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CME Objectives

After completing this CME activity, the psychiatrist should be able to:

- Summarize the various hypotheses about the natural grouping of schizoaffective disorder
- Compare the clinical characteristics that were found in samples of patients with schizoaffective disorder, with schizophrenia but without a concomitant mood disorder, and with nonpsychotic major depression
- Describe the differences on neuropsychological assessments that were found between samples of patients with schizoaffective disorder, with schizophrenia but without a concomitant mood disorder, and with nonpsychotic major depression

Statement of Need and Purpose

Physicians responding to articles in *The Journal of Clinical Psychiatry* and its related CME activities have indicated a need to know more about the diagnostic status of schizoaffective disorder. The purpose of this CME enduring material is to present the results of a study that addresses this need. There are no prerequisites for participating in this CME activity.

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None of the authors of this article has significant commercial relationships to disclose relative to the presentation.

Schizoaffective Disorder: A Form of Schizophrenia or Affective Disorder?

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Background: The diagnostic status of schizoaffective disorder continues to be controversial. Researchers have proposed that schizoaffective disorder represents a variant of schizophrenia or affective disorder, a combination of the 2, or an intermediate condition along a continuum between schizophrenia and affective disorder.

Method: We compared outpatients aged 45 to 77 years with DSM-III-R diagnosis of schizoaffective disorder (N = 29), schizophrenia (N = 154), or nonpsychotic mood disorder (N = 27) on standardized rating scales of psychopathology and a comprehensive neuropsychological test battery. A discriminant function analysis was used to classify the schizoaffective patients based on their neuropsychological profiles as being similar either to schizophrenia patients or to those with nonpsychotic mood disorder.

Results: The schizoaffective and schizophrenia patients had more severe dyskinesia, had a weaker family history of mood disorder, had been hospitalized for psychiatric reasons more frequently, were more likely to be prescribed neuroleptic and anticholinergic medication, and had somewhat less severe depressive symptoms than the mood disorder patients. The schizophrenia patients had more severe positive symptoms than the schizoaffective and mood disorder patients. The neuropsychological performances of the 2 psychosis groups were more impaired than those of the nonpsychotic mood disorder patients. Finally, on the basis of a discriminant function analysis, the schizoaffective patients were more likely to be classified as having schizophrenia than a mood disorder.

Conclusion: These findings suggest that schizoaffective disorder may represent a variant of schizophrenia in clinical symptom profiles and cognitive impairment.

(J Clin Psychiatry 1999;60:874–882)

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Supported, in part, by grants 5 P30 MH49671, 5 R37 MH43693, and 5 P30 MH49671-01S1 from the National Institute of Mental Health (Dr. Jeste); by VA San Diego Healthcare System; and by a Young Investigator Award from the National Alliance for Research on Schizophrenia and Depression (Dr. Paulsen).

Portions of this work were presented at the 35th annual meeting of the American College of Neuropsychopharmacology, December 9–13, 1996, San Juan, Puerto Rico.

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Kraepelin[1] initially classified schizophrenia and mood disorder as separate disease entities, and contemporary clinical practice and classification systems continue to do so. The diagnosis of schizoaffective disorder has, however, remained both a clinical and a scientific conundrum. Some investigators have concluded that the disorder represents a variant of either schizophrenia or mood disorder,[2] whereas others consider it to be on a continuum of illness intermediate between schizophrenia and mood disorder.[3–5] Lapierre[6] proposed that, over time, schizoaffective disorder becomes a subtype of either schizophrenia or mood disorder (i.e., schizoaffective disorder is not a true clinical syndrome, but represents a phenotypic variation of either schizophrenia or mood disorder). Consequently, at least 5 hypotheses regarding the status of schizoaffective disorder have been proposed: (1) schizoaffective disorder patients have "true" schizophrenia, with incidental affective symptoms; (2) schizoaffective disorder patients have "true" mood disorder, with incidental schizophrenia symptoms; (3) schizoaffective disorder patients are heterogeneous, some having true schizophrenia and others true mood disorder; (4) schizoaffective disorder patients have

coexisting schizophrenia and mood disorder; or (5) schizoaffective disorder is intermediate between schizophrenia and mood disorder.[7,8]

Some recent investigations[9,10] have assessed the diagnostic validity of schizoaffective disorder as defined by DSM-III-R.[11] Maj et al.[9] examined the risks for schizophrenia and mood disorder among first-degree relatives of schizoaffective disorder patients (depressed type) compared with patients with schizophrenia, psychotic depression, or nonpsychotic depression. These authors noted that the relatives of the schizoaffective disorder group had the same risk of schizophrenia as those of the schizophrenia group. An earlier study of the relatives of patients with chronic schizoaffective disorder and schizophrenia also revealed no difference in the relatives' risk of schizophrenia. In addition, a similar incidence of mood disorder (both bipolar and unipolar) was found in relatives of probands of both groups (schizoaffective disorder and schizophrenia).[12] Taken together, these findings support the notion that schizoaffective disorder corresponds closely to schizophrenia.

Different conclusions were suggested by one recent study[10] that examined the clinical features, outcome, and familial psychopathology among schizoaffective disorder patients compared with patients with schizophrenia or mood disorder. Results showed that schizoaffective disorder patients differed significantly from both schizophrenia and mood disorder patients. Specifically, although schizoaffective disorder patients had positive psychotic symptoms similar to schizophrenia patients, the schizoaffective disorder patients had a greater number of affective symptoms, fewer negative symptoms, and a better global course and outcome than did the schizophrenia patients. Furthermore, relatives of probands with schizoaffective disorder had higher rates of schizophrenia compared with mood disorder probands. These authors concluded that schizoaffective disorder was a syndrome that differed meaningfully from both schizophrenia and mood disorder, according to DSM-III-R criteria. This finding of better global outcome among schizoaffective disorder patients compared with schizophrenia patients was also seen in a Scandinavian study[13]; however, a diagnosis of mood disorder or the presence of mood symptoms in addition to a psychotic illness was associated with a more favorable outcome relative to a primary diagnosis of a psychotic disorder among all patients.

Bertelsen and Gottesman[14] reviewed the literature relevant to genetic predisposition to schizoaffective disorder. Results from family, twin, and adoption studies were somewhat divergent, but generally supported the concept that schizoaffective disorder was either a phenotypic variation or an expression of a genetic interform between schizophrenia and mood disorder. Kendler et al.[4] also examined the notion of an underlying continuum of liability to the "schizophrenia spectrum" of illness and concluded that schizoaffective disorder lay along a continuum of a range of disorders that varied in severity.

In an effort to discriminate affective from psychotic illness, Taylor and Amir[15] examined similarities and differences between DSM-III–diagnosed[16] schizoaffective disorder or schizophrenia patients and mood disorder patients on the basis of ratings of psychopathology. Results differentiated chronic schizophrenia from mood disorder patients, but schizoaffective disorder patients overlapped with both groups. The schizoaffective disorder patients with unipolar depression more closely resembled the schizophrenia patients, while the schizoaffective disorder patients with bipolar depression were more similar to the mood disorder group.

Some work has been done to compare the patterns of neuropsychological performance among schizoaffective disorder and schizophrenia patients. Bornstein and colleagues[17] examined the pattern of cognitive deficit among paranoid and nonparanoid schizophrenia patients as well as schizoaffective disorder patients compared with that of an age-matched healthy control group. The nonparanoid schizophrenia group had the greatest neuropsychological impairment, whereas the paranoid schizophrenia and schizoaffective disorder patients had a similar level of cognitive impairment. Other research suggests that frontal and/or subcortical dysfunction is common in both schizoaffective disorder and schizophrenia patients and that both groups exhibit comparable levels of deficits on tests of global mental status, attention, problem solving, and verbal and nonverbal fluency.[18] Recent work in our Clinical Research Center at the University of California, San Diego, has documented that the overall levels of psychopathology and cognitive impairment in patients with psychotic depression are similar to those in schizophrenia patients but greater than those in nonpsychotic depressed patients.[19]

In summary, the literature supports varying hypotheses regarding the natural grouping of schizoaffective disorder, since the syndrome has similarities to both schizophrenia and mood disorder. The purpose of the present investigation was to examine clinical and neuropsychological characteristics of schizoaffective disorder patients in relationship to samples of schizophrenia patients without a concomitant mood disorder and a mood disorder group who did not have psychotic symptoms.

METHOD

Subjects

Patients were recruited from the San Diego Veterans Affairs Medical Center; the University of California, San Diego, Medical Center; the San Diego County Mental Health Services; and private physicians to participate in our Clinical Research Center. Our Center focuses primarily on middle-aged and elderly patients with schizophrenia. We used data from all 29 available outpatients with schizoaffective disorder and then selected 154 of the 256 available schizophrenia patients as well as 27 of 32 available nonpsychotic mood disorder patients who were comparable in age to the schizoaffective disorder patients (age range, 45–77 years). The schizophrenia sample comprised mainly patients with the paranoid subtype (N = 86; 55.8%). Eight schizoaffective disorder patients were considered to have depressed subtype, 13 were diagnosed as having bipolar subtype, and subtype could not be determined in the remaining 8 patients. Of the mood disorder patients, 15 were diagnosed with major depressive disorder and the remaining 12 as having bipolar disorder. All subjects gave written informed consent after the procedures involved in the study were described to them.

The details of the evaluation procedures have been described previously.[19] Briefly, all the subjects were screened with a medical history questionnaire and with physical and appropriate laboratory examinations to exclude those with the following: (1) history of significant head trauma (i.e., head injury with loss of consciousness greater than 30 minutes); (2) other major neurologic disorder (e.g., dementia or seizure disorder); (3) current alcohol or other substance abuse or dependence meeting DSM-III-R[11] criteria; or (4) systemic medical disease severe enough to require recent hospitalization. Psychiatric diagnosis based on DSM-III-R[11] was established with the Structured Clinical Interview for DSM-III-R (SCID),[20] administered by trained geriatric psychiatrists or psychologists. The patients were reevaluated with the SCID annually ("blind" to previous SCID diagnosis) to reassess their psychiatric diagnoses over a mean period of 4 years. None of the patients selected for this study exhibited such a change in the symptom picture over the course of the follow-up period that a change in the diagnosis was warranted.

Clinical Evaluation

Neurologic, other medical, and socioeconomic histories were obtained, and physical examinations were performed by staff physicians. The current daily neuroleptic dose was converted to milligrams of chlorpromazine equivalents (CPZ)[21] and the anticholinergic dose was converted to milligrams of benztropine equivalents (BNZ).[22] Family history of psychosis or mood disorder was defined as having any blood relative with that disorder.

The following rating scales were used: the Brief Psychiatric Rating Scale (BPRS),[23] the Hamilton Rating Scale for Depression (HAM-D),[24] and the Abnormal Involuntary Movement Scale (AIMS).[25] These assessments were performed by members of the research team who were not treating the patients, and the raters were kept "blinded" or "masked" to other clinical (including diagnosis) and neuropsychological information. The interrater reliability (intraclass correlation coefficients) ranged from .77 to .89.

Neuropsychologic Assessment

The subjects were administered a comprehensive neuropsychological test battery[26,27] consisting of the core Halstead-Reitan Battery,[28] the Wechsler Adult Intelligence Scale-Revised (WAIS-R),[29] the Wisconsin Card Sorting Test,[30] the California Verbal Learning Test (CVLT),[31] the Digit Vigilance Test,[26] the Boston Naming Test,[32] the Grooved Pegboard Test,[33] the Benton Controlled Oral Word Association Test (FAS),[34] the Story Memory Test,[26] and the Figure Memory Test.[26]

The individual test measures that contributed to the assessment of each of 7 major ability areas were as follows:

1. Verbal Ability: Aphasia Screening Test verbal score,[28] WAIS-R vocabulary, Boston Naming Test, WAIS-R similarities, Thurstone Written Fluency,[26] and total correct on FAS.
2. Psychomotor Speed: Part A of the Trailmaking Test,[28] WAIS-R object assembly, WAIS-R digit symbol, WAIS-R block design, Tactual Performance Test (total time),[28] and Digit Vigilance Test (time).
3. Abstraction/Cognitive Flexibility: Booklet Category Test,[35] Part B of the Trailmaking Test,[28] and Wisconsin Card Sorting Test (perseverative responses).
4. Attention: WAIS-R digit span and Digit Vigilance Test (errors).
5. Learning and Incidental Memory: CVLT (trials 1–5), Figure Memory Test (learning), and Story Memory Test (learning).
6. Retention: CVLT long delayed recall, Figure Memory Test delayed recall, and Story Memory Test delayed recall.
7. Motor Skills: Finger Tapping Test (dominant and nondominant hands),[28] Grooved Pegboard Test

(dominant and nondominant hands), and hand dynamometer (dominant and nondominant hands).

All the raw scores on the neuropsychological tests were converted to age-, education-, and gender-corrected T-scores.[26,31,36,37] In normal subjects, the T-scores are normally distributed with a mean of 50 and a standard deviation of 10. A T-score cutoff of 40 has been found to provide maximum discrimination between large samples of subjects with versus those without documented brain lesions.[26] Mean area T-scores for the entire test battery and for the 7 major ability areas were calculated.[38] In addition, a global mean T-score was computed (sum of all available test scores divided by the total number of tests) for each subject.

Statistical Analysis

To correct for a lack of normal distribution of scores among groups, log transformations were performed on the BPRS subscale and total scores and the AIMS total score prior to parametric analyses. For purposes of clarity, nontransformed data are presented in the Results section.

Categorical data were compared using chi-square tests. If the overall Pearson chi-square test was significant for the 3 groups, it was followed up by pairwise comparisons using Ryan's procedure to protect for the overall number of comparisons being made.[39,40]

Separate omnibus multivariate analysis of variance (MANOVA) tests were performed on the following demographic and clinical variables: (1) age and years of education; (2) age at onset of illness and duration of illness; (3) BPRS, HAM-D, and AIMS total scores; and (4) BPRS subscale scores. If the multivariate F value was significant, it was followed up with multivariate comparisons to test for pairwise differences between groups. The accompanying p values are presented in Tables 1 through 3. Univariate analyses of variance (ANOVAs) were performed on the global neuropsychological T-score and on daily doses of neuroleptics, anticholinergics, antidepressants, and lithium. If the ANOVAs were significant, they were followed up with Tukey post hoc tests.

Analysis of the mean neuropsychological T-scores (except for the global T-score) was conducted using a profile MANOVA to determine if there were significant differences among the 3 groups across cognitive domains. If a significant interaction of group by cognitive domain was noted, it was followed up with univariate ANOVAs. If individual domain ANOVAs were significant, they were followed up by conservative ($p < .01$) multiple comparison procedures. Finally, a discriminant function analysis was performed to examine the degree to which cognitive performance could correctly classify individual subjects as having schizoaffective disorder, schizophrenia, or mood disorder.

Given the different sample sizes among the 3 groups, separate analyses were done with an age-, gender-, and education-matched subsample (N = 27 each) of patients to determine if the pattern of results would be similar to that found with the larger sample.

RESULTS

Clinical Variables

Demographic and clinical information on the groups is presented in Table 1. The omnibus MANOVA for age and education did not reach significance ($F = 2.29$, $df = 4,412$; $p = .06$), indicating that the 3 groups were fairly similar in these demographic characteristics. The subjects were predominately male and white, with a greater proportion of mood disorder patients being white relative to the other 2 groups. The omnibus MANOVA on age at illness onset and duration of illness was significant ($F = 2.40$, $df = 4,394$; $p = .050$), as was the follow-up test on age at onset; the mood disorder patients had a later age at illness onset relative to the schizoaffective disorder and schizophrenia patients.

Significant group differences were noted in treatment regimens. More schizoaffective disorder and schizophrenia patients compared with mood disorder patients were taking neuroleptics and anticholinergics, whereas more mood disorder and schizoaffective disorder patients were taking lithium compared with schizophrenia patients. There were no significant differences, however, in the proportion of patients receiving antidepressants. For those patients within each diagnostic group who were prescribed neuroleptics, anticholinergics, or lithium, no significant differences in the current daily doses were noted.

Table 2 presents clinical comparisons of the 3 patient groups on ratings of psychopathology and other clinical variables. The omnibus MANOVA on the BPRS, HAM-D, and AIMS total scores was significant ($F = 7.85$, $df = 6,284$; $p < .0001$). Follow-up comparisons found that mood disorder patients had higher HAM-D scores compared with schizoaffective disorder and schizophrenia patients. In addition, the mood disorder patients had lower levels of tardive dyskinesia, as measured by the AIMS, compared with both schizoaffective disorder and schizophrenia patients. No significant differences were noted in the BPRS total score. In examining the BPRS subscale scores, the omnibus MANOVA was significant ($F = 4.82$,

Table 1. Demographic and Clinical Comparison of the 3 Patient Groups[a]

Variable	SA (N = 29)	SC (N = 154)	MD (N = 27)	χ^2	F	p Value	Group Effects
Age, y	57.3 ± 9.8	58.9 ± 8.9	61.4 ± 10.5		1.40	.25	
Education, y	13.1 ± 2.4	12.3 ± 2.6	13.4 ± 3.1		2.79	.06	
Gender, N (%) male	23 (79.3)	110 (71.4)	19 (70.4)	0.82		.66	
Ethnicity, N (%) white	21 (72.4)	116 (75.3)	26 (96.3)	6.34		.04	SA, SC < MD
Age at onset of illness, y	30.5 ± 12.0	34.4 ± 15.1	42.2 ± 16.0		4.22	.016	SA, SC < MD
Duration of illness, y	26.6 ± 13.4	24.6 ± 15.1	19.9 ± 15.9		1.40	.25	
History of previous psychiatric hospitalization, N (%)[b]	14 (87.5)	73 (76.8)	7 (38.9)	13.00		.002	SA, SC > MD
Positive family history of SA or SC, N (%)[b]	3 (18.8)	12 (12.6)	3 (16.7)	0.55		.76	
Positive family history of MD, N (%)[b]	2 (12.5)	17 (17.9)	9 (50.0)	10.1		.006	SA, SC < MD
Currently on neuroleptic treatment, N (%)	20 (69)	103 (66.9)	8 (29.6)	14.21		.00	SA, SC > MD
Daily neuroleptic dose, mg CPZe[c]	784 ± 1900	515 ± 1221	62.5 ± 210		2.34	.10	
Currently on anticholinergic treatment, N (%)	10 (34.5)	54 (35.1)	0 (0.0)	13.59		.00	SA, SC > MD
Daily anticholinergic dose, mg BNZe	2.3 ± 3.9	1.9 ± 3.5	0.0 ± 0.0		4.30	.02	SA, SC > MD
Currently on lithium treatment, N (%)[b]	6 (37.5)	3 (3.2)	4 (22.2)	21.7		< .0001	SC < SA, MD
Daily lithium dose, mg	1478 ± 661	1100 ± 755	710 ± 512		2.15	.16	
Currently on antidepressant treatment, N (%)	3 (10.3)	12 (7.7)	5 (18.5)	2.96		.23	

[a]Values for continuous variables shown as mean ± SD; other values shown as N (%). Abbreviations: BNZe = benztropine equivalents,[41] CPZe = chlorpromazine equivalents, MD = mood disorder, SA = schizoaffective disorder, SC = schizophrenia.
[b]Total Ns: SA = 16, SC = 95, MD = 18.
[c]Because of the wide variability in neuroleptic dose, the median CPZe amounts for the 3 groups were as follows: SA = 162 mg/day, SC = 137 mg/day, and MD = 0 mg/day.

Table 2. Clinical Rating Scale Scores[a]

Rating Scale	SA (N = 27)	SC (N = 128)	MD (N = 24)	F	p Value	Group Effects
BPRS total	32.5(9.2)	33.0(9.3)	33.6(7.1)	0.2	.82	
BPRS depression subscale	7.2(4.1)	6.1(2.6)	9.0(3.8)	7.23	.001	SC < SA, MD
BPRS positive symptom subscale	4.7(2.2)	6.2(3.4)	4.4(1.4)	5.95	.003	SC > SA, MD
BPRS negative symptom subscale	5.5(1.9)	5.5(2.8)	5.9(2.6)	0.53	.59	
HAM-D total	11.6(7.1)	9.1(5.5)	16.8(8.4)	13.50	<.0001	SA, SC < MD
AIMS total	5.0(4.0)	4.8(4.4)	2.2(2.1)	3.98	.02	SA, SC < MD

[a]All values shown as mean ± SD. Abbreviations: AIMS = Abnormal Involuntary Movement Scale, BPRS = Brief Psychiatric Rating Scale, HAM-D = Hamilton Rating Scale for Depression.

df = 8,352; p < .0001). Follow-up univariate comparisons on the BPRS subscales found that both the schizoaffective disorder and mood disorder patients reported more severe depressive symptoms than the schizophrenia patients and that the schizophrenia patients reported more severe positive symptoms relative to the mood disorder and schizoaffective disorder patients. (The BPRS depression finding differed from the HAM-D result.) The mood disorder patients were more likely to have a positive family history of mood disorder compared with the other 2 groups. In contrast, the schizoaffective disorder and schizophrenia patients reported a greater past history of psychiatric hospitalization relative to the mood disorder patients.

Neuropsychological Variables

Table 3 presents the summary of cognitive measures for the 3 subject groups. The sample of subjects with neuropsychological data was smaller than the overall sample, with a total of 177 subjects (24 schizoaffective disorder, 128 schizophrenia, and 25 mood disorder) having at least a global mean T-score. The respective diagnostic subgroups with versus without neuropsychological testing did not differ significantly from one another on demographic or psychopathologic measures. The 1-way ANOVA on the global neuropsychological T-score was significant (F = 4.12, df = 2,174; p = .018), with follow-up comparisons showing that mood disorder subjects differed from both schizoaffective disorder and schizophrenia subjects. The profile MANOVA (N = 161) yielded significant main effects for both group (F = 4.98, df = 2,158; p = .008) and ability area (F = 15.3, df = 4.85,766.6; p < .0001); however, the group × ability area interaction was not significant (F = 1.16, df = 12,948; p = .31). (Given the differences in ethnic composition of the 3 groups, this profile

Table 3. Neuropsychological Ability Area Mean (SD) T-Scores

Neuropsychological Ability Area	SA (N = 24)	SC (N = 115)	MD (N = 22)	F	p Value	Group Effects
Verbal	45.0(10.0)	45.2(7.9)	48.7(7.7)	1.80	.16	
Psychomotor speed	40.8(7.8)	41.9(6.6)	46.0(6.5)	4.03	.02	SA, SC < MD
Abstraction/cognitive flexibility	38.3(9.4)	41.4(9.0)	45.5(9.6)	3.56	.03	SA < MD
Attention	43.1(9.5)	44.5(7.4)	49.1(8.7)	3.83	.02	SA, SC < MD
Learning	34.2(11.7)	38.1(9.8)	44.6(7.5)	6.62	.002	SA, SC < MD
Retention	39.9(11.8)	43.1(9.6)	46.1(7.6)	2.34	.10	
Motor	41.2(9.9)	41.8(8.3)	43.9(7.6)	0.71	.49	
Global[a]	40.9(8.1)	42.2(6.2)	45.7(5.1)	4.12	.018	SA, SC < MD

[a]Univariate ANOVA. The Ns for the respective patient groups were as follows: SA, N = 24; SC, N = 128; MD, N = 25. The sample for global neuropsychological T-scores was greater because scores in only 5 of the 7 ability areas are needed to generate a global T-score.

analysis was repeated with only white subjects, but the results did not differ from those presented above; therefore, the entire sample was used in subsequent analyses.)

With regard to specific cognitive ability areas, we found simple effects group differences in psychomotor speed ($F = 4.03$, $df = 2,158$; $p = .02$), abstraction/cognitive flexibility ($F = 3.56$, $df = 2,158$; $p = .03$), attention ($F = 3.83$, $df = 2,158$; $p = .02$), and learning ($F = 6.62$, $df = 2,158$; $p = .002$). Simple effects contrasts (all p values $\leq .01$) showed that schizoaffective disorder patients were different from mood disorder patients in psychomotor speed ($p = .01$), abstraction/cognitive flexibility ($p = .009$), attention ($p = .01$), and learning ($p = .0005$). The schizophrenia patients also differed from the mood disorder patients in psychomotor speed ($p = .01$), attention ($p = .01$), and learning ($p = .005$). No differences were noted, however, between schizoaffective disorder and schizophrenia patients in any cognitive domain (ability area).

The analyses of the age-, gender-, and education-matched subsamples of schizoaffective disorder, schizophrenia, and mood disorder patients (N = 27 each) produced results similar to those with the larger groups across clinical and neuropsychological domains under study.

Finally, to determine if the above neuropsychological differences were sufficient to classify patients as having schizophrenia, schizoaffective disorder, or mood disorder, stepwise discriminant function analyses were performed on the mood disorder and schizophrenia patients and the resultant formula was applied to the schizoaffective disorder patients. The discriminant analysis included 161 subjects with neuropsychological data (24 with schizoaffective disorder, 115 with schizophrenia, 22 with mood disorder). Two canonical functions were generated, which used 4 ability area scores: psychomotor speed, attention, learning, and retention. These functions were able to correctly classify 84 (73%) of the schizophrenia group and 16 (72%) of the mood disorder patients. When applying this function to the schizoaffective disorder group, 19 (79%) of 24 were classified as schizophrenia patients, and only 5 (21%) as mood disorder patients.

Post Hoc Analyses

Given the significant differences with regard to the proportion of patients taking lithium in each group and in view of past research suggesting possible detrimental effects of lithium on cognitive performance,[42] we compared the global neuropsychological T-scores of the patients taking lithium to those of patients not taking lithium. A 2×2 (schizoaffective disorder vs. mood disorder and taking vs. not taking lithium) factorial ANOVA was performed. There was a significant interaction of group by medication status ($F = 6.19$, $df = 1,45$; $p = .017$), as well as significant main effects for both group ($F = 8.42$, $df = 1,45$; $p = .006$) and treatment ($F = 12.3$, $df = 1,45$; $p = .001$). The schizoaffective disorder patients were more impaired than the mood disorder patients (mean T-score = 40.9 vs. 45.7), and the patients taking lithium were more impaired than those not taking lithium (mean T-score = 36.9 vs. 44.8). In terms of the interaction effect, schizoaffective disorder patients taking lithium demonstrated more cognitive impairment relative to schizoaffective disorder patients not taking lithium and mood disorder patients. We similarly examined the cognitive performances of the subjects controlling for neuroleptic and anticholinergic use and found no significant interaction of group by treatment.

DISCUSSION

The literature has been divided over the diagnostic validity of schizoaffective disorder. Researchers have argued that the disorder represents a variation of either schizophrenia or a mood disorder[2] or that it is an intermediate illness within the spectrum of major psychiatric illnesses

from schizophrenia to mood disorder.[3] In terms of the different conceptual models of schizoaffective disorder proposed by other researchers,[7,8] our findings suggest that schizoaffective disorder represents a variant of schizophrenia in terms of clinical symptoms, family history, treatment regimen, and cognitive impairment. In the absence of larger sample sizes, we cannot rule out the other hypotheses of coexisting schizophrenia and mood disorder or of greater heterogeneity in schizoaffective disorder. The schizoaffective disorder group did not differ significantly in cognitive profile from the schizophrenia group, consistent with previous studies.[17,18] This finding suggests that the level and pattern of cognitive impairment are similar in both groups of patients with psychotic illness and may illustrate similar neurobiological underpinnings for cognitive deficits in schizoaffective disorder and schizophrenia. In addition, a discriminant function analysis classified schizoaffective disorder patients as being more similar to schizophrenia than to mood disorder patients.

The concept of, as well as the diagnostic criteria for, schizoaffective disorder has changed considerably over the past several decades. Thus, the criteria for schizoaffective disorder in the DSM-III-R[11] are quite different from those in the Research Diagnostic Criteria.[43] Hence, the results of investigations of schizoaffective disorder are, at least to a degree, definition dependent. In the present study, we used DSM-III-R criteria[11] for schizoaffective disorder.

One may argue that the diagnosis of schizoaffective disorder is not stable and that, as such, it does not represent either end of the symptom spectrum (schizophrenia vs. mood disorder) but rather a fluctuating midpoint along the continuum.[5] On the other hand, although changes might occur over a longer follow-up period, the diagnosis of all the patients in the present study remained stable over a mean period of 4 years. Other studies have suggested that the subtype of schizoaffective disorder plays a role in the similarity to either schizophrenia or mood disorder; specifically, the bipolar subtype of schizoaffective disorder would look more "affective" and the depressed subtype would look more "schizophrenia-like."[12] This subtype division, however, has not been reported consistently.[10] The present results cannot support either view owing to the small subsamples of patients along with difficulties in determining subtype in some schizoaffective disorder patients.

One issue that should be mentioned in this context is the relative independence of the potential validating criteria used. The diagnosis of schizoaffective disorder was based on DSM-III-R criteria.[11] The clinical psychopathology measures, including the BPRS and the HAM-D, did not contribute to the diagnostic process, and the neuropsychological performance had no bearing on the diagnosis. Different members of the research team performed diagnostic, psychopathologic, and neuropsychological assessments. We do not know, however, about the relative value of these putative validators compared with long-term validators such as course and treatment response.

The cognitive differences noted among these groups were not due to global psychopathologic differences, since the groups had similar BPRS total scores. In terms of demographic factors, the T-score approach corrects for differences in age, education, and gender. Furthermore, given the group differences in certain demographic factors, an analysis of age-, gender-, and education-matched samples, as well as an analysis of a white-only subsample, produced patterns comparable to those seen in larger samples. The schizoaffective disorder, schizophrenia, and mood disorder groups differed in the use of neuroleptics, anticholinergics, and lithium. Some studies have reported cognitive deficits associated with the use of anticholinergics[44] and lithium.[42,45–47] Limited evidence of greater cognitive impairment was seen for schizoaffective disorder patients taking lithium, but not for the mood disorder patients taking that drug. The literature on the effects of neuroleptics on neuropsychological performance suggests somewhat variable results.[42,48,49] A post hoc analysis suggested that the effects of medication and group membership were variable. It may be stressed, however, that these subsamples were relatively small and might not have provided adequate power to examine the issues of medication effects on cognition. The use of the cognitive performance variables may offer "stable" evidence of an underlying psychosis continuum that may be responsible for the neurocognitive impairments seen in these psychotic illnesses.

A recent study conducted in our Clinical Research Center noted that patients with psychotic depression had a cognitive profile similar to that seen in schizophrenia.[19] The psychotic depressed patients in that study were more impaired in their cognitive abilities compared with the nonpsychotic depressed patients. The present study shows that schizoaffective disorder also is associated with greater impairment in cognitive performance than nonpsychotic mood disorder. Taken together, these findings suggest that the presence of psychotic symptoms has a similar association with cognitive performance, such that the neuropsychological deficits do not appear to be specific to schizophrenia, but rather extend to the full spectrum of psychotic illness.

Our sample was restricted to patients between the ages of 45 and 77 years. The rationale for this was as follows. In our Clinical Research Center, we focus on middle-aged and elderly patients with psychotic disorders. Hence, our patients are typically over the age of 45 years. In the present study, the primary group of interest was that of patients with schizoaffective disorder. We included all the available subjects in this diagnostic category within our Center. The 29 schizoaffective disorder patients ranged in age from 45 to 77 years. The upper age limits for the patients in the other 2 groups (schizophrenia and mood disorder) happened to be somewhat greater. As a result, those 2 groups had higher mean ages than the schizophrenia patients. A comparison of groups with different ages poses a problem in terms of several variables such as age at onset and duration of illness, daily dosages of medications, and some of the psychopathology ratings. We therefore decided to restrict the comparison samples to the same age range as that of the schizophrenia group to reduce possible confounds due to age differences. Nonetheless, we realize that our results may or may not generalize to patients in other age groups.

A majority (55.8%) of the schizophrenia patients had the paranoid subtype. This finding is probably related to the higher current age (mean = 58.9 years) as well as the higher age at onset of illness (mean = 34.4 years). It is known that later onset schizophrenia is usually of the paranoid subtype.[50] Furthermore, paranoid schizophrenia has a better prognosis than nonparanoid type[51] and is therefore likely to be overrepresented in an older population of outpatients that have survived the ravages of the illness during the earlier adult years.

We excluded subjects with a history of head injury with loss of consciousness for greater than 30 minutes. Although the cutoff of 30 minutes is admittedly arbitrary, it was meant to differentiate individuals with minor head injuries that are common in the general population from those with severe head injuries with substantial impact on brain function. This distinction was especially important because of the use of neuropsychological performance as a variable of interest in differentiating the 3 psychiatric patient groups.

Several limitations should be noted with regard to the present study. The present investigation was limited to middle-aged and elderly outpatients, and the mean age at onset of schizoaffective disorder was 29.6 years. Although unlikely, it is possible that schizoaffective disorder may yield a somewhat different clinical and neurocognitive profile vis-à-vis schizophrenia and mood disorder in younger adults with an earlier age at onset of illness. Next, as noted above, the smaller sample sizes in the post hoc comparisons increase the possibility of type II errors. The family history data were based on all blood relatives, not just the first-degree relatives of the patients, and were obtained from other sources of information rather than independent clinical examination of each family member. Finally, it is possible that the schizoaffective disorder and schizophrenia groups differ on measures that were not included in the present study. The present work also has several strengths, however. It included carefully diagnosed and well-characterized age-comparable groups of patients who had extensive neuropsychiatric assessment.

Implications of the present study support combining schizoaffective disorder and schizophrenia patients into a single patient group when cognitive performance is the parameter of interest being studied. Future work should examine whether the cognitive differences from mood disorder could be related to different neuropathologic and neuroanatomic substrates among schizoaffective disorder/schizophrenia versus mood disorder patient groups. Further research needs to compare long-term outcome and treatment response in patients with schizoaffective disorder with those patients with schizophrenia or mood disorder. If the results of those investigations are similar to the present findings, one may question the utility of having a separate diagnostic category of schizoaffective disorder as distinct from schizophrenia.

Drug names: benztropine (Cogentin and others), chlorpromazine (Thorazine and others).

Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, no investigational information about pharmaceutical agents has been presented in this article that is outside U.S. Food and Drug Administration–approved labeling.

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