survey is a nationally representative sample of U.S. adults that contains information on the prevalence and correlates of psychiatric disorders.

Adults who met DSM-III-R criteria for panic disorder (N=186) were selected for participation. An appropriate statistical weight from the National Comorbidity Survey, part 2, public use database was used to make the data representative of the general population. Respondents were queried about symptoms typically experienced during their most severe panic attacks. Responses to the depersonalization-related question (“Did you or things around you seem real?”) were used to assign participants to either a depersonalization group (N=109) or a nondepersonalization group (N=77).

Relative to the nondepersonalization group, the depersonalization group more frequently reported a history of serious neglect as a child (N=15, 13.8%, versus N=3, 3.9%, respectively), having been raped before age 16 (N=12, 11.0%, versus N=1, 1.3%), experiencing physical abuse as a child (N=18, 16.5%, versus N=7, 9.1%), and a history of molestation before age 16 (N=17, 15.6%, versus N=9, 11.7%). The differences regarding childhood neglect and rape were statistically significant ($\chi^2=5.0$, df=1, $p<0.03$, and $\chi^2=6.5$, df=1, $p<0.02$, respectively).

It is possible that the relatively high endorsement of depersonalization by those with a history of either neglect or rape may reflect greater severity of panic attacks rather than a more specific tendency to experience depersonalization during panic attacks. However, this alternative explanation was not supported by a series of additional chi-square analyses. Specifically, the other panic attack symptoms were not more frequently endorsed by those with a history of childhood neglect than by those without such a history and were not more frequently endorsed by those with a history of rape than by those without such history.

In contrast to the findings of Dr. Marshall and colleagues (1), the present results suggest there is a link between traumatic childhood events and depersonalization during panic attacks. A large representative sample arguably would provide a more complete picture of the proposed relationship between depersonalization and trauma. We suggest that further research in this area is warranted.

References

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Dr. Marshall and Colleagues Reply

To the Editor: Dr. McWilliams and colleagues investigated our hypothesis that patients with dissociative symptoms during panic attacks would have higher rates of childhood trauma than those without such symptoms and found significant findings where we found none. It remains then to attempt to explain these differences as well as to place them in perspective.

First, our study groups were notably different: ours was clinical; theirs, epidemiological. As we discussed, studies with clinical study groups are limited by factors associated with selection bias (e.g., subjects are seeking treatment and are willing to participate in clinical research), and these subjects typically have higher levels of distress and comorbidity than do community samples. Conversely, epidemiologic studies are usually limited by the use of data based on nonclinician assessments and may tend to inflate rates of clinically significant psychiatric disorders since distress or impairment is typically much lower than in clinical settings.

Second, our study group was relatively free of comorbidity, whereas the comorbidity of the sample of Dr. McWilliams et al. was not examined. This is important because comorbidity is a major confound in the study of dissociation. The exclusion of significant comorbidity in our clinical study group therefore represented a strength of the study, rather than a limitation. Early studies showing more depersonalization during panic attacks were conducted in clinical study groups with high rates of comorbid disorders that are also associated with childhood trauma and dissociative symptom profiles. It is possible that depersonalization/derealization during panic attacks is mediated by the presence of comorbid disorders, since dissociative symptoms are also associated with general psychopathology (1).

Third, there may be differences in the severity of panic attacks between the two study groups. Dr. McWilliams and colleagues attempted to operationalize the severity of panic at-
tacks by examining the frequencies of panic symptoms other than depersonalization/derealization. Other potentially important markers of severity not examined by Dr. McWilliams et al. are the presence or absence of agoraphobia (found in 87% of our study group), the severity of depersonalization/derealization (we required severity that was moderate or greater), and the frequency of panic attacks (our study required at least one attack per week). It is surprising that the report by Dr. McWilliams et al. includes a higher proportion of patients with derealization (59%) than ours (46%), given the fact that ours was a clinical group. This suggests differences in both assessment and group selection between the two studies.

In any case, the main findings of Dr. McWilliams et al. of significantly higher rates of serious neglect and rape before age 16 in patients with panic attacks with derealization/depersonalization are important and consistent with those of an earlier report (2). The National Comorbidity Survey data set should be reexamined to investigate the role of the factors we noted in explaining the findings.

It is also noteworthy, however, that the rates of serious childhood trauma in the National Comorbidity Survey panic disorder sample are still relatively low and the group differences in these rates, although statistically significant, are small. In both studies, the majority of panic patients with depersonalization/derealization did not report serious childhood trauma.

Both our study and the present report are limited by the absence of a trait measure of dissociation. More important, both studies are post hoc examinations of this question in a data set collected for other purposes. Future studies should develop a more inclusive multifactorial model of vulnerability to dissociation, since both studies indicate that childhood trauma does not account for the presence of depersonalization/derealization during panic attacks in most cases.

References

Personality Disorders in the Literature
To the Editor: Roger K. Blashfield, Ph.D., and Vincent Intoccia, B.A. (1), reviewed data from MEDLINE searches from 1966 to 1995 and concluded that, unlike published works on schizophrenia, Alzheimer’s disease, and posttraumatic stress disorder (PTSD), the literature on personality disorders has had only modest expansion. They further concluded that the growth rate actually dropped with the publication of DSM-III. Although the authors were somewhat vague regarding the specific methods by which the MEDLINE data were compiled, they may not be aware that the journal pool from which MEDLINE incorporates articles is continually changing. As a former chairman of the National Library of Medicine’s Literature Selection Technical Review Committee (which reviews and makes recommendation to the National Library of Medicine regarding which journals should be included in Index Medicus), I participated in the review of literally hundreds of journals and could see how the choice of which journals are included can shape a field. It is entirely possible that the journals that typically include personality disorders were systematically dropped from Index Medicus and those with a focus in other areas (e.g., schizophrenia, PTSD) were added. As such, the change in bibliographic entries could be a function more of a change in the journals that contributed to the denominator of articles in the database than a change in the actual number of published articles regarding personality disorders. Thus, the authors would need to track changes in the journals included in MEDLINE from 1960 to 1995 to assess the validity of their conclusions. They may also want to assess whether these findings generalize to bibliographic databases that are more inclusive of the behavioral science literature (e.g., PsychLIT).

Of course, if researchers and clinicians do not have access to journals containing articles regarding personality disorders, then the impact of research in this area may be like a tree falling in a forest with no one there to hear it.

Reference

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Ondansetron for Tardive Dyskinesia
To the Editor: We read with great interest the article by Pinkhas Sirota, M.D., and colleagues (1) on the use of ondansetron in the treatment of neuroleptic-induced tardive dyskinesia. The findings are especially remarkable in light of reports on the efficacy of clozapine and olanzapine in treating tardive dyskinesia (2, 3); these drugs having some affinity for the serotonin 5-HT3 receptor.

In the Method section of their article, the authors stated that their patients had received a stable psychotropic drug regimen for at least 6 months before study entry. It would, however, be interesting to know what type of antipsychotics the patients had been receiving, especially if clozapine or olanzapine could have biased the results. It would also be interesting to know if concomitant medications could have induced an increase in plasma concentrations of the given antipsychotics. Increasing a dose of antipsychotics may, although transiently, alleviate tardive dyskinesia.

A literature search by the authors did not reveal any effects of ondansetron on the metabolism of other medications. In vitro studies have, however, shown that ondansetron is a competitive inhibitor of the CYP2D6-dependent O-demethylation of dextromethorphan, with a Kᵢ value of 29 μM, and a competitive inhibitor of the CYP3A4-dependent metabolism of cyclosporine A, with a Kᵢ of 31 μM (4). Pharmacokinetic interactions between ondansetron and antipsychotic drugs,
LETTERS TO THE EDITOR

The authors stated that 85% of the 104 patients were randomly assigned to either nortriptyline or fluoxetine. Recalling that 48 of the total were nondepressed and demonstrated no significant differences, we are really looking at the remaining 56 patients. Of the depressed fluoxetine group of 23, only 14 (61%) were randomly assigned. Likewise, of the 16 in the depressed nortriptyline group, only eight (50%) were actually randomized. It is hard to feel assured of the superiority of nortriptyline to fluoxetine when comparing only 14 randomized patients to eight. In addition, only one patient's data on nortriptyline treatment after placebo were analyzed.

It is not surprising that pushing elderly patients up to a mandatory dose of 40 mg/day of fluoxetine would lead to akathisia, gastrointestinal symptoms, and dropout. After pollling our colleagues, we found it exceedingly rare that any of our patients over 65 years of age were taking 40 mg/day of fluoxetine, and, anecdotally, no one could think of a reference equating that dose to 100 mg/day of nortriptyline.

Although the authors may have used a Hamilton Depression Rating Scale score of 12 or higher as the criterion for depression, most studies have used 17 or greater as an inclusion criterion (2). Using a smaller interval set at the lower level may capture different patients. Compounding that variable is the broad range of weeks poststroke in the fluoxetine group (mean=16, SD=35) in contrast to that of the nortriptyline group (mean=5, SD=4). The highest incidence of depression, to our knowledge, was reported at 2–7 weeks poststroke (3). One wonders how this might influence such small, randomly assigned groups.

Of concern is the 12-week cutoff point. Elderly patients are known to respond to antidepressants much later than other patients, and that is particularly so for selective serotonin reuptake inhibitors (SSRIs). In addition, there are now data indicating that patients taking SSRIs gain weight after 12 weeks, so this would not have been noted (4). Granted, patients taking tricyclics may keep gaining weight longer. This is not always the case.

There are other studies that have shown SSRIs to be efficacious in treating poststroke depression (3–5). Methodological flaws in this study make it difficult to draw firm conclusions that can be applied to patient treatment until larger populations are studied.

References

Dr. Sirota and Colleagues Reply

To the Editor: We appreciate the comments of Dr. Zullino et al. in regard to the possible interaction of ondansetron with clozapine or olanzapine. We have reviewed the files of all patients who participated in our study, and none was taking atypical antipsychotics. Furthermore, the patients were maintained with stable antipsychotic treatment throughout the study and were not given additional medication on a regular basis. On the basis of the previous information, we believe that the possibility that tardive dyskinesia improved because of a pharmacological intervention other than ondansetron can be discarded.

We cannot exclude the last possibility raised by Dr. Zullino et al., however, regarding a possible interaction of ondansetron and classical neuroleptics at the level of the liver, thus slowing down their disposition and resulting in an elevated antipsychotic plasma level. However, to our knowledge, this hypothesis is not supported by published data on humans. Furthermore, if such an interaction had been of clinical significance, we would have expected worsening of other neuroleptic-induced side effects, such as parkinsonism or somnolence, and those were not observed. Thus, on the basis of current knowledge and the clinical response to ondansetron, we favor a direct effect of ondansetron in alleviating tardive dyskinesia.

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Poststroke Depression

To the Editor: We compliment the efforts of Robert G. Robinson, M.D., and colleagues (1) on the study of the treatment of poststroke depression. However, there are several limitations that caution against complete acceptance of their results.
Dr. Robinson Replies

TO THE EDITOR: Drs. Franco and Malhotra appropriately point out that additional treatment trials are needed before firm conclusions about the most effective treatments for poststroke depression can be drawn. Given the medical vulnerabilities of this population, studies such as ours must always confront a number of challenges in achieving optimal randomization and truly blind placebo control. Some of the criticisms from Drs. Franco and Malhotra may be due to a lack of understanding of the medical constraints that apply to the whole population, not just the depressed subgroup. For example, they state that only 61% of the depressed fluoxetine group and 50% of the depressed nortriptyline group were randomized. Actually, the patients who were not randomized because of contraindications for either nortriptyline or fluoxetine were not all depressed patients but, rather, were divided between depressed and nondepressed groups. In fact, 87% of the depressed fluoxetine patients and 81% of the depressed nortriptyline patients were randomly assigned. In addition, although some patients were not randomly assigned to fluoxetine or nortriptyline, they were all randomly assigned to active or placebo treatment by using double-blind methodology. With the exception of sex distribution, there were no significant differences between the fluoxetine, nortriptyline, and placebo groups.

Drs. Franco and Malhotra next question our use of fluoxetine at a dose of 40 mg/day. It is possible that some of the side effects experienced with fluoxetine could have been dose related; however, this does not necessarily detract from its comparison to nortriptyline in terms of antidepressant efficacy. The authors may wish to note that we analyzed our data by looking at the comparison between 20 mg/day of fluoxetine and 75 mg/day of nortriptyline at 6 weeks and continued to find a significantly greater improvement in the nortriptyline than in the fluoxetine group. In addition, if we had used only the 20-mg/day dose of fluoxetine and had not tried to increase the dose to see if some further improvement would have occurred, we may have been criticized for not trying a higher dose of fluoxetine.

Furthermore, there is increasing evidence that even subsyndromal depressive symptoms may have important clinical and functional implications (1), which are likely to be particularly evident in elderly patients. It is erroneous to assume that reference ranges for rating scales developed in nonelderly populations necessarily apply to geriatric and special populations such as elderly patients in the poststroke condition. Therefore, we relied on clinical diagnosis first, which we then quantified through use of the Hamilton depression scale.

The next criticism was that we used patients with Hamilton depression scale scores of 12 or greater as the criterion for depression. In fact, the criterion for entering the study was meeting DSM-IV diagnostic criteria for either major or minor depressive disorder. A Hamilton depression scale score of at least 12 was used only to ensure at least a mild to moderate level of severity. Since fluoxetine has been demonstrated to be effective in treating milder forms of depression (2), and minor depressive disorder has been shown in our previous treatment trial to respond to treatment with nortriptyline (unpublished data), it was appropriate to include patients with both major and minor depressive disorders in the study group. Drs. Franco and Malhotra comment that the range of weeks poststroke for the fluoxetine group was greater than for the nortriptyline group. Perhaps they failed to note that we actually reanalyzed the data, including only patients who were treated during the first 12 weeks of the study. In that analysis, there was no difference in the time since stroke—i.e., a mean of 5 weeks poststroke for both the fluoxetine and the nortriptyline groups. We still showed that the effect of nortriptyline was greater than the effect of fluoxetine on Hamilton depression scale scores over 12 weeks. Only five of the 23 fluoxetine-treated patients were treated during the second 12-week period. The majority (18 patients) had been treated during the first 12-week period.

Drs. Franco and Malhotra next point out that patients taking SSRIs may gain weight after 12 weeks. Although this may be true, it was beyond the scope of the study presented here and may be an interesting project for Drs. Franco and Malhotra themselves to pursue. In our estimation, 12 weeks is now becoming the standard period for treatment trials, and 12 weeks is an adequate period of time for response to SSRIs. As our outcome of interest was depression response, it would have been outside our hypothesis testing to extend the study for the purposes of measuring weight. We were concerned that weight loss was presumably related to the anorexic effect of the medication (not a symptom of depression) and that the feeling of nausea associated with fluoxetine treatment led to the weight loss. This also happened, by the way, among patients who were nondepressed, demonstrating that this was not simply an interaction among a relatively small group of patients who were depressed but a side effect of fluoxetine treatment in elderly patients after a stroke.

Finally, Drs. Franco and Malhotra point out that SSRIs have been found to be efficacious in the treatment of poststroke depression. We are familiar with the studies they are referring to, one of which did not actually study poststroke depression. That is, the Dam et al. study examined recovery from physical impairment and did not require patients to be depressed to be included in the study nor was any depressive diagnosis made. The Andersen et al. study, however, was a double-blind randomized treatment study showing a significantly greater improvement among patients treated with citalopram than placebo. It may be worthwhile to note that in the Andersen et al. study, there was a 41% decline in Hamilton depression scale score during the 6 weeks of treatment, whereas our original double-blind study of nortriptyline over 6 weeks showed a 77% decline in Hamilton depression scale score; we found a 60% decline in our current study.

As we readily acknowledged in our article, there were methodological limitations in our comparison of fluoxetine with nortriptyline in poststroke depression, and we tried our best to reanalyze the data by looking at each of those potentially confounding methodological limitations. It is certainly possible, as we acknowledged in the article, that lower doses of fluoxetine (i.e., 10 mg/day) may be effective in the treatment of...
poststroke depression, and we certainly encourage other studies to be undertaken. Given the public health importance of research in this area, we feel it is critical to find ways to effectively treat individuals suffering from poststroke syndromes. Building on the findings of others in a mutually supportive way will help us achieve this end, as opposed to giving in to the distraction of searching for the perfect efficacy study.

References

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Verbal Working Memory Impairment in Schizophrenia

TO THE EDITOR: In a recent article, Heather M. Conklin, B.S., and colleagues (1) reported that schizophrenia patients as well as their first-degree, nonafflicted relatives showed impairment on the backward digit recall portion of the Wechsler Digit Span task, but relatives did as well as nonpsychiatric comparison subjects on digits forward. The authors concluded that these results support a diathesis in schizophrenia for verbal working memory deficits. In pointing out that verbal working memory impairments may be an endophenotypic marker, like impaired smooth-pursuit eye movements, they unintentionally implied that this may be a fixed and untreatable feature of this disorder. However, our work and that of a few other investigators have suggested that it is possible to remediate these impairments.

More than 25 years ago, investigators began reporting that some cognitive impairments in schizophrenia could improve with training. The possibility of restoring lost elemental function through neurocognitive retraining has gained support from studies of brain plasticity in animals and recently from direct applications of training methods with patients (2, 3).

In a current U.S. Department of Veterans Affairs study, we used the Wechsler Digit Span task in the pre- and postneurocognitive assessment of a 6-month cognitive remediation and work rehabilitation program. Thirty-one subjects with schizophrenia or schizoaffective disorder were randomly assigned to neurocognitive training while participating in a work therapy program, and 34 received work therapy alone. Memory training was performed by using computer-based exercises designed for patients with traumatic brain injury but were modified to our specifications. Subjects began reading short lists of words or digits presented on-screen, followed by cues to retrieve the information. In a hierarchically arranged progression, tasks were made more difficult by shortening the exposure time, increasing the latency period, and increasing the number of items. Subjects had no direct training on digits backward, a task that requires manipulating remembered numbers so that they can be repeated in reverse order.

Results indicated improvement in the Wechsler Digit Span scaled score for the training group (paired t-test=2.96, df=30, p<0.01), and an analysis of covariance revealed significantly greater improvement than in the control group (F=3.63, df=2, 61, p<0.05). Moreover, the most dramatic results occurred in the digits backward task. More than 60% of the subjects receiving training showed significant effect size improvements (0.2 standard deviations or greater) compared with 25% of those in the work-only condition (χ²=6.81, df=1, p<0.01), and 40% had large effect size improvements (0.8 standard deviations or greater) compared with 18% for those who received work therapy only. Thus, the neurocognitive training of memory had improved verbal working memory, generalizing from our training procedures to the unpracticed task of digits backward.

We are encouraged by these findings and expect refinements in remediation methods in the future. Although we have no disagreement with Ms. Conklin et al. regarding a diathesis for verbal working memory impairment in schizophrenia, we do not want to equate genetic vulnerability with irreversibility. Our findings suggest that remediation of verbal working memory deficits is possible in schizophrenia.

References

Ms. Conklin and Colleagues Reply

TO THE EDITOR: We appreciate the letter by Dr. Bell and colleagues regarding our recent report of verbal working memory impairment in schizophrenia patients and their first-degree relatives. It is noteworthy that cognitive deficits in schizophrenia may be open to rehabilitation. When we reported that verbal working memory impairment may be an endophenotypic marker for the genetic diathesis for schizophrenia, we did not intend to imply that this deficit is “fixed and untreatable.”

Endophenotypes are stable, heritable, endogenous characteristics that identifies genetic risk for a given disorder (1). Although stability is a key component of this definition, it does not signify that such characteristics cannot be changed through targeted intervention. Just as individuals with stable patterns of behavior or attributional styles may benefit from psychotherapy, individuals with otherwise stable cognitive abilities may benefit from “neurocognitive retraining.”

We agree with Dr. Bell et al. that genetic vulnerability should not be equated with irreversibility. We are all familiar with phenylketonuria, a disorder transmitted by a recessive gene, in which the genetic vulnerability for mental retarda-
tion can be prevented through environmental intervention (i.e., diet).

We were pleased to see that Dr. Bell et al. used different batteries for training and testing working memory in their participants, as their findings suggest that improvement in performance is not task specific. It would be interesting to see if the improvement in working memory generalized to less similar tasks, such as spatial working memory and self-ordered tasks, on which schizophrenia patients have also demonstrated impairment (2). Just as one might not expect training on tasks such as the Tower of London to carry over to all executive function tasks, working memory improvements may also be limited in scope.

In our report, we noted that cognitive deficits in schizophrenia are open to some criticism because factors associated with chronic mental illness (e.g., active psychotic symptoms or medication effects) could potentially color performance and limit conclusions. It may be that the significant (25%) improvement in the control condition of Dr. Bell et al. supports this assertion. For this reason, it would be useful to look at similar training in unaffected relatives of schizophrenia patients for whom the aforementioned criticisms do not apply. Differential rates of improvement in relatives and normal control subjects might be suggestive of ongoing working memory deficits.

In summary, the findings of Dr. Bell and colleagues are not at odds with ours nor do they detract from their significance. Although it is useful to consider the potential for rehabilitation of cognitive deficits in schizophrenia, with reference to endophenotypes, it would be more useful to consider rehabilitation of working memory deficits in their unaffected but at-risk relatives and, ultimately, to determine if such intervention reduced the likelihood of their developing schizophrenia.

References

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Reprints are not available; however, Letters to the Editor can be downloaded at http://ajp.psychiatryonline.org.