## Olanzapine-Induced Somnambulism

TO THE EDITOR: Somnambulism has been reported with the use of classical antipsychotics (1). However, to our knowledge, there have been no reports of somnambulism associated with the use of atypical antipsychotics. We present two cases of somnambulism induced by olanzapine in patients with no previous history of somnambulism despite several years of antipsychotic pharmacotherapy.

**Mr. A was a 63-year-old man with a 41-year history of schizophrenia who was seen as an outpatient in a specialized clinic for schizophrenia. He had taken risperidone for several years but was switched to olanzapine, which was increased over 10 months to 20 mg at bedtime. After 1 week at this dose, he complained of sleepwalking most nights, during which no injuries occurred. The sleepwalking was witnessed by a roommate. Mr. A's olanzapine dose was gradually decreased over 6 months, and he began taking risperidone. Even when he was taking only 5 mg of olanzapine, his sleepwalking persisted, but it ceased immediately when he stopped taking it. He reported no personal or family history of epilepsy, somnambulism, or other parasomnias. A computerized tomography scan of his head and EEG were normal. His other medications included valproate, 1750 mg/day, and procyclidine, 15 mg/day.**

**Ms. B was a 62-year-old woman with a 35-year history of schizophrenia who was being treated with loxapine. She started taking olanzapine and reached a maximum dose of 20 mg at bedtime. She then reported sleepwalking for 6 months. Valproate was added to her medication regimen, but her somnambulism persisted. She was switched from olanzapine to risperidone over 3 months; the somnambulism decreased in frequency with tapering doses and ceased after discontinuation of olanzapine.**

Somnambulism arises during slow-wave sleep (stages 3 and 4) (1) and reflects impairment in the normal mechanisms of arousal from sleep, resulting in partial arousals during which motor behaviors are activated without full consciousness. Drug-induced somnambulism may represent a physiological state during slow-wave sleep that mimics primary somnambulism (1). Periodic leg movements of sleep may trigger sleepwalking by increasing arousal. Periodic leg movements of sleep and restless legs syndrome have been reported in conjunction with olanzapine therapy (2).

Two recent studies (3, 4) have demonstrated that olanzapine significantly increases slow-wave sleep. This is likely mediated by serotonin 5-$HT_{2C}$ receptor blockade because ritanserin, a 5-$HT_{2C}$ antagonist, increases slow-wave sleep (5). In contrast, clozapine decreases slow-wave sleep in patients with schizophrenia who were previously antipsychotic free (6).

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## Charles Bonnet Syndrome and Multiple Sclerosis

TO THE EDITOR: Charles Bonnet syndrome refers to formal, complex, persistent, stereotypical visual hallucinations that are not accompanied by any other psychotic symptoms in cognitively unimpaired individuals (1). Although multiple sclerosis can produce diverse neuropsychiatric manifestations, we know of no reports of Charles Bonnet syndrome in patients with this illness.

**Ms. A, a 56-year-old woman with no cognitive impairment, claimed to see vivid and complicated images after losing her vision for 4 months as a result of optic neuritis. These images changed in shape, color, and size and included Chinese and English characters, vegetables, and small animals that could penetrate into her abdomen. She recognized them as unreal, but they existed at all times, whether she had her eyes open or closed.**

**She had suffered from multiple sclerosis for about 20 years and had no comorbid psychiatric disorders. Besides her temporary loss of vision, she experienced effects on her cervical and thoracic spinal cord. She became bedridden and completely dependent on the care of others. In an assessment of cognitive functioning, she scored 25 out of 30 points on the Mini-Mental State Examination, excluding the items that require vision (5 points). Magnetic resonance imaging of her brain revealed high signal intensity in both periventricular and white matter regions of the parietal lobes. Carbamazepine treatment, 200 mg t.i.d., was initiated, and Ms. A's visual hallucinations were significantly reduced. However, after she stopped taking carbamazepine, the visual hallucinations returned, but they disappeared after she resumed taking carbamazepine.**

A literature search revealed that a greater risk of Charles Bonnet syndrome has been found with advanced age, cerebral impairment, and ocular pathology (2). It is therefore not unusual that Charles Bonnet syndrome has been found in younger people with certain diseases involving the eyes and brain. Therapy targeting the underlying ocular or cerebral diseases might alleviate the hallucinations. In addition, anticonvulsants such as carbamazepine and valproate are effective for treatment because their antiseizure properties can reduce "irritable cortex," a condition that has been hypothesized to cause a "phantom visual phenomenon" (3). Despite prevalent ocular and cerebral involvement in multiple sclero-

sis, to our knowledge, there have been no reports of hallucinations that are consistent with the Charles Bonnet syndrome. Plausible explanations are 1) that visual hallucinations seldom occur without cognitive impairment and other psychotic symptoms in multiple sclerosis, 2) that there are few voluntary expressions of visual hallucinations, and 3) that physicians are unfamiliar with this syndrome. The last two explanations might account for an underestimation of Charles Bonnet syndrome in multiple sclerosis. It is suggested that psychiatrists, neurologists, and ophthalmologists pay more attention to the nature of hallucinations in order to diagnose Charles Bonnet syndrome, which can be treated effectively with anticonvulsants.

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## Prodissociative Effects of Metyrapone

TO THE EDITOR: We present case vignettes of three patients with panic disorder (per DSM-IV) who underwent neuroendocrine testing of hypothalamic-pituitary-adrenocortical axis activity with the 11β steroid hydroxylase inhibitor metyrapone (3 g given orally at midnight, i.e., 27.3–31.3 mg/kg of body weight). They were the first three patients in our hospital to participate in this single-blind, placebo-controlled study, and they unexpectedly developed transient dissociative symptoms after metyrapone administration but not after placebo ingestion. All patients had been free from psychotropic medication for at least 1 week and had negative urinary screens for illegal drugs.

**Mr. A was a 30-year-old man who had suffered from panic disorder (without other lifetime axis I disorders) for 1.5 years. Thirty minutes after metyrapone ingestion, he felt dreamy and disconnected from his body and his surroundings, similar to how he felt right before losing consciousness during administration of general anesthesia. However, he did not feel panicky and did not experience the somatic symptoms of a panic attack.**

**Mr. B was a 57-year-old man who had suffered from panic disorder with agoraphobia for 28 years; he also had lifetime diagnoses of benzodiazepine abuse and major depression (both in remission for 1 year). Forty minutes after metyrapone ingestion, he felt unreal, developed tunnel vision, perceived objects as "swinging back and forth," and concurrently had a typical panic attack.**

**Mr. C was a 20-year-old man who had suffered from panic disorder with agoraphobia for 4 years and had comorbid secondary alcoholism; the latter had been in remission for 3 months. One hour after metyrapone ingestion, he developed tunnel vision, felt unreal and detached from his surroundings, and perceived objects as diminished in size. No other symptoms of a panic attack emerged.**

These acute dissociative symptoms that developed shortly after metyrapone intake subsided completely in all three patients within 1 hour. Although all these patients regularly experienced derealization during their spontaneous panic attacks (as seen in about 70% of patients with panic disorder [1]), two of them reported experiencing only isolated dissociative symptoms after metyrapone administration and no simultaneous symptoms of panic. These unexpected prodissociative side effects of metyrapone were reported spontaneously by all three patients. After placebo ingestion, no side effects were experienced, with the exception of a slight transient stomach pain in one patient. Metyrapone administration remarkably elevated mean adrenocorticotropic hormone levels to 630% of baseline by 8:00 a.m.

Before further speculation about a potentially greater vulnerability of patients with panic disorder to the prodissociative side effects of metyrapone, a prospective double-blind study using standardized scales to measure acute dissociation is needed. Such an investigation should also include normal comparison subjects and other patient groups, since one patient with posttraumatic stress disorder has also been reported to have developed a dissociative episode approximately 1 hour after metyrapone ingestion (2).

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## Venlafaxine-Induced Hair Loss

TO THE EDITOR: We report on a depressed woman who complained of hair loss during treatment with venlafaxine, a serotonin-noradrenaline reuptake inhibitor.

**Ms. A was a 50-year-old woman who had suffered from a severe major depressive episode of a melancholic subtype. She did not fulfill DSM-IV criteria for any other axis I or personality disorder. She was medically healthy and did not take any medications. Her general practitioner began treatment with venlafaxine, 75 mg/day. After 15 days, her dose of venlafaxine was increased to 150 mg/day. Four weeks later, Ms. A was much better. However, she reported moderate side effects, such as nausea and somnolence, that began after 2 days of treatment. After 2 weeks, she also noticed hair loss when she brushed or washed her hair. Ms. A considered hair loss a moderate but disturbing side effect and decided to discontinue the treatment after 3 months. Her hair loss stopped completely 1 month later.**

**Ten months later, Ms. A developed a new major depressive episode. She began taking venlafaxine again; this was associated with a complete remission of the previous depressive episode. She started taking venlafaxine at a mean dose of 75 mg/day and then increased it to 150 mg/day af-**

**ter 2 weeks. Three weeks later, Ms. A decided to stop taking the medication again because of the hair loss that she had observed 10 days after beginning treatment. A complete remission was achieved with sertraline, 50 mg/day, without hair loss, which completely stopped 3 weeks after the discontinuation of venlafaxine.**

Our patient had never experienced hair loss before and had no history of endocrine illness. Hair loss has been reported with selective serotonin reuptake inhibitors such as fluoxetine (1, 2), sertraline (3), and paroxetine (4), but it is considered a rare side effect. To our knowledge, this is the first report of hair loss associated with venlafaxine therapy. Clinicians should be aware of this surprising and potentially distressing side effect.

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## E-Maternity Leave

TO THE EDITOR: E-maternity leave may be a useful option for some psychiatrist mothers. I covered my patients during my recent maternity leave primarily by means of e-mail and telephone. My small, relatively healthy caseload of patients under medication management were encouraged to contact me during my leave as needed. I gave all patients my home e-mail address and home telephone number. I offered traditional cross-coverage as an option, but no patients took it. I also made each patient aware of my limited availability and the necessity of going to the emergency room if they could not reach me and needed emergency attention. The therapists working with my patients were aware of this plan.

I received approximately one e-mail message a day and one telephone call a week from my patients and their therapists. There was no billing for these contacts. One patient was hospitalized during this time, and I arranged for this admission after extensive telephone contacts.

There were some pluses to e-maternity leave for my patients. First, there was less loss of continuity in treatment. The psychiatrist who knew them best continued to manage their medications during leave. Second, when I returned from leave, I was well informed of their progress. Third, there seemed to be fewer clinical worsenings during my absence than during my first, traditional maternity leave. The patients seemed touched that I would care enough to continue to be available. Fourth, I got to know a couple of patients better because these anxious patients seemed to communicate better by means of computer than in person.

Online maternity leave also worked well for me. First, patients seemed to respect my leave and contacted me only in an appropriate manner—and when they needed help. I did not receive one trivial e-mail message or telephone call throughout this time. Second, the medium of e-mail allowed the contacts I received to enter my home without a telephone ring, so my newborn's sleep went uninterrupted. And unlike with the telephone, I was able to answer e-mails at times convenient to me and my baby. Third, it was nice not to impose cross-coverage on a colleague.

Certainly there were downsides to this approach. There were a couple of patients who did not remain in close contact. My oldest patient, who was perhaps the least familiar with the computer, did not contact me throughout this time. And, of course, there must have been aspects of my patients' status that eluded me since a mental status examination is impossible online.

Generalizing my experience with e-maternity leave is of limited use. I carry few patients regularly, and these are relatively well functioning. I have no patients with psychosis or bipolar disorder, who perhaps would be most difficult to evaluate online. Nonetheless, I continue to be impressed by the possibilities the computer offers our patients and ourselves and believe we should cautiously explore new uses of this powerful medium.


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## Virtual Psychiatric Clinics

TO THE EDITOR: The Internet is an increasing popular means of communicating for physicians and their patients. Psychiatry and psychotherapy seem to be two of the most promising medical fields in which to carry on diagnostic and therapeutic activities in virtual reality (1). We designed and implemented a noncommercial virtual psychiatric clinic (http://www.psychpark.net/clinic). Web visitors can ask questions about psychiatric problems by e-mail, then our professionals e-mail the answers back. Then clients can ask further questions. Our service is free of charge for clients. There are more than 80 volunteer professionals in our clinic, including psychiatrists, psychologists, social workers, occupational therapists, and psychiatric nurses.

The characteristics of the 66 clients in our virtual clinic were compared with 42 clients on their first visits to a psychiatric outpatient clinic located in downtown Taipei. There were significant differences between them. The clients of our virtual clinic were significantly younger than the outpatients (mean age=28.9 years, SD=6.1, versus 35.8 years, SD=14.3, respectively) (t=2.93, df=49.4, p=0.005, two-tailed), more had a college education (N=44, 66.7%, versus N=12, 28.6%; Pearson's $\chi^2$=35.4, df=5, p=0.001, two-tailed), and more had never previously visited a psychiatric clinic (N=29, 43.9%, versus N=6, 14.3%; p=0.001, Fisher's exact test, two-tailed). Among clients who had visited real psychiatric clinics, there were significant differences in the types of previous diagnoses between the two groups (Pearson's $\chi^2$=12.33, df=4, p=0.02, two-tailed). The most common diagnosis of clients of the virtual clinic was anxiety disorder (panic disorder, obsessive-compulsive disorder, or generalized anxiety disorder) (N=36, 54.5%); the most common diagnosis for the clients of the real clinic was mood disorder (depression or bipolar disorder) (N=20, 47.6%).

In a study by Milton et al. of an Internet anxiety disorder program (2), all patients were young, well-educated, male, and of high socioeconomic status—all characteristics of Internet users. He suggested that anxiety plays a part in the different ways in which they sought help, and such patients could be predisposed to using computers to obtain information or to obtain access to resources to understand their problems (2). Our study results were compatible with those of Milton et al. Our web clients were also young and highly educated, they had more anxiety-related disorders, and most of them had not visited a real psychiatric clinic before. Clients who might have had trouble expressing their feelings in face-to-face sessions were able to discuss them freely through e-mail (3). The convenience and privacy of virtual psychiatric clinics may increase some patients' motivation to seek help from mental professionals. Although, to our knowledge, there are no articles comparing the efficacy of web-based treatment and real clinics, the Internet is a way to educate and reach potential patients. Understanding the characteristics of web clients may improve further online services to meet the needs of different health care consumers.

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## Childhood Chronic Fatigue Syndrome

TO THE EDITOR: In spite of the medically unexplained nature of the condition, children with chronic fatigue syndrome and their parents often believe that the illness is primarily physical in nature. In adults the strength of these biological attributions has been linked to high levels of impairment and to poor outcome. Understanding illness attributions and health attitudes may help guide clinical practice in treating chronic fatigue syndrome in children.

As part of a follow-up study of adolescents with chronic fatigue syndrome, we explored health attributions and attitudes in 25 youngsters (15 girls and 10 boys) and their parents who were seen in tertiary pediatric centers a mean of 45.5 months (SD=21.5) after the start of their illness. The mean age at follow-up was 15 years (SD=2). Seventeen out of the 25 subjects had recovered, but eight remained ill. None had developed explanatory physical disorders (1). We compared health attitudes in the youngsters with chronic fatigue syndrome and in 15 healthy community comparison subjects.

The attributions of chronic fatigue syndrome were predominantly biological in the affected children and their parents and were related to outcome. Ninety percent of the children and 72% of the parents believed the illness was precipitated primarily by biological factors. Parental failure to subscribe to the possibility that psychological factors could be contributing to the maintenance of the disorder was associated with poor outcome (six of eight [75%] of the poor-outcome group and six of 17 [35%] of the good-outcome group; p=0.02, Fisher's exact test).

In the youngsters with chronic fatigue syndrome, we found evidence of unrealistic views of normative fatigue levels. On an 11-point visual analogue scale (0=no fatigue), and regardless of recovery status, expected adolescent normative fatigue levels were significantly lower in the subjects with chronic fatigue syndrome (median=1.2, quartiles 0.5 to 1.5) and in their parents than in healthy comparison subjects (median=4.0, quartiles 3.0 to 4.5) (p=0.001, Mann-Whitney U test). Together with the documented tendency by children with chronic fatigue syndrome and their parents to underestimate the children's actual levels of activity, this lends some support to the presence of distorted health perceptions or expectations.

These expectations were not found to be an expression of generalized overconcern about illness, pain, bodily function, and death on the Illness Attitudes Scale (2). This is in contrast to findings in a general population sample of young people with somatic symptoms (2). We did identify, however, a tendency in the subjects with chronic fatigue syndrome to enhance general "disease conviction" on the Illness Attitudes Scale (i.e., the belief in the presence of disease in spite of medical evidence and reassurance to the contrary). This was somewhat more intense in the recovered group (p=0.09, Mann-Whitney U test) and may represent enduring attitudes.

Our findings point to the importance of exploring selective health attitudes and expectations among children with chronic fatigue syndrome who are attending specialist pediatric clinics.

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## Untreated Initial Psychosis

TO THE EDITOR: Beng-Choon Ho, M.R.C.Psych., et al. (1) concluded that the duration of initially untreated psychosis is not related to outcome early in the course of schizophrenia. This interpretation is at odds with most previous research (2) and even with their own data.

Dr. Ho and colleagues referred to data from the EPPIC program, an epidemiological sample of patients with first-episode psychosis (3), in which the duration of initially untreated psychosis was meticulously assessed (4, 5). Moderate correlations between the duration of initially untreated psychosis and key outcome variables (positive symptoms, negative symptoms, and psychosocial functioning) were evident at 1 year across the full group of patients with first-episode psychosis (N=352). The outcome variance explained by the duration of initially untreated psychosis ranged from 4% to 11%, and the duration of initially untreated psychosis was one of the strongest predictors, constituting 19%–38% of the total

explained variance. Within the schizophrenia subgroup of patients with first-episode psychosis (N=149), the duration of untreated psychosis was significantly associated with psychosocial functioning at 6 months (r=–0.20, p=0.02) and 12 months (r=–0.23, p=0.008). The PEP program in London, Ont., Canada, has also found associations of similar magnitude.

Dr. Ho et al. found in their study that these moderate correlations were not significant; however, their capacity to detect effects of this magnitude was weakened by their modest group size (N=74), resulting in low statistical power, and further weakened by their decision to apply Bonferroni corrections.

A second attenuating factor was their decision to exclude patients with schizophreniform disorder. When the study group was expanded to include these, more robust relationships emerged, e.g., between the duration of untreated psychosis and psychosocial outcome at 6 months (r=–0.29, p<0.0001). The criterion of 6 months for schizophrenia censored the study group, which created a floor effect. It was inappropriate to retain this criterion in a study of this nature. The outcome for this subgroup was more uniformly poor, as reflected in the relatively poor recovery rates reported by Dr. Ho et al. Reduction of outcome variance attenuates or conceals the relationship with the duration of untreated psychosis (6). This jars with the authors' assertion that the findings "bode well for patients."

Reducing treatment delay is only one pillar of the early intervention paradigm; however, it is important practically and symbolically, as treatment delay is one of the few potential malleable risk factors for poor outcome. We agree there is minimal evidence that prolonged duration of untreated psychosis is biologically toxic, but it is clearly psychosocially toxic.

Even small improvements in outcome could greatly reduce morbidity if applied to large numbers of people. We are concerned that, notwithstanding the endorsement of early intervention by Dr. Ho et al. (1), their uncritical interpretation of their data and the literature may undermine the still fragile efforts to implement early detection and timely treatment of psychotic disorders in the real world.

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## Dr. Ho and Colleagues Reply

TO THE EDITOR: While our interpretation may have been "at odds" with the literature on the duration of initial untreated psychosis, our findings were in keeping with those of more recent studies (1–3). We feel our conclusions were based on a fair analysis of our data. Twenty-three of the 28 Spearman correlation coefficients we examined (14 outcome measures times two measures for duration of untreated psychosis) were less than 0.20. The remaining five correlation coefficients were no more than 0.27. Although the term "moderate" is arbitrary, we cannot agree with Dr. McGorry et al. that these were "moderate correlations." In addition, at such magnitudes of correlation, the concerns regarding low statistical power from a group size of 74 and Bonferroni correction become less consequential. We had initially opted not to correct for multiple comparisons in our original manuscript, but we subsequently acceded to requests from reviewers.

Dr. McGorry et al. raise the question of which diagnostic categories are appropriate for studies of the duration of untreated psychosis. They suggest that a "second attenuating factor" for our lack of significant correlations was the purported exclusion of patients with schizophreniform disorder. One might argue that if the goal is to examine the effects of untreated initial psychosis, it may be appropriate to include any patient with first-episode psychosis, irrespective of diagnosis. However, using such a heterogeneous group may be methodologically less rigorous, since diagnosis can be a confounder. Patients with affective psychoses tend to have a shorter duration of untreated psychosis and better outcomes than patients with schizophrenia. Hence, the magnitudes of the correlations between duration of untreated psychosis and outcome can be erroneously inflated when such a heterogeneous group of patients with first-episode psychosis is studied. All 74 subjects in our study had a diagnosis of schizophrenia by the 6-month follow-up.

However, 23 (31%) did *not* have schizophrenia at the time of intake into our longitudinal study: 15 had an intake diagnosis of schizophreniform disorder, two had schizotypal personality disorder, two had substance-induced psychotic disorder, one had major depressive disorder with psychotic features, and three had psychotic disorder not otherwise specified. This important information had been in the original manuscript but was inadvertently deleted in subsequent revisions. We apologize for having misled Dr. McGorry et al. and other readers into thinking we had excluded patients with schizophreniform disorder. Our assertion that our findings "bode well for patients" referred to the weak associations between lengthy duration of untreated psychosis and poor outcome, not to the poor quality of life at 6 months per se.

Treatment-seeking behavior is a complex phenomenon for which duration of untreated psychosis is a simplistic quantification of the obstacles that hinder timely initial treatment

for patients with schizophrenia. We definitely support efforts to better understand these obstacles and to bring patients to treatment sooner. Our findings must not be misconstrued as attempts to undermine the prevention of schizophrenia. We feel the interest of patients will be best served if preventive research proceeds cautiously and remains data driven as it negotiates the ethical minefield. Finally, we greatly appreciate the leading role taken by Dr. McGorry and colleagues in championing the cause of prevention in psychiatry.

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## Cytokines in Clinical Psychiatry

TO THE EDITOR: As pointed out by Ziad Kronfol, M.D., and Daniel G. Remick, M.D. (1), recent developments in the neurobiology of cytokines have opened exciting perspectives for psychiatry. A review on this topic for the information of clinical psychiatrists, therefore, is fully justified and timely. However, the review by Drs. Kronfol and Remick suffers from a number of approximations, omissions, and even gross mistakes that do not allow the readership to fully appreciate the importance of the field and its exact implications.

In contrast to what Drs. Kronfol and Remick presented, cytokines are not ready-made hormones of the immune system that are secreted into the bloodstream to reach their target organs, but communication signals that are produced only when needed and, once released, act in a paracrine and autocrine manner. This means that, unlike hormones, circulating levels of cytokines tell nothing about the functional state of the affected organ. Clinical findings on the cytokine system in psychiatric patients need, therefore, to be put into perspective. Most of the data regarding depressed patients come from a report by Maes (2), and they are not easily replicable. The strength of the article lies more in the convergence of different lines of research, from antidepressant drugs' attenuation of the effects of cytokines on the brain to the psychiatric side effects of cytokines (3). Also, alterations in the peripheral cytokine system of patients with schizophrenia are nonspecific concomitants of activation of the brain cytokine system that are associated with brain swelling and disruption of the blood-brain barrier during acute exacerbations of the disease (4, 5). Causal factors are still uncertain but include autoimmunity, prenatal virus infection, and transcriptional activation of endogenous retroviruses. Concerning the side effects of cytokines, several important new findings are missing from the article, especially the early occurrence of mood disorders (5) and the demonstration of an individual vulnerability to these effects (6). Other major omissions, despite their relevance to the consultation-liaison psychiatrist, include the high prevalence of psychiatric disorders with conditions of chronic inflammation and the alterations in mood and cognition in AIDS patients.

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ROSE-MARIE BLUTHÉ, PH.D.
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## Drs. Kronfol and Remick Reply

TO THE EDITOR: We thank Dr. Capuron and colleagues for their interest in our article. They object to our comparison of cytokines to hormones. This comparison is not new and has often been made to underscore both the similarities and the differences in their regulation and mechanism of action (1). One major difference with regard to regulation is that cytokines are usually secreted on demand in massive amounts relative to their baseline levels, which are often undetectable. Cytokine secretion puts into motion a series of events, most of which are initiated by binding to a specific cytokine receptor, and in this regard, cytokines are similar to hormones. A significant difference between cytokines and hormones, however, is that cytokine-induced cell activation often causes the release of soluble receptors, sometimes in concentrations a hundred times higher than the specific cytokine released (2). The purpose of this tight regulation of cytokine secretion and action may be to initiate an immune and/or inflammatory response at the local level while protecting the rest of the organism from the potentially devastating effects of unchecked levels of cytokines (3). We therefore agree that differences in circulating levels of any specific cytokine between two subject groups are unlikely to provide useful information about cytokine regulation in these subjects. This was explicitly stated in our article. For this reason, we limited our review of the literature on human stress and cytokines to in vitro cytokine production by stimulated leukocytes.

As to the issue of cytokine regulation in psychiatric patients, we were careful to emphasize in our article only studies in which cytokine secretion or other indices of cytokine phys-

iology were measured directly. Indirect evidence for a possible role for cytokines in major depression—no matter how appealing—remains more in the realm of speculation and theory awaiting confirmation than as reproducible fact. Also, we think it is premature to link evidence of cytokine dysregulation in schizophrenia to brain swelling or disruption of the blood-brain barrier, since direct evidence for these observations remains slim. Last, many "omissions" referred to in the letter pertain to publications that have appeared since the submission of our manuscript. We would welcome the opportunity to add them to our overview.

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## Comparing Psychotherapy and Pharmacotherapy

TO THE EDITOR: In his review article, Donald F. Klein, M.D. (1) critiqued the work of my colleagues and me in several ways. Dr. Klein asserted that "Gould et al. [2] performed only a MEDLINE database search that was limited to 20 years, from 1974 to March 1994" (pp. 1205–1206). This statement is incorrect. In fact, we also performed a CD-ROM PsycLIT search for the same years, examined secondary references to locate articles, and included studies that were in press at the time of publication that we had knowledge of because of their presentation at national conferences.

Dr. Klein argued that three of our 43 studies were "problematic" and should not have been included in the meta-analysis and that another study should have been included. We agree with Dr. Klein that the Black et al. study (3) should have been included and are unclear as to why our original MEDLINE search did not capture this study. We also agree with Dr. Klein that the subjects in the study by Charney et al. (4) were not properly randomized and should be excluded. Dr. Klein argued that the study by Klosko et al. (5) should not be included for several reasons, one of which was that "Since alprazolam is effective in the treatment of panic disorder, this trial lacked assay sensitivity (i.e., the ability to detect specific treatment effects)" (p. 1206). Was Dr. Klein saying that a pharmacotherapy study was invalid if it did not replicate previous pharmacotherapy findings? We agree with McNally's comments (6) that Dr. Klein's assertions (7) about assay sensitivity suffered from circular reasoning: when a manipulation check and an outcome measure are the same, there exists an inherent tautology. Independent criteria are needed to establish assay sensitivity.

It is of interest that even if we agreed wholeheartedly with Dr. Klein and had eliminated three studies from our meta-analysis and added one, the results and conclusions from our original work would have remained unchanged. Our original analysis yielded an effect size of 0.68 for cognitive behavior therapy and 0.47 for drugs in 43 studies. A reanalysis with these changes resulted in an effect size of 0.65 for cognitive behavior therapy and 0.49 for pharmacotherapy in 41 studies. The conclusions of our original analysis remain the same: pharmacological and cognitive behavior therapy both produce better results than contrast conditions, and cognitive behavior therapy is at least as effective as pharmacotherapy in the treatment of psychiatric disorders.

Finally, Dr. Klein (1) asserted that "Gould et al. [2]…included nine studies that lacked any contrast group, making it difficult to understand how a comparative effect size was calculated" (p. 1206). This statement is incorrect; all of our studies were required to have control conditions that included no treatment, wait list, drug placebo, or psychological placebo, and from these we derived effect sizes.

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ROBERT A. GOULD, PH.D.
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TO THE EDITOR: In an interesting review, Dr. Klein critically examined four meta-analyses "that claim to quantitatively compare the benefits of psychotherapy to pharmacotherapy in patients with psychiatric disorders" (p. 1204). The article dealt with some important aspects of meta-analyses that must be taken into account in evaluating their conclusions. For example, Dr. Klein correctly pointed out the economic and ideological consequences that may play a role in claims derived from meta-analyses. Although we agree that a meta-analysis is no substitute for direct comparisons in adequately designed studies, we have some remarks concerning his selection of the meta-analyses discussed and his comments.

First, he discussed two meta-analyses of panic disorder that were published in 1995 and 1989 but paid no attention to our more recent meta-analyses from 1997 and 1998 (1, 2). In these studies, we addressed several criticisms that he made. We did control for a possible publication bias toward positive results (it probably would not change the conclusions for panic disorder), checked for potential differences between a

wait-listed control group and a placebo group (we found comparable effect sizes), and performed quality assessments (we found no relationship between quality and outcome). In both meta-analyses, we found that the combination of antidepressants and exposure in vivo was superior to either therapy given separately.

Second, Dr. Klein discussed our meta-analysis of treatments for obsessive-compulsive disorder (OCD) (3) and criticized the noncomparative effect size we used because it was "vulnerable to several artifacts" (p. 1208) without specifying these artifacts. He also stated that "since only one of the 86 studies directly compared psychological with pharmacological interventions and showed no significant a priori distinctions between the two treatments, this conclusion [that behavior therapy is more effective for the treatment of OCD than antidepressants] goes far beyond the data" (p. 1208). As we pointed out in the introduction of the article, the scarcity of direct comparisons was precisely the reason we undertook the meta-analysis: as a next-best answer to the question of relative efficacy. Unfortunately, to our knowledge, even to this date no direct comparisons of antidepressants and cognitive behavior therapy in OCD have been published. We hope that the field picks up the recommendation to conduct comparative studies in both fields.

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TO THE EDITOR: The review by Dr. Klein concerning psychotherapy and pharmacotherapy for the treatment of some conditions elegantly showed that studies comparing cognitive behavior therapy and pharmacotherapy for severe depression have not demonstrated that cognitive behavior therapy equals or surpasses drug treatment. The reader might then infer that this conclusion does not apply to nonsevere depression, especially since the APA practice guideline on this topic (1) supports the use of psychotherapy as acceptable treatment for nonsevere depression. However, if one agrees with Dr. Klein, as I do, that a pill placebo control is necessary for comparing psychotherapy and drug therapy in order to determine that the sample includes subjects who were responsive to drug treatment, then the conclusion that Dr Klein drew for severe depression should apply to nonsevere depression: viz, there are insufficient data to conclude that psychotherapy equals or surpasses drug treatment.

The methodological difficulties of robustly testing this question indicate that we need large multisite studies to ensure expert pharmacotherapy and psychotherapy. Considering the enormous use of psychotherapy, it seems odd that in the 21st century we still lack good evidence for its efficacy for the many mental disorders for which we have substantial, pivotal evidence for the efficacy of drug treatment. I cannot imagine that the proponents of psychotherapy would object to such studies. We cannot depend on drug companies to fund such studies (although that would be nice), so that leaves it up to the National Institute of Mental Health. Perhaps we need a Food and Drug Administration (FDA) counterpart for psychotherapy. Doesn't the public deserve to know that psychotherapy is safe and effective and how it compares to drug treatment?

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## Dr. Klein Replies

TO THE EDITOR: Dr. Gould objects that my criticism of the meta-analysis by him and his colleagues neglected to mention their CD-ROM PsycLIT search from 1974 to 1994, as well as secondary references, etc. I regret these omissions, but my relevant point is the existence of appropriate studies from before 1974 as well as the incompleteness of the computerized review. The authors' failure to achieve the meta-analytic goal of comprehensive unbiased review still stands.

Dr. Gould states that the Klosko et al. study provided valid data, although active drug could not be differentiated from placebo. Dr. Gould objects to my "circular reasoning." However, such trials failed because their inability to distinguish an already validated drug from placebo indicates that something was wrong with the sample or the procedures or that a sampling fluctuation called any findings into question, etc. The FDA does not accept such studies (1; Klein, 1996).

Dr. Gould misses my major point. Regardless of effect size calculations, the relative merits of treatments that have not been directly compared in a properly controlled study of a randomized sample cannot be discerned. Psychiatric diagnosis is insufficient. The differences between patients in psychotherapy and patients receiving medication (which are not subtle) confound such comparisons. That cognitive behavior therapy is "at least as effective as pharmacotherapy," as restated by Dr. Gould, has no factual or logical basis.

Dr. Bakker et al. object to my criticism of their noncomparative effect size without specifying its problems. However, I cited an article (2) that presents such a detailed critique. Dr. Bakker et al. are concerned that I did not refer to two recent meta-analyses; however, like Dr. Gould, they do not address my central criticism of the lack of sample comparability. They justify their meta-analysis by the scarcity of direct comparisons, which requires developing the "next-best answer." I disagree with this conclusion.

The pseudoexactness of meta-analysis misapplied to such chaotic data provides an altogether unwarranted assurance of well-founded comparative inference. The authors' wish to support direct comparisons could be better served by tabulating relevant studies with regard to both outcome and valid-

ity issues, e.g., randomization, blindness, and nature of control group. This would provide the correct basis for possible recommendations about direct comparisons. Such old-fashioned literature reviews yield a substantially better understanding than effect size manipulations when the data are so partial, limited, and irrelevant. Such meta-analyses are not second best; rather, they are off the validity scale.

Finally, Dr. Rifkin argues that I should have extended my criticisms to the lack of direct valid comparative evidence regarding psychotherapy and medication in the treatment of less severe depression. I entirely agree and regret the constricting space limitations for articles.

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2. Klein DF: Listening to meta-analysis but hearing bias. Prevention and Treatment 1998, at http://journals.apa.org/prevention/volume1/pre0010006c.html

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## Reformulating the Diagnosis of Schizophrenia

TO THE EDITOR: The article by Ming T. Tsuang, M.D., Ph.D., D.Sc., F.R.C.Psych., et al. (1) represents a courageous attempt to redefine the nosology of schizophrenia. The authors favor the concept of schizotaxia and encourage the formulation of diagnostic criteria for this entity. Our group, which has been actively working on psychophysiology in patients with schizophrenia and their first-degree relatives, has encountered findings that bolster the concept of schizotaxia. In a recent study (2), we measured "bereitschaftspotential" (a cognitive-evoked potential evaluating motor preparation in a voluntary self-paced paradigm) in patients with schizophrenia, their nonpsychotic first-degree relatives, and healthy comparison subjects. Neurological signs, both soft and hard, were also assessed in these groups. The abnormality in bereitschaftspotential as well as the neurological abnormalities in the first-degree relatives were greater than those for the healthy comparison subjects but less than those for the patients. Moreover, in what we believe to be the first study of its kind, we attempted to find correlations between bereitschaftspotential and neurological abnormalities and obtained significant positive correlations between these two substrates. In addition, negative symptoms in patients with schizophrenia showed significant correlations with both abnormal bereitschaftspotential and neurological signs, which indicate a common etiopathological process underlying these features. As conceptualized, negative symptoms, neurological signs, and neuropsychological impairment represent the constituents of schizotaxia. Bereitschaftspotential is a psychophysiological measure of movement planning and decision making in voluntary movement paradigms and thus represents the neurophysiological counterpart of neuropsychological impairment. Bereitschaftspotential and other cognitive-evoked potentials have been studied across various psychiatric populations, but there is a dearth of studies comparing patients with schizophrenia and their first-degree relatives. Hence, such studies are encouraged to improve our understanding of the concept of schizotaxia.

Regarding the constituent features of the proposed entity of schizotaxia, we add a caveat. Neurological signs, negative symptoms, and even brain abnormalities are not limited to schizophrenia. For example, a study (3) demonstrated that poverty of speech, a negative symptom, is associated with a smaller perfusion of the left dorsolateral prefrontal cortex in depression and schizophrenia in a manner that is independent of diagnosis. Hence, we support the authors' proposal of field trials with adequate specificity and sensitivity to discern abnormalities before their inclusion in the diagnostic criteria for schizotaxia. In this scenario, cognitive-evoked potentials represent an area that calls for further exploration.

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## Dr. Tsuang Replies

TO THE EDITOR: Drs. Duggal and Nizamie make several interesting points in their response to our article outlining an alternative approach to the diagnosis of schizophrenia. For one, they describe evidence of a neurophysiological abnormality in the bereitschaftspotential in both schizophrenic patients and their nonpsychotic first-degree relatives that may be relevant to our conception of schizotaxia. The finding is especially interesting because bereitschaftspotential is a neurobiological marker of planning, which is a neuropsychological function that is impaired in schizotaxia (1). Moreover, bereitschaftspotential abnormalities correlated significantly with negative symptoms (which are also associated with schizotaxia) in schizophrenic patients.

Drs. Duggal and Nizamie use these findings to raise the issue of whether this type of abnormality might reflect a neurobiological component of schizotaxia. More generally, their findings underscore questions about how to define and validate the syndrome. It is clear that research over several decades shows a wide range of clinical, social, neurobiological, and neuropsychological deficits in the first-degree relatives of patients with schizophrenia. Nevertheless, while these features may resemble those that occur in schizophrenia, and may even differ significantly from those of normal comparison subjects, they are not all necessarily good candidates for use as diagnostic criteria (2). This is true, for example, if performance variability on a particular measure precludes useful estimates of sensitivity or specificity. In fact, Drs. Duggal and Nizamie make a similar point when they describe how negative symptoms may occur in unrelated clinical conditions.

This highlights the need for field trials to determine the utility of including particular symptoms as diagnostic criteria in schizotaxic syndrome.

In addition to the need to define a syndrome that demonstrates acceptable levels of sensitivity and specificity, the validation of schizotaxia must adhere to other guidelines. Among these, the diagnostic criteria need to be reliable and heritable. The use of negative symptoms and neuropsychological deficits in our preliminary formulation of schizotaxia reflects their robust occurrence in family studies (2–4). Moreover, if the symptoms of schizotaxia reflect an underlying vulnerability to schizophrenia, it is important to show that they are stable.

Thus far, several neuropsychological deficits in the relatives of patients, such as those in long-term verbal memory, have remained stable after a 4-year follow-up period (5). Evidence for the reliability, heritability, and stability of schizotaxia adds to its validity. Further evidence for the validity of the syndrome comes from a preliminary study (6) showing that subjects who meet the criteria for schizotaxia perform worse on several independent clinical measures (e.g., the Global Assessment of Functioning Scale and the Social Adjustment Scale) than subjects who do not. While encouraging, these results show that the definition and validation of schizotaxia is at a formative stage. One way to proceed at this point would be to use neurobiological abnormalities, such as those seen in bereitschaftspotential, to establish the external validity of the proposed syndrome and then evaluate their suitability for incorporation into the syndrome itself. In this way, the definition of the condition will hopefully evolve along with its conceptual and pragmatic utility.

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## Respect From Our Medical Colleagues

TO THE EDITOR: Cheers to Jack M. Gorman, M.D., for his Introspections piece (1). I work as a consultation psychiatrist in a general medical hospital in which I have regular interaction with medical and surgical colleagues, as he described. There are many cases in which a negative evaluation or a lack of clear diagnostic findings leads to the presumption that residual somatic symptoms are the result of psychiatric pathology. At such times, psychiatric consultation is often requested and may signify a certain respect from our medical colleagues because of the expectation that we can contribute to the care of the patient and effectively diagnose, treat, and ameliorate the patient's suffering. In cases such as this, however, I often feel that I have been left to diagnose and treat presumed causative psychiatric symptoms by default. It is not surprising that I pause, scratch my head, bring my own diagnostic thinking to bear on the case, and do my best to reconsider the interplay between, and the differential diagnosis of, medical and psychiatric illness. This is not always an easy position to be in, because our medical colleagues can stand more confidently behind their quantitative findings borne of modern technology and refute the suggestion that the patient's current woes are the result of interval worsening of the primary medical illness: the echocardiogram is unchanged; therefore, worsening congestive heart failure does not explain the anergic presentation.

One response is to examine the patient more closely for index psychiatric pathology, a potentially adaptive approach as it may lead to more accurate diagnosis but a potentially problematic approach as well in that it is based on a relative lack of data and thus may force a diagnosis where it does not belong (for "when all you have is a hammer…"). Another response is to return the volley and clearly describe the lack of findings on which to base a diagnosis of causative psychiatric disease. In this case, the patient is often left undiagnosed and uncertain, and physicians, patients, and their families are left unsatisfied. Somewhere in between or in addition to these two responses and far more helpful to patients, families, and involved physicians is the more internal response described by Dr. Gorman: consideration of the effect that the death and dying of a patient has on all of us. Thanks for a humanistic and psychodynamically informed take on this common clinical encounter.

#### Reference


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COLIN J. HARRINGTON, M.D.
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TO THE EDITOR: As a consultation-liaison psychiatrist, I read with great interest Dr. Gorman's eloquent description of the end-of-life comanagement of an elderly patient with his medical colleagues. Dr. Gorman's experience will certainly resonate with psychiatrists who work intensively with medically ill patients who have comorbid psychiatric disorders. One troubling aspect of this and many similar cases that Dr. Gorman did not address is the readiness with which many of our nonpsychiatric medical colleagues attribute critical somatic symptoms to patients' psychiatric disorders. This can occur despite intensive psychiatric consultation with recommendations for further medical evaluation and treatment. I have seen patients die because their psychiatric disorder was viewed as the etiology of their somatic symptoms.

Do psychiatrists really have *too much* respect from their colleagues? Until we do, and as long as bias toward our pa-

tients and our profession exists, psychiatrists must continue to advocate for their patients in the health care system. In addition, we need to take every opportunity to educate colleagues, residents, and medical students in the diagnosis and treatment of comorbid medical and psychiatric disorders.

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## Growth of Interest in Personality Disorders

TO THE EDITOR: Roger K. Blashfield, Ph.D., and Vincent Intoccia, B.A. (1), after a search of MEDLINE, 1966–1995, reported that the growth rate in the literature on personality disorders has not increased since the introduction of DSM-III. There are problems involved in the methodology chosen. The leading journals in the field, *Personality and Individual Differences,* official journal of the International Society for the Study of Individual Differences (founded in 1983), and the *Journal of Personality Disorders,* official journal of the International Society for the Study of Personality Disorders (founded in 1988), are indexed in a variety of databases but not in MEDLINE. Thus, MEDLINE seems to be an insufficient source from which to elucidate the growth of literature in the field. Furthermore, the MeSH heading "personality disorder" in MEDLINE is not used to cover personality disorders as they are usually defined in the literature. Furthermore, the MeSH headings of individual personality disorders have been imprecise and have changed during the years. Dr. Blashfield and Mr. Intoccia (1) had to search for individual personality disorders and total them. However, it has been more common to use broad personality questionnaires to cover all personality disorders, and often individual personality disorders are not reported in the title or as key words.

Thus, we have made a reevaluation through a search of PsycINFO, in which both of the previously mentioned journals are indexed. The search was performed on "personality disorders," both as a key word and as title text.

In 1980 and after, the number of publications concerning personality disorders increased rapidly. The best-fitting trend line is an exponential curve. Before 1980 (1968–1979), the mean number of publications per year was 39.3 (SD=16.4), and in 1980 and after, it increased to 241.5 (SD=142.8) articles a year ($z=4.06$, $p<0.0001$, Mann-Whitney U test). We searched the 5 years immediately before the introduction of DSM-III (1975–1979) and the last 5 years (1991–1995), and we found that the number of publications increased from 50.2 (SD=6.0) to 403.2 (SD=36.5) articles a year ($z=2.61$, $p<0.01$, Mann-Whitney U test). The rate of increase is more pronounced than the growth of the general medical literature, which doubles about once every 23 years (1).

In a recent article (2), McDonald et al. demonstrated that out of the 977 psychiatry journals identified in *Ulrich's International Periodicals Directory,* 38% were indexed in PsychLIT, 34% in EMBASE, 25% in BIOSIS, and only 24% in MEDLINE. However, a total of 213 abstracting and indexing services were identified. Thus, it is easy to agree with McDonald et al. (2) that it is important to search more than one or even two databases to ensure optimal coverage of the literature.

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## Dr. Blashfield Replies

TO THE EDITOR: Pincus (1) noted that MEDLINE is constantly adding and deleting journals from its database. He worried that the results Mr. Intoccia and I reported about changes in the personality disorder literature over time might be influenced by these decisions. Dr. von Knorring et al. make the plausible suggestion that searching another literature database, such as PsycINFO, might help avoid this problem.

We decided not to report the results from PsycINFO in our search because this database, even more than MEDLINE, appears to have undergone substantial changes regarding the journals it includes. We generated a plot from the PsycINFO database of all articles, chapters, and such that were indexed per year. The resulting plot was scalloped in shape. There were years of clear growth, followed by a sudden drop, followed by more growth. In contrast, the plot of total number of articles on MEDLINE per year showed little deviation from a straight line. To us, this result suggests that the PsycINFO database has undergone major changes in the journals it was indexing, especially in the late 1970s and mid-1980s.

Second, Dr. von Knorring et al. suggest that using "personality disorders" as a general search term would be preferable to the tactic that we used of searching on all individual personality disorder terms (e.g., "schizotypal") and summing the results. Wells and I (2) performed a detailed analysis of the 1985 personality disorders literature and reached a similar conclusion. The reason that Mr. Intoccia and I used a more detailed search tactic was that a major goal of our analysis was to compare how the literatures for individual personality disorders were changing relative to the total literature.

Dr. Pincus (1) and Dr. von Knorring et al. are correct in expressing concern about potential sources of systematic measurement error when performing empirical studies using journal article databases. Wells and I (2) demonstrated surprising differences in the literatures generated by MEDLINE and PsycINFO, as well as with a literature sample found from a manual search of the same journals. Leininger (3) showed that there are substantial reliability issues when using major categories as search terms in PsycINFO. Assessing the growth of scientific literatures involves complicated methodological decisions that can have dramatic effects on the results.

A minor point: the *Journal of Personality Disorders* is indexed in MEDLINE but only since 1997. Back cataloging may lead to the inclusion of all articles from this journal in the future.

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## Unusual Book Review

TO THE EDITOR: It was a pleasant surprise to see the review by Stephen A. Young, M.D. (1), of *I Know This Much Is True* by Wally Lamb (2). This is one of the 10 best books that I have ever read. However, after reading the review, I was moved to write this letter. Dr. Young was concerned about Lamb's negative portrayal of psychiatry and the lack of a caring and empathic psychiatrist, while a social worker and psychologist are viewed as empathic and skilled patient advocates. The psychologist also turns out to be a compassionate and wise psychotherapist.

Perhaps Dorothy Allison (3) was accurate: "Literature is the lie that tells the truth, that shows us human beings in pain and make us love them, and does so in a spirit of honest revelation."

In part, psychiatry has brought its woes on itself. It did not heed the warning made by Engel (4) in his landmark article on the dangers of a limited biological focus. It seems that psychiatry has gone the way of the rest of medicine and dropped its emphasis on the psychosocial and psychotherapy. This development, coupled with managed care, has yielded large numbers of psychiatrists who prescribe medications, not psychotherapy. Former APA President Allan Tasman lamented that "the art of talk therapy is in danger of being lost" (5). He has also maintained that not only do current residents disdain talk therapy; they do not know how to do it. Furthermore, he added that young psychiatrists lack empathy. Dr. Tasman has done a lot to counter this ominous development. For example, last year's APA annual meeting theme was "The Doctor-Patient Relationship" and its healing nature. He also catalyzed the reintroduction of training in psychotherapy. Starting in January 2001, psychiatric residency directors have to certify that each resident has at least some basic competency in psychotherapy. Perhaps in the future, psychiatry and psychiatrists will fare better in novels about psychiatric patients.

### References

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## Dr. Young Replies

TO THE EDITOR: I am pleased to reply to Dr. Rosen's thoughtful comments on my review of Lamb's *I Know This Much Is True*. I agree that this book reveals many truths about mental health practice in the current environment. As he points out, the role of effective psychotherapy practice and teaching has diminished in importance for many psychiatrists.

However, while Lamb's novel may reflect this truth, it also provides a decidedly inaccurate portrayal of modern psychiatry and psychiatrists. Indeed, the blurring of roles between patients and therapists has been a popular theme in books and cinema for some time. This trend predates managed care and the changes in our practice environment by many years. An excellent example is Conroy's *Prince of Tides* (1), published in 1986 (quite early in the managed care era in American psychiatry). In this novel, in which a psychotherapeutic relationship is also central, numerous boundaries between patient and therapist become blurred. Their relationship evolves into a sexual one. The clear message is that the relationship's intimacy, both emotional and sexual, is what heals the patient. Gabbard and Gabbard (2) documented numerous other examples from the world of cinema. The truth reflected in these examples, including *I Know This Much Is True,* may be the age-old fantasy of the patient who wishes to break through the confines of the therapeutic alliance and enjoin the therapist in a "real" relationship.

My problems with Lamb stem from his overly dramatized descriptions, especially of the forensic facility. The hospital is depicted as an out-of-control, nonempathic, and dangerous place. For example, on the night of Thomas's admission, a security officer assaults his brother. Later the brother uses this incident to blackmail the staff into providing freedoms for his brother. Having worked in a number of forensic settings, I found this depiction to be unfair and inaccurate.

Nonetheless, Lamb has crafted a wonderful novel that depicts struggles between siblings and generations in a unique and often moving way. I just wish the psychiatrists had been portrayed with a bit more empathy and realism. Current and future patients will read this book. To some extent, we have a duty to speak up and educate them about what is real and what truly is fiction.

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## DNA Polymorphisms and Bipolar Disorder

TO THE EDITOR: I read the article by Francis J. McMahon, M.D., and colleagues (1) with special interest. Although their discussion on the lack of association of bipolar disorder and mitochondrial DNA haplogroups is reasonable, basing that conclusion on four mitochondrial DNA polymorphisms whose odds ratios were greater than 2 or less than 0.5 is not persuasive. While the findings on 1888 and 10463 polymorphisms reflected only slightly higher rates of T haplogroups in subjects with bipolar disorder, the findings on 709 and 10398 polymorphisms were not related to haplogroup. In other words, these two polymorphisms were associated with bipolar disorder in comparison with haplogroup-matched comparison subjects. The authors concluded that these two polymorphisms were not associated with bipolar disorder

because the direction of any nominal differences between patients and comparison subjects varied across haplogroups. However, the number of subjects in each haplogroup was too small to draw such a conclusion.

My colleagues and I recently reported that two mitochondrial DNA polymorphisms, 5178 A/C (2) and 10398 G/A (3), were associated with bipolar disorder. The 5178 site is not polymorphic in Caucasians because most of them have the 5178C genotype. In these positions, the 5178C and 10398A genotypes were more frequently seen in patients with bipolar disorder than in comparison subjects in our study group. In Japanese people, the 10398A genotype was found in 33% (44 of 133) of the subjects with bipolar disorder and in 22% (38 of 171) of the comparison subjects (odds ratio=1.7, $p<0.05$). The finding by Dr. McMahon and colleagues that the odds ratio of the 10398A genotype was higher than 2 (78% in bipolar subjects and 64% in comparison subjects) coincides with our results. Since these two independent studies among different ethnic groups showed similar tendencies, the 10398 polymorphism in mitochondrial DNA may be one risk factor for bipolar disorder, although its effect is small.

#### References


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## Dr. McMahon and Colleagues Reply

TO THE EDITOR: We thank Dr. Kato for his kind letter commenting on our report of a nominal association between a mitochondrial DNA variant at nucleotide position 10398 and bipolar disorder. We are intrigued by his finding that this same variant may also be associated with bipolar disorder in a Japanese population. The association of the same mitochondrial DNA variant with bipolar disorder in two ethnically distinct populations increases the likelihood that the association is genuine rather than due to the ethnic particulars of a single study population. But the story is not straightforward.

The A/G polymorphism at nucleotide position 10398 occurs within the gene for NADH dehydrogenase subunit 3, a major component of cellular respiration. This single nucleotide polymorphism changes a threonine to an alanine and introduces a DdeI restriction site, making for easy detection in the laboratory. (Subjects who lack this restriction site may or may not carry the A allele; this can be established definitively only by sequencing.) A GENBANK search showed that both threonine and the alanine residues have been observed among primates, arguing against a significant physiological effect.

The two alleles at nucleotide position 10398 subdivide the mitochondrial DNA superhaplogroup L3, which encompasses all mitochondrial DNA seen in Europe and Asia, into two major subsets (1). The subset defined by the A allele is quite common among Europeans, occurring in 74% of those studied by Torroni et al. (2). Thus, it appears that the nucelotide position 10398 polymorphism arose early in human history, before the divergence of the European and Asian populations (2).

We compared the rates of the A allele in the two groups of probands and in comparison populations. In the Kato (Japanese) clinical group, 22% of the comparison subjects and 33% of the bipolar probands had the A allele. In our (European American) clinical group, 64% of the comparison subjects and 78% of the bipolar probands had the A allele. In the Torroni et al. population sample (2), 34% of the Asian subjects and 74% of the Caucasian subjects had the A allele.

These data show that the differences between probands with bipolar disorder and comparison subjects observed within Dr. Kato's and our studies are small compared to the differences between the populations from which the subjects were drawn. Furthermore, the A allele occurred less frequently in both groups of clinical comparison subjects than in the corresponding population sample for each ethnicity. Although the population samples presumably included some people carrying susceptibility alleles for bipolar disorder, the meaning of these differences is not immediately apparent. Could this reflect a common susceptibility allele of low penetration? A recently published study of a British population (3) also failed to show an association between bipolar disorder and the nucleotide position 10398 polymorphism. On the basis of these data, we stand by our original conclusion that a pathogenic role of the nucleotide position 10398 polymorphism in bipolar disorder appears unlikely, but we agree that it cannot be entirely ruled out, especially in light of Dr. Kato's new results. More data from larger groups of Europeans and Asians might clarify the situation.

#### References


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