Brief Reports

Incidence of Tardive Dyskinesia in Early Stages of Low-Dose Treatment With Typical Neuroleptics in Older Patients

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Objective: The authors studied the risk of tardive dyskinesia for older patients in the early stages of treatment with typical neuroleptics. **Method:** They examined the cumulative incidence of tardive dyskinesia 1, 3, 6, 9, and 12 months after the institution of neuroleptic therapy among 307 psychiatric outpatients over age 45. The patients' median dose was 68.4 mg/day of chlorpromazine equivalent. **Results:** In the patients who had never received neuroleptics at baseline (N=87), the mean cumulative incidence of tardive dyskinesia was 3.4% and 5.9% at 1 and 3 months, respectively. There was no significant difference in the 12-month cumulative incidence of tardive dyskinesia among patients who had been neuroleptic-naive at baseline (22.3%) and the 89 patients who had received neuroleptics before baseline for 1–30 days (24.6%); however, the 131 patients who had received neuroleptics before baseline for more than 30 days tended to have a greater cumulative 12-month incidence of tardive dyskinesia (36.9%). **Conclusions:** The risk of tardive dyskinesia in older outpatients is high, even with relatively short treatment with low doses of conventional neuroleptics.

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Tardive dyskinesia, by definition, occurs late in the course of neuroleptic treatment. The minimum duration of neuroleptic use necessary to produce tardive dyskinesia is usually thought to be 3 months (1), although DSM-IV criteria specify that this may be 1 month in individuals 60 years of age or older. Two studies (2, 3) have reported a cumulative annual incidence of tardive dyskinesia of greater than 25% among older patients; however, we found no published studies of the incidence of tardive dyskinesia among neuroleptic-naive patients after 1 and 3 months of treatment and no studies comparing the 12-month cumulative incidence of tardive dyskinesia in patients with a history of receiving neuroleptics for 30 days or less compared with those receiving neuroleptics for more than 30 days. Therefore, we undertook the present study of the incidence of tardive dyskinesia among middle-aged and elderly outpatients.

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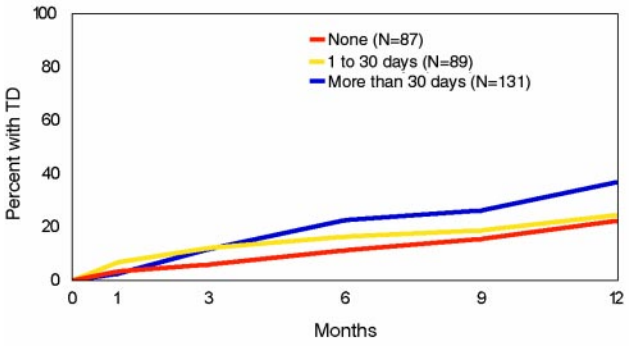
METHOD

The subjects were 307 psychiatric outpatients; all provided informed consent. None of the subjects had tardive dyskinesia at baseline, and as a group the duration of their total lifetime use of neuroleptic medication was 5 years or less. All of the patients were treated with conventional (but not atypical) antipsychotics during at least a portion of the study. A previous report (3) provided data on 189 of these 307 patients. The patients were recruited from a variety of sources, but most were from the San Diego Veterans Affairs Medical Center or the University of California, San Diego, Medical Center.

FIGURE 1. Cumulative Incidence Curves for Tardive Dyskinesia Among Three Groups of Patients With Different Lengths of Previous Neuroleptic Use at Study Entry[a]



[a] Patients with more than 30 days of neuroleptic use at baseline had a trend for a greater cumulative incidence of tardive dyskinesia than those with 0–30 days of neuroleptic use (p=0.08, Peto-Prentice).

The majority of the patients were men (N=248, 80.8%) and Caucasian (N=252, 82.1%). Their mean age was 66.2 years (SD=12.2).

The patients' DSM-III-R-based psychiatric diagnoses were dementia (N=98, 31.9%), schizophrenia (N=51, 16.6%), schizoaffective disorder (N=10, 3.3%), delusional disorder (N=5, 1.6%), "organic" psychoses (N=34, 11.1%), psychotic disorder not otherwise specified (N=13, 4.2%), mood disorders (N=48, 15.6%), and other (N=48, 15.6%). All patients were prescribed conventional neuroleptics for psychotic or other severe behavioral disturbances. The two most commonly used neuroleptics were haloperidol and thioridazine: 135 (44.0%) of the patients were treated with haloperidol, and 52 (16.9%) were treated with thioridazine. We used the following formulae for dose equivalence: 2.4 mg of haloperidol or 111.1 mg of thioridazine were considered equivalent to 100 mg of chlorpromazine (4). The median neuroleptic dose prescribed at baseline was 68.4 mg/day of chlorpromazine equivalent (4). Forty-five (14.7%) of the patients received anticholinergics at baseline, usually at low doses.

The Abnormal Involuntary Movement Scale (AIMS) (5) was used to assess dyskinesia at baseline and 1, 3, 6, 9, and 12 months later. Tardive dyskinesia was diagnosed by using Schooler and Kane's criteria (1) except for an absence of the required minimum duration of neuroleptic treatment. Additional assessments included measures of global neurocognitive status (Mini-Mental State [6]), depressive symptoms (Hamilton Depression Rating Scale [7]), and extrapyramidal symptoms (modified Simpson-Angus Rating Scale [8]).

For purposes of analysis, subjects were classified into three groups on the basis of the duration of their previous use of neuroleptics: 1) neuroleptic-naive (N=87), 2) 1–30 days of previous use (N=89; median=10.0 days) and 3) more than 30 days of previous use (N=131; median=115.0 days).

The cumulative incidence of tardive dyskinesia was calculated by using life-table survival analysis (9), and specific risk factors were determined by using Cox regression analysis (10).

RESULTS

For the neuroleptic-naive group, the mean cumulative incidence of tardive dyskinesia was 3.4% at 1 month (95% confidence interval=0.0% to 7.3%) and 5.9% at 3 months (95% confidence interval=0.9% to 10.9%). There was no significant difference in the 12-month cumulative incidence of tardive dyskinesia between patients who were neuroleptic-naive (22.3%) and those with 1–30 days of total lifetime neuroleptic use at baseline (24.6%) (p=0.36, Peto-Prentice). Therefore, we combined these two groups for subsequent analyses. The patients with more than 30 days of previous neuroleptic tended to have a greater 12-month cumulative incidence of tardive dyskinesia (36.9%) than those with 0–30 days of neuroleptic use (p=0.08, Peto-Prentice) (figure 1).

The groups with 0–30 days versus more than 30 days of previous neuroleptic use were similar in sex, ethnicity, presence of diabetes, history of alcohol abuse or dependence, and Hamilton depression scale and modified Simpson-Angus scale scores at baseline. The groups differed, however, in other respects. Patients with 0–30 days of neuroleptic use were older, were more likely to have a diagnosis of dementia or organic mental syndrome, had lower Mini-Mental State and global AIMS scores at baseline, received lower daily neuroleptic doses, and were less likely to receive anticholinergics. To determine if these group differences contributed to the differential risk of tardive dyskinesia, the following variables were used in a Cox regression: age, diagnostic type ("organic" versus primary psychiatric disorder), Mini-Mental State score, global AIMS score, duration of previous neuroleptic use (0–30 days versus more than 30 days), daily neuroleptic dose, and use of anticholinergics. The only significant predictor of tardive dyskinesia risk in this model was duration of previous neuroleptic use at study entry.

We compared the 12-month cumulative incidence rate of the previously reported 189 patients (3) with that of the 118 new patients. There was no significant difference in tardive dyskinesia incidence (p=0.78, Peto-Prentice). Twelve-month mean cumulative incidence rates for tardive dyskinesia in the total study group (N=307) were 34.1% in patients younger than 60 years of age, and 27.1% in those 60 years old or older. Among patients who were 60 years old or older, the 12-month mean cumulative incidence rates for tardive dyskinesia for patients with versus those without dementia were 24.9% and 30.2%, respectively. These differences were not significant. The nonsignificantly lower rates in patients who were 60 years old or older and in patients with dementia seemed to be related to lower neuroleptic doses and duration of previous use in those groups. In terms of severity of tardive dyskinesia, the breakdown of the 62 tardive dyskinesia patients by total AIMS score at the time of initial diagnosis of tardive dyskinesia was as follows: 30 (48.4%) had total scores of 5 or less; 27 (43.5%) had scores of 6 to 8; and five (8.1%) had scores of 9 or higher.

DISCUSSION

We studied outpatients being treated with relatively low doses of typical neuroleptics. Our findings suggest that a substantial proportion of middle-aged and elderly patients develop tardive dyskinesia relatively early in the course of neuroleptic treatment. The cumulative

incidence of tardive dyskinesia after only 3 months of treatment was 5.9%, whereas younger adults need at least 1 year of neuroleptic use for a 4% to 5% cumulative incidence (11). Therefore, one would be able to determine the relative risk of tardive dyskinesia associated with typical versus atypical antipsychotics among older patients by using relatively short-term longitudinal studies.

One limitation of our study was the absence of a control group of older patients with similar diagnoses who did not receive neuroleptics. Given the elevated risk of spontaneous dyskinesia in older patients (12), it is conceivable that some of the subjects in our study might have developed dyskinesia even in the absence of neuroleptic use. It is impractical, however, to have a true control group because it would be unethical to deny the use of neuroleptics to patients who need them for controlling their psychotic or severe behavioral disturbances. Nevertheless, it is highly unlikely that a large proportion of patients would develop dyskinesia spontaneously over a relatively short period of time.

Given that some of our subjects developed tardive dyskinesia after only 1 month of neuroleptic use, the DSM-IV criterion of 1 month, instead of the usual 3 months, of minimum neuroleptic use for a diagnosis of tardive dyskinesia in elderly patients should be broadened to include middle-aged patients (45–60 years).

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Body Weight and Leptin Plasma Levels During Treatment With Antipsychotic Drugs

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Objective: Leptin is produced by fat cells and is presumed to signal the size of the adipose tissue to the brain. The authors investigated whether antipsychotic drugs that often induce weight gain affect circulating levels of leptin. **Method:** Weight, body mass index, and leptin plasma level were measured weekly over 4 weeks in psychiatric inpatients who received clozapine (N=11), olanzapine (N=8), haloperidol (N=13), or no psychopharmacological treatment (N=12). **Results:** In patients receiving clozapine or olanzapine, significant increases in weight, body mass index, and leptin level were found, whereas these measures remained stable in patients who received haloperidol or no pharmacological treatment. **Conclusions:** Weight gain induced by clozapine or olanzapine appears to be associated with an increase in leptin level that cannot be attributed to dietary changes upon hospitalization.

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Weight gain frequently occurs during treatment with clozapine (1) or olanzapine (2) and sometimes limits treatment compliance. Clozapine has been shown to increase circulating levels of leptin (3), a hormone produced by fat cells that is thought to signal the size of the adipose tissue to the brain. Mice and humans deficient in leptin are obese (4, 5). In *ob/ob* mice, leptin administration reduces food intake and weight (6, 7), indicating a role for this hormone in weight regulation. In humans, circulating leptin level correlates positively with body mass index; patients with anorexia nervosa, for example, have low leptin levels that increase in parallel to weight during treatment (8).

To explore the pathophysiology of weight gain during antipsychotic treatment, we longitudinally investigated weight, body mass index, and leptin level in patients treated with clozapine or olanzapine. In addition, we included a group of patients treated with haloperidol, which is known to induce only minor changes in weight (2). To control for the effect of minor dietary changes upon hospitalization, we also investigated patients who did not receive any pharmacological treatment.

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METHOD

Consecutively admitted inpatients fulfilling the DSM-IV diagnostic criteria for a schizophrenic disorder were assigned according to clinical decisions to monotherapy with clozapine (N=11), olanzapine (N=8), or haloperidol (N=13). The clozapine group comprised seven women and four men, whose mean age was 37 years (SD=19). In the olanzapine group there were five women and three men, and their mean age was 26 years (SD=6). The haloperidol group contained seven women and six men, and their mean age was 36 (SD=16). The mean doses (in milligrams per day) during weeks 1, 2, 3, and 4, respectively, were as follows: clozapine—85 (SD=50), 145 (SD=63), 199 (SD=80), and 251 (SD=117); olanzapine—11 (SD=3), 13 (SD=3), 13 (SD=3), and 14 (SD=4); haloperidol—5 (SD=3), 5 (SD=3), 5 (SD=3), and 6 (SD=3). Twelve patients (seven women and five men; mean age=30, SD=12) suffering from various psychiatric disorders other than schizophrenia received no psychopharmacological treatment. The absence of medication was due either to diagnostic purposes (N=4) or to the fact that the patients were treated with behavioral psychotherapy exclusively (N=8). All patients received a standard hospital diet. After complete description of the study, all patients gave informed written consent to participate in the investigation, which had been approved by an independent ethics committee.

Weight was assessed at baseline and weekly thereafter. The body mass index was calculated by dividing the weight (in kilograms) by the squared height (in meters). The plasma levels of leptin were assessed by using radioimmunoassay (DRG Instruments, Marburg, Germany). The limit of detection was 0.5 ng/ml, and the intra- and interassay coefficients of variation were 7% and 9%, respectively. For statistical analysis, multivariate analysis of variance (MANOVA) for repeated measures was used. Post hoc comparisons were

TABLE 1. Weight, Body Mass Index, and Leptin Plasma Level Over 4 Weeks in Psychiatric Inpatients Receiving Clozapine, Olanzapine, Haloperidol, or No Psychopharmacological Treatment

Drug Treatment and Measure	Baseline		Week 1		Week 2		Week 3		Week 4		Univariate F Test		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	F	df	p
Clozapine (N=11)													
Weight (kg)	68.7	11.7	69.3	11.3	69.7	11.4	70.5[a]	11.4	71.0[a]	10.7	3.9	4, 40	0.01
Body mass index (kg/m²)	22.1	2.3	22.3	2.1	22.4	2.2	22.7[a]	2.1	22.9[a]	2.0	4.2	4, 40	0.007
Leptin (ng/ml)	6.7	3.9	8.7[a]	5.8	9.4[a]	6.0	10.0[a]	6.6	10.7[a]	8.4	4.6	4, 40	0.004
Olanzapine (N=8)													
Weight (kg)	66.7	6.3	67.5	5.4	68.7[a]	5.0	69.8[a]	5.1	70.6[a]	5.3	14.5	4, 28	<0.001
Body mass index (kg/m²)	22.4	2.2	22.7	2.0	23.0[a]	1.8	23.4[a]	1.7	23.7[a]	1.6	15.0	4, 28	<0.001
Leptin (ng/ml)	6.1	4.2	7.8	4.5	9.5[a]	7.7	10.0[a]	5.6	10.1[a]	5.4	4.5	4, 28	0.006
Haloperidol (N=13)													
Weight (kg)	64.1	8.1	64.0	7.9	64.4	7.3	64.2	7.3	64.2	7.6	0.2	4, 48	0.94
Body mass index (kg/m²)	22.2	3.0	22.2	3.0	22.3	2.7	22.3	2.7	22.3	2.7	0.2	4, 48	0.95
Leptin (ng/ml)	6.4	6.0	7.1	5.5	6.7	4.7	7.4	5.6	7.0	5.2	0.8	4, 48	0.54
No psychopharmacological treatment (N=12)													
Weight (kg)	69.7	11.1	69.4	11.2	69.3	11.4	69.3	11.6	69.1	11.4	0.7	4, 44	0.63
Body mass index (kg/m²)	23.5	2.4	23.4	2.4	23.3	2.4	23.3	2.5	23.3	2.4	0.9	4, 44	0.50
Leptin (ng/ml)	8.0	6.0	7.4	4.7	7.7	4.7	7.9	4.8	7.3	4.4	0.3	4, 44	0.86

[a] Statistically significant difference from baseline (test with contrast in MANOVA, $p<0.05$).

performed by tests with contrasts. As the nominal level of significance an alpha level below 0.05 was accepted and corrected according to Bonferroni for the post hoc tests. To account for baseline differences in weight, body mass index, and leptin level between groups, all values were divided by the mean at baseline for the respective treatment group before statistical analysis.

RESULTS

Analysis of variance revealed a significant overall treatment-by-time interaction (averaged Wilks's multivariate test of significance: $F=1.9$, df=36, 476, $p=0.001$). Weight ($F=4.4$, df=12, 160, $p<0.05$), body mass index ($F=4.6$, df=12, 160, $p<0.05$), and leptin plasma level ($F=2.3$, df=12, 160, $p<0.05$) all contributed significantly to this interaction term.

As can be seen from table 1, clozapine and olanzapine treatment significantly increased weight, body mass index, and plasma leptin level. In the clozapine-treated group, leptin plasma level was significantly increased from baseline already at the end of the first treatment week; effects on body mass index and weight were evident from the third week onward. In the patients treated with olanzapine, plasma leptin level, weight, and body mass index were significantly increased from baseline starting at the end of the second week of treatment. MANOVA did not reveal a significant difference between the clozapine- and olanzapine-treated patients in the time course of any of the variables assessed.

In the drug-free patients and those treated with haloperidol, weight, body mass index, and leptin level showed no significant changes across time. MANOVA did not reveal a significant difference between these two groups in the time course of any of the variables assessed.

DISCUSSION

The present study confirms that clozapine-induced weight gain is associated with an increase in circulating leptin level (3). Moreover, we showed that olanzapine has similar effects, whereas weight, body mass index, and leptin level remain stable in patients receiving haloperidol or no psychopharmacological treatment. Therefore, the increases in weight and leptin level induced by clozapine and olanzapine cannot be explained by dietary changes upon hospitalization.

It has been shown that 75% of patients treated with clozapine report an increased desire to eat, and some patients report binge eating (3), suggesting that overeating leads to weight gain. Although we did not gather the respective information in the present study, it is likely that overeating underlies olanzapine-induced weight gain as well. Hence, the most probable reason for clozapine- and olanzapine-induced increases in leptin levels are overeating and weight gain. These may be due to the drugs' effects on various neurotransmitter systems involved in the regulation of appetite (1–3). Alternatively, clozapine and olanzapine might reduce the feedback sensitivity of the CNS to the leptin signal, thus leading to a cascade of increased appetite, leptin secretion, and weight gain.

Apart from its involvement in the regulation of appetite, leptin has CNS effects such as blunting of stress responses (9). Because weight gain has some predictive value for a positive response to clozapine treatment (1, 10), it seems worthwhile to investigate leptin levels and psychopathology in parallel to test the hypothesis that leptin mediates the beneficial effects of neuroleptic treatment.

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Prevalence of Depressive Symptoms Early in the Course of Schizophrenia

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Objective: The rate of depressive symptoms early in the course of schizophrenia was determined. **Method:** Seventy subjects with recent-onset schizophrenia were followed for 5 years by using semistructured interview instruments. The initial assessment included ratings of each criterion A symptom of a DSM-III-R major depressive episode. The rates of symptoms experienced with at least moderate severity were calculated, and an algorithm based on DSM identified subjects meeting the criteria for a major depressive episode. **Results:** Four symptoms were present to at least a moderate degree in a majority of subjects, while no symptom was present in fewer than 12% of subjects. More than one-third of the subjects met the algorithmic criteria for a major depressive episode at the time of intake. **Conclusions:** Depressive symptoms are common early in the course of schizophrenia. This finding is consistent with other recent data and has potential implications for current diagnostic and treatment practices.

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The ability to distinguish schizophrenia from depression is perhaps most difficult early in the course of a schizophrenic illness. The prodrome of schizophrenia may resemble depression, and many symptoms used in the DSM-III-R and DSM-IV algorithms for a major depressive episode (e.g., anhedonia, concentration difficulties, psychomotor abnormalities, sleep disturbance) are nonspecific, being extremely common in schizophrenia as well (1). It is not surprising, therefore, that many patients who go on to develop schizophrenia "pass through" the diagnosis of a mood disorder early in their illnesses. This may also, in part, reflect a clinical bias, in the face of uncertainty, to diagnose depression in favor of schizophrenia because of the more favorable prognosis and response to treatment and the lesser stigmatization of affective illness (2, 3).

This inherent overlap of symptoms between depression and schizophrenia renders attempts to assess the prevalence, specificity, and predictive validity of those symptoms tautological. The ability to test the sensitivity and/or specificity of any phenomenological measure is constrained by the accuracy with which true "caseness" can be determined. As there are no definitive pathophysiological tests for either schizophrenia or mood disorder, we must settle for other measures to validate the diagnoses. Among the types of validators proposed by Robins and Guze (4), longitudinal course/outcome is arguably the most powerful and perhaps best proxy for true caseness in differentiating schizophrenia from mood disorders.

To determine, therefore, the prevalence of depressive symptoms in early schizophrenia, we analyzed subjects whose depressive symptoms had been objectively rated in the initial phase of the illness (often at a time when the diagnosis was unclear) and who went on to develop clear-cut schizophrenia as assessed at a prospective 5-year follow-up. We hypothesized that the DSM-III-R criteria A symptoms for a major depressive episode would be frequent early in the course of schizophrenia.

METHOD

The subjects were enrolled in a prospective longitudinal study of recent-onset psychosis, details of which have been described previously (5). This study recruits patients hospitalized for the first time for a psychotic disorder within the previous 5 years. The exclusion criteria include serious neurological illness or a primary diagnosis of substance abuse or dependence. Written informed consent was obtained from all subjects. Follow-up of more than 5 years has now been achieved for 70 subjects who received DSM-III-R or DSM-IV diagnoses of schizophrenia based on semistructured face-to-face diagnostic interviews at both 2- and 5-year follow-up. Of these 70 subjects, 54 were male and 16 were female; their average age at intake was 24.63 years (SD=5.23), and their average age at onset of illness was 20.36 years (SD=4.22).

At intake, the subjects were assessed with the Comprehensive Assessment of Symptoms and History (CASH) (6), which provides,

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among a wealth of other information, a detailed assessment of symptoms related to mood disorders. Each DSM-III-R criterion A symptom for a major depressive episode was rated on a 0–5 scale (0=not present, 1=questionable, 2=mild severity, 3=moderate, 4=severe, and 5=extreme). These symptoms include dysphoria, loss of interest or pleasure, altered appetite, insomnia or hypersomnia, psychomotor agitation or retardation, loss of energy, feelings of worthlessness and guilt, diminished concentration, and thoughts of death or suicide. The proportion of subjects experiencing each symptom with at least a moderate level of severity (rating of 3 or greater) at intake was calculated. To test whether each subject would have met the criteria for a depressive episode, we applied an algorithm based on DSM that requires the presence (rating of 3 or greater) of at least five of the nine symptoms, one of which had to be either dysphoric mood or loss of interest/pleasure.

Diagnostic conferences were held for each patient at index admission and at the 2- and 5-year follow-ups, with the primary purpose of establishing a consensus diagnosis. The clinical history was presented to a group of at least three research psychiatrists (including M.F., P.N., and N.C.A.) along with postdoctoral fellows, research nurses, and others. The patient was interviewed by one research psychiatrist, and time was left for questions from others for clarification. After the interview, each of the research psychiatrists independently filled out a form indicating his or her opinion of the diagnosis by DSM-III-R criteria, following which a discussion was held and a consensus diagnosis generated.

RESULTS

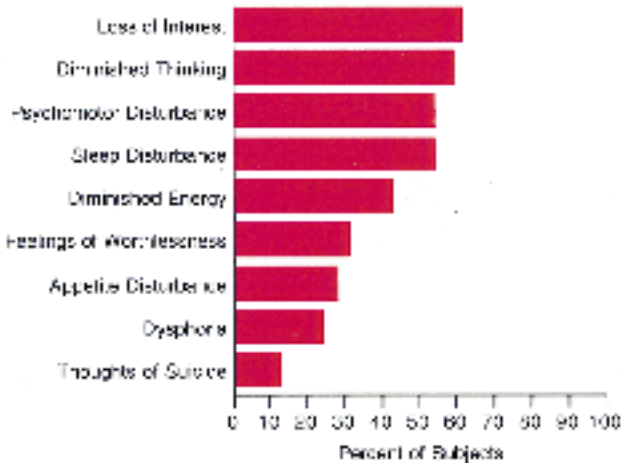
The rate of each depressive symptom at intake is shown graphically in figure 1. Four depressive symptoms were present to at least a moderate degree (rating of at least 3) in a majority of the subjects. These included loss of interest or pleasure (61.4%), concentration difficulties (60.0%), hypersomnia or insomnia (54.3%), and psychomotor agitation or retardation (54.3%). Diminished energy (42.9%), feelings of worthlessness (31.4%), dysphoric mood (24.3%), and appetite disturbance (28.6%) were also common. Twenty-four subjects (34.3%) met our algorithmic criteria for a major depressive episode at the time of intake.

DISCUSSION

In this 5-year prospective study of recent-onset schizophrenia, we found a high rate of depressive symptoms early in the course of illness. More than one-half of the depressive symptoms were present to a substantial degree in a majority of subjects, and even dysphoria, often used as a discriminator between the illnesses, was present in nearly 25% of the subjects. These data are consistent with findings from a number of other prospective studies that have examined this issue. Johnson (7) found nearly one-half of subjects with new-onset schizophrenia to be depressed. House et al. (8) identified depression in 22% (15 of 68) of first-episode subjects, and Koreen et al. (9) found that 75% of first-episode subjects had depressive symptoms when a liberal definition of depression was used and 22% when a more stringent definition was used.

The data also highlight the apparent nonspecificity of the current diagnostic criteria for depression versus early schizophrenia. More than one-third of the subjects who went on to develop clear-cut schizophrenia satisfied the algorithmic criteria for a major depressive episode at the time of their admission to the study. In accord with this and with the potential diagnostic bias mentioned at the outset of this paper, many of the subjects in this study were diagnosed with and treated extensively for depression before the diagnosis of schizophrenia finally "declared itself." Given the improved side effect profiles of newer antipsychotics and evidence suggesting a potentially detrimental effect of untreated psychosis (10), we suggest that this bias toward diagnosing affective disorder in the face of uncertainty may need to be reconsidered.

FIGURE 1. Percent of 70 Subjects With Recent-Onset Schizophrenia Who Experienced DSM Depressive Symptoms of at Least Moderate Severity at Intake



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B Lymphocyte Antigen D8/17 and Repetitive Behaviors in Autism

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Objective: Monoclonal antibody D8/17 identifies a B lymphocyte antigen with expanded expression in rheumatic fever, Sydenham's chorea, and subgroups of obsessive-compulsive disorder and Tourette's syndrome with repetitive behaviors. The authors examined the rate of D8/17 expression in children with autism and its correlation with severity of repetitive behaviors. **Method:** Blood samples from 18 patients with autism and 14 comparable medically ill children were evaluated for percentage of D8/17-positive B cells by immunofluorescence and for streptococcal antibodies. Severity of repetitive behaviors was also determined. **Results:** The frequency of individuals with ≥11% D8/17-positive cells was significantly higher in the autistic patients (78%) than the comparison subjects (21%), severity of repetitive behaviors significantly correlated with D8/17 expression, and D8/17-positive patients had significantly higher compulsion scores than D8/17-negative patients. **Conclusions:** D8/17 expression is high in patients with autism and may serve as a marker for compulsion severity within autism.

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Autism is a neurodevelopmental disorder that begins in infancy and is characterized by three distinct symptom dimensions: social deficits, speech and communication impairment, and repetitive behaviors and restricted interests (DSM-IV). The etiology, pathophysiology, and genetic transmission of autism are not known, but autism may be best understood as a heterogeneous disorder resulting from multiple genetic and environmental factors, often complicated by neurologic, cytogenetic, neurotransmitter, and immunologic abnormalities.

Recent studies of immunologic aspects of autism suggest that the disorder may have an autoimmune basis in a subset of patients. We previously described (1) how the disorder shares features of autoimmune diseases, including genetic susceptibility, association with viral infection, and immunologic dysfunction. A link between autism and autoimmune illnesses, such as rheumatoid arthritis, was first described in 1971 (2). Since then, investigators have described cellular and humoral dysfunction and abnormalities associated with complement and the major histocompatibility complex gene expression. Immune abnormalities include evidence of T cell activation, abnormality in the numbers and proportions of T cell subsets, abnormal B and T cell function in vitro, poor antibody production, low levels of IgG and IgA subclasses, abnormal cytokine levels in the sera, and a high frequency of the C4B null allele (1, 3–6). Clear evidence of autoimmunity is also present, since antibrain and antimyelin antibodies are found at high frequencies in the sera of autistic children (7, 8). In a preliminary study of autistic children who received intravenous immunoglobulin treatment, Gupta et al. (9) demonstrated immune system abnormalities at baseline and improvement in commu-

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nication and behavioral functions following treatment. However, this study did not use adequate behavioral assessment measures and requires replication in a controlled trial.

The monoclonal antibody D8/17 reacts with an antigen on at least 20% of the peripheral blood B cells of all rheumatic fever patients. In comparison subjects, the D8/17-positive B cells range from 0% to 7% (10). First-degree relatives of rheumatic fever patients demonstrate an intermediate percentage of D8/17-positive B cells. Expression of the D8/17 marker is low in patients with rheumatoid arthritis, multiple sclerosis, and systemic lupus erythematosus and in those with poststreptococcal glomerulonephritis, suggesting that D8/17 expression on a B cell is not solely the result of chronic autoimmune stimulation of B cell activation by an undefined streptococcal antigen. The function of this antigen and its role in the pathophysiology of rheumatic fever have not yet been established (11), although in Sydenham's chorea, which occurs in 10% of rheumatic fever patients, antibodies to group A β-hemolytic streptococcus cross-react with neuronal cells and cause repetitive behaviors.

Autoimmune findings have been demonstrated in obsessive-compulsive disorder (OCD) as well. Cross-sectional and longitudinal studies support a relationship among group A β-hemolytic streptococcal infections, positive antineuronal antibody titers, and neuropsychiatric dysfunction in a subgroup of children with OCD, tics, and Tourette's syndrome (12). Swedo et al. (13) and Murphy et al. (14) determined the frequency of D8/17 positivity in patients with childhood OCD and Tourette's syndrome by using an immunofluorescence assay. Both groups found significantly more peripheral B cells expressing D8/17 in the OCD patients than in healthy comparison subjects. These results suggest that D8/17 may serve as a marker for susceptibility among some forms of childhood-onset OCD and Tourette's syndrome. However, additional research is needed to determine the full impact of this finding in OCD. We have suggested (15) that if D8/17 levels are found to be correlated with repetitive behaviors as measured by the severity rating on the Yale-Brown Obsessive Compulsive Scale, there might be support for a dimensional approach to D8/17 mediation of compulsive symptoms and repetitive behaviors across traditional diagnostic boundaries.

In the current study, we hypothesized that D8/17 might serve as a marker for susceptibility to autism, especially for the repetitive behaviors present in autistic patients. Thus, our goals were 1) to compare a cohort of autistic subjects with comparable medically ill subjects on the prevalence of dichotomized D8/17 expression; 2) to correlate D8/17 expression with severity of repetitive behaviors in the autistic subjects; and 3) to compare the D8/17-positive and D8/17-negative autistic subjects with regard to severity of repetitive behaviors.

METHOD

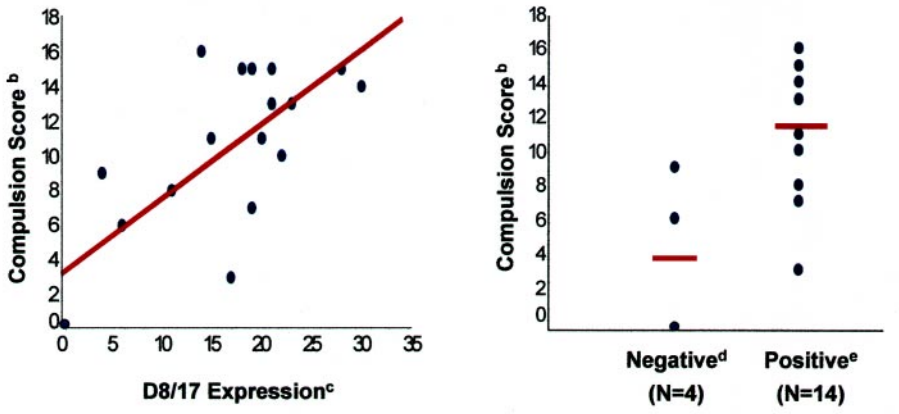
Eighteen children with autism (14 boys, four girls) ranging in age from 4 to 13 years (mean=6.9, SD=3.1) completed the protocol. They met the DSM-IV criteria for autistic disorder and were free of major comorbid psychiatric disorders. The DSM-IV diagnosis of autism for each of the 18 patients was made by semistructured interview by a psychiatrist who specializes in autism research (E.H. or C.C.). In addition, for nine of the subjects the diagnosis was confirmed by the Autism Diagnostic Interview (16), with complete agreement between the DSM-IV and Autism Diagnostic Interview diagnoses. The subjects' full-scale IQs ranged from 52 to 109 (mean=80, SD=20). Fourteen medically ill children (six boys, eight girls) ranging in age from 1 to 18 (mean=6.0, SD=4.6), who were comparable on socioeconomic, racial, and geographic factors, were used as comparison subjects. The illnesses in this group included surgery for small bowel resection, cardiac catheterization, asthma, sepsis, Kawasaki's disease, and polycystic kidney disease complicated by hypertension.

The Yale-Brown Obsessive Compulsive Scale (17), a clinician-administered 10-item questionnaire that uses 5-point scales to rate time spent, interference, distress, resistance, and control, was administered to assess the severity of repetitive thoughts and behaviors. It is a reliable and valid scale for severity of obsessions and compulsions, and the compulsion subscale reliably assesses compulsive and repetitive behaviors in autistic subjects and is sensitive to change in treatment studies (18). All patients and their parents gave written informed assent and consent, respectively, for participation in this study.

Heparinized blood for immunofluorescent studies was collected from the autistic subjects and comparison subjects on the same day and stored at room temperature for no more than 24 hours before the assay. Monoclonal antibody D8/17 is a mouse monoclonal IgM antibody originally prepared from fusions of spleen cells from mice repeatedly immunized with isolated B cells obtained from patients with rheumatic fever or rheumatic heart disease. The monoclonal antibody D8/17 was produced in the Laboratory of Clinical Microbiology and Immunology at Rockefeller University, and the immunofluorescent assay was run as described elsewhere (11, 19). In brief, by means of an indirect immunofluorescence assay, B cell staining was determined on fresh mononuclear cell preparations. The peripheral blood B cells were then stained with monoclonal antibody D8/17 and fluoresceinated antimouse IgM and counted with a fluorescent microscope. B cells were identified by using concomitant staining with phycoerythrin-conjugated monoclonal anti-DR human leukocyte antigen class II reagents. The results were expressed as the percentage of positive cells among 500 counted. All of the readings were done by an examiner blinded to subject status, and they were checked by another examiner for accuracy. On the basis of previous studies, a D8/17-positive case was defined as a value of one standard deviation above historical comparison values, i.e., ≥11% antigenic expression. The normal comparison mean values range from 0% to 7% (10). To assess for recent streptococcal infection, blood samples were collected and assayed for streptococcal antibodies (antistreptolysin-O and antiDNase B).

The results of the immunofluorescence assays were classified as negative (0%–10% D8/17 expression) or positive (≥11%). All tests of significance used the 0.05 level of significance and were two-sided. For goal 1, the proportion of positive expression, out of positive plus negative, was the estimate of the occurrence, and Pearson's chi-square test was applied. For goal 2, the autistic subjects' D8/17 assay value was correlated with their Yale-Brown Obsessive Compulsive Scale compulsion score by means of Pearson correlation. For goal 3, we compared the compulsion scores of the D8/17-negative and -positive autistic subjects, conservatively using the less significant of the pooled and separate variance estimate t tests.

FIGURE 1. Correlation Between Percentage of B Cells Positive for the D8/17 Monoclonal Antibody and Compulsion Score on the Yale-Brown Obsessive Compulsive Scale for 18 Autistic Children (left) and Compulsion Scores of D8/17-Positive and -Negative Patients (right)[a]



[a] Because of overlapping values, some points represent more than one subject.
[b] 0=none, 20=extreme.
[c] Significant correlation (r=0.73, df=16, p=0.001).
[d] "Negative": <11% cells positive.
[e] "Positive": ≥11% cells positive.

RESULTS

The autistic and medically ill groups did not significantly differ in age (t=0.62, df=22, p=0.54) or sex distribution (p=0.07, Fisher's exact test), and age did not significantly influence D8/17 level (r=0.23, df=16, p=0.35). Fourteen (77.8%) of the 18 autism subjects were positive for the D8/17 marker (≥11%) and four (22.2%) were negative (<11%). In contrast, three (21.4%) of the 14 comparison subjects were positive and 11 (78.6%) were negative for the marker. Thus, the autistic subjects were significantly more likely than the comparison subjects to be classified as D8/17 positive (Pearson χ^2=10.04, df=1, p=0.002).

Of interest, the severity of repetitive behaviors among the autistic children, as measured by the compulsion subscale of the Yale-Brown Obsessive Compulsive Scale, significantly positively correlated with D8/17 values (r=0.73, df=16, p=0.001), such that the autistic patients with greater compulsive/repetitive behavior had greater D8/17 antigen positivity (figure 1, left side). In contrast, there was no significant (or nearly significant) correlation between D8/17 value and score on the Autism Diagnostic Interview social (r=0.01) or communication (r=0.29) algorithm. When a dichotomous approach was used it was seen that the D8/17-positive autistic patients had a significantly higher mean Yale-Brown Obsessive Compulsive Scale compulsion score (mean=11.9, SD=3.8) than did the D8/17-negative patients (mean=3.7, SD=4.5) (t=3.29, df=4.29, p=0.03) (figure 1, right side). Thus, D8/17 positivity was associated with greater compulsive severity in children with autism, and the D8/17-positive patients had greater compulsive severity.

Only one (5.6%) of the 18 autistic subjects had a high antistreptolysin-O titer (≥200 IU/ml), and only four (22.2%) had high levels of antiDNase B (≥1:64 for preschool and ≥1:170 for school-age children; smaller ratio equals greater dilutional titer, which corresponds to higher antistreptococcal antibody level), suggesting that the majority of the autistic children had had no recent streptococcal exposure. The study subjects and their parents did not report any history of rheumatic fever.

DISCUSSION

The cause of autism is not known, although there is evidence of immunologic dysfunction in the disorder (1, 3–8). Monoclonal antibody D8/17 identifies a B cell antigen that denotes susceptibility to rheumatic fever (10). Recently, high levels of D8/17 have been documented in a subgroup of OCD patients (13, 14).

Our data demonstrate significantly greater expression of monoclonal antibody D8/17 in a subgroup of autistic children than in matched medically ill children. D8/17 has been proposed as a trait, rather than state, marker of rheumatic fever, and thus it has been suggested that D8/17 should be treated as a dichotomous variable (i.e., positive or negative) (20). However, the percentage of B cells positive for D8/17 may fluctuate with disease exacerbation (J.B. Zabriskie, personal communication), and severity of repetitive behavior in autism may fluctuate in response to antiobsessional treatment with serotonin reuptake inhibitors (21), suggesting that a continuous or dimensional approach to studying their relationship may be justified. Severity of repetitive behaviors as assessed by the compulsions

score on the Yale-Brown Obsessive Compulsive Scale strongly positively correlated with D8/17 expression. Alternatively, in a dichotomous approach, the D8/17-positive patients had significantly higher scores for repetitive behavior than did the D8/17-negative patients.

D8/17 antigen expression may represent a genetic vulnerability to autism and an environmental susceptibility to autism. The nature of the association between D8/17 positivity in autism and abnormal immune response to group A β-hemolytic streptococcal is unclear at this time. A major manifestation of rheumatic fever is Sydenham's chorea, in which antibodies to β-hemolytic streptococcal cross-react with neuronal cells and cause motoric and behavioral abnormalities, including obsessive-compulsive symptoms (13, 14), and autoantibodies directed against the caudate and subthalamic nuclei have been identified (22). D8/17 expression and red cell Na^+/H^+ antiporter activity were positively correlated in rheumatic fever patients in one study (23), and it was suggested that D8/17 may be associated with cation transport in cell membranes (23), not just of erythrocytes but perhaps of brain cells as well (24).

Our preliminary data suggest that the B cell alloantigen identified by the monoclonal antibody D8/17 may identify a subgroup of autistic subjects. Future research should examine whether antineuronal antibodies are involved in the pathogenesis of autism and should compare D8/17-positive and D8/17-negative autistic subjects for the presence of antineuronal antibodies, differences in familial transmission, and differential response to specific therapeutic strategies.

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Attitudes Toward DSM-IV Dissociative Disorders Diagnoses Among Board-Certified American Psychiatrists

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Objective: The authors assessed the opinions of American psychiatrists regarding the diagnostic status and scientific validity of the DSM-IV categories of dissociative amnesia and dissociative identity disorder. **Method:** A one-page questionnaire was mailed to a random national sample of 367 board-certified American psychiatrists. **Results:** Three hundred one responses were received—a rate of 82%. Only about one-third of respondents replied that dissociative amnesia and dissociative identity disorder should be included without reservations in DSM-IV; a larger proportion replied that these categories should be included only as proposed diagnoses. Only about one-quarter of respondents felt that diagnoses of dissociative amnesia and dissociative identity disorder were supported by strong evidence of scientific validity. **Conclusions:** Among board-certified American psychiatrists, there currently appears to be little consensus regarding the diagnostic status or scientific validity of dissociative amnesia and dissociative identity disorder.

(Am J Psychiatry 1999; 156:321–323)

The diagnostic categories of DSM-IV attempt to reflect "a consensus of current formulations of evolving knowledge in our field" (p. xxvii). Some diagnoses, such as premenstrual dysphoric disorder and binge eating disorder, do not meet DSM-IV standards for consensus and appear only as proposed diagnoses in appendix B (p. 703). But other diagnoses, including dissociative amnesia and dissociative identity disorder, attained official status in DSM-IV despite apparent controversy (1, 2). The official recognition of these diagnoses in DSM-IV is cited by some (3) as evidence that they are generally accepted within the field. What is the actual degree of consensus regarding dissociative amnesia and dissociative identity disorder today? To address this question, we surveyed a random national sample of board-certified American psychiatrists.

METHOD

We began by consulting the 1995 edition of *The Official ABMS Directory of Board-Certified Medical Specialists* (4), which contains more than 400 pages listing board-certified general psychiatrists alphabetically by state. We mailed a questionnaire, described later, to one psychiatrist on each page, who was selected by a prescribed formula (omitted here to preserve respondents' confidentiality). American psychiatrists practicing outside of the 50 states were excluded. Retired psychiatrists and psychiatrists with incomplete biographical information were replaced with the next available name. Individuals who failed to respond were sent second and third requests, the last by certified mail.

If a questionnaire was returned as undeliverable, we sought the individual's updated address in the 1998 edition of the directory. If the new address was in the same state, we mailed the questionnaire to the new address. If the individual had left the state or lacked a new address, we mailed the questionnaire to the next psychiatrist in that state, who met the previously described criteria, from the corresponding page of the 1998 directory. Some of these letters, in turn, were returned as undeliverable; we replaced these individuals by the same method.

The one-page questionnaire asked the respondent's principal professional activities, ranked by time spent; theoretical orientation; and authorship on published papers. The remaining four questions, shown in table 1, asked the respondent's opinions regarding the diagnostic status and scientific validity of dissociative amnesia and dissociative identity disorder. The accompanying cover letter was signed by only one investigator (A.J.G.) because she had published no papers related to dissociative disorders and was unknown to most respondents. We used the generic letterhead of McLean Hospital, a large institution including psychiatrists with diverse views, to further minimize response bias.

RESULTS

Of 406 questionnaires initially sent, 36 were returned as undeliverable despite two rounds of replacement. No receipt was received on three other questionnaires sent on the third round by certified mail. Thus,

Received April 3, 1998; revision received July 14, 1998; accepted Aug. 25, 1998. From the Biological Psychiatry Laboratory, McLean Hospital; and the Department of Psychiatry, Harvard Medical School, Boston. Address reprint requests to Dr. Pope, McLean Hospital, 115 Mill St., Belmont, MA 02178.

TABLE 1. Responses of 301 Board-Certified American Psychiatrists Regarding the Diagnoses of Dissociative Amnesia and Dissociative Identity Disorder

Question and Diagnosis	N	%	95% CI	N	%	95% CI	N	%	95% CI	N	%	95% CI
	Should not be included at all			*Should be included only with reservations*[a]			*Should be included without reservations*			*No opinion*		
If DSM-IV were to be revised today, how should it treat the diagnosis of												
Dissociative amnesia	27	9	6–12	143	48	42–53	104	35	29–40	27	9	6–12
Dissociative identity disorder[b]	45	15	11–19	128	43	37–48	106	35	30–41	22	7	4–10
	Little or no evidence of validity			*Partial evidence of validity*			*Strong evidence of validity*			*No opinion*		
In your opinion, what is the status of scientific evidence regarding the validity of												
Dissociative amnesia	56	19	14–23	145	48	43–54	69	23	18–28	31	10	7–14
Dissociative identity disorder	59	20	15–24	153	51	45–56	62	21	16–25	27	9	6–12

[a] The full text of this response option was, "Should be included only with reservations (e.g., only as a 'proposed diagnosis')."
[b] The full text of the first response option here was, "Should not be included at all (or included only as an 'iatrogenic' phenomenon)."

367 psychiatrists actually received a questionnaire. Of these, 301 responded—a rate of 82%. The 1998 directory showed that 219 (73%) of these were men, 165 (55%) were at least 50 years old, 261 (87%) were members of APA, and 193 (64%) held an academic appointment. Five respondents left the first three questions blank. Of the rest, 248 (84%) listed their principal activity as patient care, nine (3%) as research, seven (2%) as teaching, 28 (10%) as administration, and four (1%) as other. In addition, 119 (40%) rated their theoretical orientation as psychodynamic-psychoanalytic, 123 (41%) as biological, eight (3%) as cognitive-behavioral, and 46 (16%) as other. (On these questions, respondents who gave equal rank to two or more categories were classified as "other.") Finally, 136 (46%) reported having published no scientific papers, 106 (36%) one to nine papers, and 54 (18%) 10 or more papers.

In response to the questions about dissociative amnesia and dissociative identity disorder (table 1), only about a third of respondents replied that these diagnoses should be included without reservations in DSM-IV; the modal response was that they should be included only as proposed diagnoses. Respondents also showed little consensus on the scientific validity of dissociative amnesia and dissociative identity disorder.

We performed logistic regression to assess the association (by using the likelihood ratio test) between acceptance of dissociative amnesia or dissociative identity disorder (favoring inclusion of the diagnoses without reservations or claiming strong evidence of validity) and gender, age (45 or younger, 46–54, and 55 or older), APA membership, an academic appointment, principal activity (patient care versus all others), theoretical orientation (psychodynamic versus biological versus other), and publications (none versus any). None of these univariate associations approached statistical significance, except those involving theoretical orientation. Psychodynamic psychiatrists were more likely than biological psychiatrists to reply that dissociative amnesia should be included in DSM-IV without reservations (44% versus 30%) (Wald test χ^2=4.23, df=1, p=0.04), that dissociative amnesia was supported by strong evidence (31% versus 20%) (χ^2=3.93, df=1, p=0.05), that dissociative identity disorder should be included in DSM-IV without reservations (46% versus 28%) (χ^2=6.97, df=1, p=0.008), and that dissociative identity disorder was supported by strong evidence (32% versus 14%) (χ^2=9.40, df=1, p=0.002). The responses of the "other" group were primarily intermediate between those of the psychodynamic and biological psychiatrists; there were no significant differences (p>0.05) between the other group and either psychodynamic or biological psychiatrists.

We also used step-up and step-down multivariate procedures to assess which combination of the predictor variables yielded the most parsimonious model. Both procedures kept only theoretical orientation in the final model, suggesting that the results of the univariate analyses presented earlier were not influenced in any important ways by the other predictor variables.

DISCUSSION

We sought to assess current opinion regarding the nosological status and scientific validity of dissociative amnesia and dissociative identity disorder in a national sample of board-certified American psychiatrists. In this group, we found little consensus on these issues. In an analysis of the attributes of respondents, only theoretical orientation appeared significantly associated with acceptance of dissociative disorders; psychodynamic psychiatrists were more likely than biological psychiatrists to endorse dissociative amnesia and dissociative identity disorder.

We should consider several methodological issues. First, serious bias seems unlikely, since our methods would be expected to yield a random sample of board-

certified psychiatrists. In addition, given the high response rate of 82%, even possible differences in attitudes among nonresponders would only modestly change the results. Second, the findings are unlikely due to chance, as evidenced by the 95% confidence intervals shown in table 1.

Finally, there is the question of whether board-certified American psychiatrists represent an appropriate source population for judging consensus. On the one hand, it might be suggested that our population is too narrow and should include all psychiatrists or even all mental health professionals. For example, one study (5) surveyed a range of professionals, from clinical social workers to Ph.D. psychologists (but not psychiatrists), and found a similar divergence of views on dissociative disorders. An earlier study (6) found that 75% of Veterans Administration psychiatrists and 83% of psychologists "believed in" multiple personality disorder, but the response rate in that survey was only 31%, raising the possibility of selection bias.

Alternatively, it might be suggested that our population is too broad and should include only leading experts, such as those in the DSM-IV Work Group on dissociative disorders. However, the latter definition of consensus seems narrower than envisioned by DSM-IV, which states, "We took a number of precautions to ensure that the Work Group recommendations would reflect the breadth of available evidence and opinion and not just the views of the specific members . . . . members were instructed that they were to participate as consensus scholars" (p. xv).

In any event, our findings suggest that DSM-IV fails to reflect a consensus of board-certified American psychiatrists regarding the diagnostic status and scientific validity of dissociative amnesia and dissociative identity disorder. This finding is perhaps not surprising, given the existing evidence of controversy surrounding these disorders. This evidence includes the growing literature acknowledging this controversy (1, 2, 7), the recent closure of several major dissociative disorders treatment units, the sharp shifts in the features of these disorders as described in successive editions of DSM, and published arguments that dissociative amnesia and dissociative identity disorder lack the degree of empirical support normally required for most other entities in DSM-IV (8, 9).

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Are Psychiatrists Cost-Effective? An Analysis of Integrated Versus Split Treatment

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Objective: Managed care organizations prefer putatively less expensive split treatment, i.e., a psychopharmacologist plus a non-M.D. psychotherapist. In this study the cost of integrated care by a psychiatrist was compared with split care. **Method:** Using 1998 fee schedules of seven large managed care organizations (with 54.3% market share and 67.8 million lives) plus Medicare (37 million people), the author modeled clinical scenarios of psychotherapy alone, medication alone, and combined treatment provided by a psychiatrist or split with a psychologist or social worker. **Results:** Brief psychotherapy by a social worker was the least expensive treatment. When treatment required both psychotherapy and medication, combined treatment by a psychiatrist cost about the same or less than split treatment with a social worker psychotherapist; it was usually less expensive than split treatment with a psychologist psychotherapist. **Conclusions:** The integrated biopsychosocial model practiced by psychiatry is both theoretically and economically the preferred model when combined treatment is needed.

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Recently, medicine and managed care organizations have embraced the primary care model, with its increased emphasis on psychological factors, behavioral health, and lifestyle issues and its belief that this biopsychosocial treatment should be provided by a single physician as opposed to the fragmented care received in the past from several specialists. In contrast, the only mental health practitioner who can provide comprehensive biopsychosocial care, i.e., the psychiatrist, is being replaced by fragmented care (psychotherapist-psychopharmacologist split).

It has been reiterated that the driving force behind managed care and health care reform is cost, cost, and cost. To reduce costs, patients who require psychotherapy and medication combined are preferentially assigned to split treatment. Also, psychiatrists are often replaced with family doctors, who are less expensive but miss diagnoses, undertreat with low doses and short time periods, and do not offer psychotherapy (1, 2). Poor treatment has its economic and human misery costs (3), and therefore, this option will not be considered further in this analysis.

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The theory and practice of optimal psychiatric care militate against the split treatment model, but is it less expensive than integrated care? This question was tested by using data from current managed care schedules.

METHOD

I collected 1998 payment schedules (received unsolicited or by direct request) from seven large managed care organizations with a combined 1996 market share of 54.3% and 67.8 million lives. These organizations, and their respective 1996 ranks, market shares, and numbers of lives covered, are as follows (4): Value Behavioral Health (1, 19.4%, 24.2 million), Merit Behavioral Care (3, 12.2%, 15.3 million), Green Spring Health Services (4, 10.0%, 12.4 million), U.S. Behavioral Health (6, 5.0%, 6.2 million), MCC Managed Behavioral Care (8, 4.1%, 5.2 million), Options Health Care (11, 2.2%, 2.7 million), and CMG Health (15, 1.4%, 1.8 million). Medicare, which covered another 36.9 million lives in 1996, was also included. Based on median rates, the costs for the following treatment scenarios were calculated.

1. Five, 10, and 15 psychotherapy sessions (initial evaluation plus 50-minute sessions) with a psychiatrist, psychologist, or social worker.

2. Three, five, and 10 medication visits (initial evaluation plus 20-minute visits) with a psychiatrist.

3. Psychotherapy and medication provided by a psychiatrist (integrated) or split between a psychiatrist and psychologist or social worker, as follows

   a. Fifteen psychotherapy sessions and 10 medication visits.

   b. Ten psychotherapy sessions and five medication visits.

   c. Five psychotherapy sessions and three medication visits.

RESULTS

The results are presented in table 1.

TABLE 1. Costs for Various Scenarios of Mental Health Treatment Provided by a Psychiatrist or by a Psychiatrist Plus Psychologist or Social Worker[a]

Variable	Cost (dollars)		
		Psychotherapy Provided by Psychologist (Ph.D.) or Social Worker (M.S.W.)	
	Psychiatrist (M.D.)	Psychologist	Social Worker
Fees			
Evaluation			
Median	106	73	60
Range	92–144	65–124	60–100
50-minute session			
Median	88	70	60
Range	70–104	55–89	50-70
Medication follow-up			
Median	43		
Range	38–60		
Psychotherapy only[b]			
15 sessions	1,331	1,053	898
10 sessions	893	703	598
5 sessions	456	353	299
Medication management only[b]			
10 visits	494		
5 visits	278		
3 visits	192		
Psychotherapy plus medication management[b,c]			
15 therapy sessions, 10 medication visits	1,331	1,547	1,392
10 therapy sessions, 5 medication visits	893	981	877
5 therapy sessions, 3 medication visits	456	544	491

[a] Based on 1998 data. The rates were provided by seven managed care organizations (see text) and Medicare.
[b] Each scenario includes the cost of an initial evaluation visit.
[c] Costs for treatments involving a psychologist or social worker include the cost of medication management by a psychiatrist.

DISCUSSION

When both medication and psychotherapy are indicated, a patient is best and most cost-effectively served by a psychiatrist providing both treatment modalities. For instance, compared to $981 for split treatment by a psychiatrist plus psychologist (five medication visits and 10 psychotherapy sessions), it costs $893 (or $88 less) for a psychiatrist integrating the two modalities. In addition, with the psychiatrist the patient makes only 10 "doctor visits" (versus 15 in split treatment), has to deal with only one person (versus two), has medication monitored at each of the 10 visits (versus five), and pays $88 less. All of these advantages hold true in the comparison with split treatment involving a social worker therapist, for which the additional cost over integrated treatment is $16. When time away from work or child care plus the expense and time of traveling are factored in, the cost-benefit analysis favors integrated care from a psychiatrist even more.

For patients who require more intensive treatment, integrated care by a psychiatrist remains economically advantageous. Fifteen psychiatrist visits for integrated care cost $1,331, compared to $1,547 for split treatment with a psychologist or $1,392 for a social worker, both of which are higher, by $216 and $61, respectively.

A recent study (5) of one managed care organization supports these findings. Of 1,517 depressed patients followed over 18 months, those "receiving integrated treatment used significantly fewer outpatient sessions and had significantly lower treatment costs" than patients in split treatment ($1,336 versus $1,854).

Sparsely monitored medication management (three or five visits) was the least expensive modality ($192 and $278, respectively) and is increasingly favored by managed care organizations (6). However, when medication costs (for example, approximately $720 per year for the newer antidepressants) are added in, treatment with medication alone becomes more expensive than short-term psychotherapy alone by a social worker ($299 for five sessions, $598 for 10 sessions).

Further research is required to differentiate a priori the patients who will respond to brief psychotherapy alone versus combined treatment. For instance, Thase et al. (7) suggested that depressed patients with Hamilton Depression Rating Scale scores over 20 did better with medication than either cognitive or interpersonal therapy. Such patients should be referred to a psychiatrist for antidepressant therapy with optional adjunctive psychotherapy. However, managed care organizations preferentially refer all patients to nonpsychiatrist therapists first, with the option of a medication evaluation later (5). This may delay effective treatment. In clinical practice, although guidelines suggest that depressed patients not responding adequately to psychotherapy within 3 months should be referred for medication evaluation (8), one study (9) showed that this referral actually took place after 6–14 months.

The data in this study suggest that the split model currently promoted by managed care organizations and health maintenance organizations and projected as the future of psychiatry is theoretically and economically unsound. However, this narrow definition of a psychiatrist, i.e., one who prescribes psychotropic medication in 15-minute blocks and does no psychotherapy, has been widely accepted and used to estimate future manpower needs (10, 11). Estimates should be revised with the assumption that psychiatrists provide psychotherapy as a part of integrated treatment to large numbers of seriously ill patients, which is precisely what is occurring today (6).

Acceptance of the integrated model as the future of psychiatric practice would also require residency training programs to continue teaching psychotherapy, with a new focus on the time-effective, cost-effective specific

forms (e.g., cognitive behavioral therapy, interpersonal therapy).

Payment schedules vary by year, region, managed care organization, and even plans within a managed care organization. The small group of 1998 rates in central New York used in this study is therefore merely illustrative. Further, the treatment scenarios used were arbitrary in their mix of number and type of sessions, but I attempted to reflect reasonable current treatment patterns. Studies of randomized assignment to integrated or split treatment with quantitative data on treatment effectiveness and cost-efficiency are needed. If findings of such studies supported the cost-effectiveness of integrated treatment, psychiatry could vigorously advocate the integrated biopsychosocial model on both theoretical and economic grounds.

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