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Prognostic Validity of the Familial Subtypes of Depression

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Summary. We examined the prognostic validity of Winokur's familial subtypes of depression in 184 inpatients with primary unipolar major depression. Patients with familial pure depressive disease had a more favorable hospital course and reported less symptoms during a 6-month follow-up evaluation than patients with depressive spectrum disease or sporadic depressive disease. Consistent with previous studies of the validity of the familial subtypes, the use of stringent thresholds to diagnose the patient's relatives increased the validity of classification.

Key words: Depression – Familial subtypes – Prognosis

Introduction

Few clinicians or researchers would assert that criteria for major depressive disorder, regardless of the diagnostic system used, identify a homogeneous group of patients. The numerous attempts to reduce the heterogeneity by subclassifying patients as unipolar or bipolar, melancholic or nonmelancholic, psychotic or nonpsychotic, primary or secondary, endogenous or nonendogenous, neurotic or nonneurotic, etc. have met with varying degrees of success. Winokur proposed a subdivision of primary unipolar patients based on patients' family history of psychiatric disorder in their first-degree relatives (Winokur et al. 1978; Winokur 1979). According to this system patients with a family history of unipolar depression but without a family history of alcoholism or antisocial personality have familial pure depressive disease (FPDD), patients with a family history of alcoholism or antisocial personality have depressive spectrum disease (DSD), and patients whose family history is negative for all three disorders have sporadic depressive disease (SDD). Patients with secondary depression, a history of mania, or a family history of bipolar illness are not classified under this trichotomy.

We have previously examined the relationship between familial subtyping and results of the dexamethasone suppression test, demographic characteristics such as sex, age, and marital status, psychosocial variables such as life events and social support, and clinical features such as symptom severity, delusions, and endogenous symptoms (Zimmerman et al. 1985a; 1986a). In the present report we examine the predictive validity of familial subtyping.

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Methods

From August 1981 until July 1983 we approached a consecutive series of depressed patients aged 18 years and older admitted to the 58-bed psychiatric inpatient unit at the University of Iowa. Because our research protocol included a dexamethasone suppression test, patients were excluded if they had any of the medical or pharmacological conditions which might invalidate this test. Faculty members, residents, and medical students obtained psychiatric histories within the first 3 days after admission. WC and BP read these histories and independently determined whether the patients met DSM-III criteria for major depression and whether the depression was primary or secondary, and unipolar or bipolar. The primary/secondary distinction was based on the Washington University criteria (Feighner et al. 1972), and unipolar major depression was diagnosed according to DSM-III. The present report is based on the 184 patients with primary unipolar major depressive disease.

The family history diagnoses used for familial subtyping were based on information collected from the patient. MZ or DS, both trained by participants of the National Institute of Mental Health (NIMH) Collaborative Study (Katz et al. 1979), followed the Family History – Research Diagnostic Criteria

(FH-RDC) guidelines to assess the presence or absence of substance use disorders, antisocial behavior, and periods of depression, mania, and psychosis (Andreasen et al. 1977). They also recorded specific details about hospitalization, types of treatment received, suicidal behavior, legal difficulties, and functional impairment.

Previous studies of the validity of the familial subtypes have found that the validity of classification was greater when more stringent diagnostic thresholds were used. Our low threshold diagnoses were based on a strict interpretation of the FH-RDC. Accordingly, we diagnosed alcoholism in someone who had alcohol-related marital problems even though these did not result in treatment. We diagnosed depression in someone with a full depressive syndrome for 2 or more weeks even if they were not treated, hospitalized, or impaired. Legal problems were not required for the diagnosis of antisocial personality. In contrast, our high threshold diagnosis for depression required that the relative was hospitalized, alcoholism was diagnosed only if the relative was treated, and the presence of legal problems were necessary for a diagnosis of antisocial personality.

We completed the Hamilton Rating Scale for depression (HRS) (Hamilton 1967), Beck Depression Inventory (BDI) (Beck et al. 1979), and Global Assessment Scale (GAS) (Endicott et al. 1976) within 1 week of admission, and weekly thereafter. Our analyses of the course during index hospitalization focused on the symptom ratings made during the weeks of admission and discharge. Following the conventions recommended elsewhere (Zimmerman et al. 1985b), we considered a patient improved if their HRS score decreased at least 50% from admission to discharge, and recovered if the discharge HRS score was 6 or less. Patients received their doctor's choice of treatment. In a naturalistic design such as ours, the speed and degree of improvement may be associated with medication dosage and trial duration. Moreover, treatment decisions will in part be based on the treatment received prior to hospitalization. Thus, we did not attempt to control for the quantity of pharmacotherapy. We did, however, divide patients into those who did and did not receive electroconvulsive therapy (ECT).

Raters blind to familial classification recontacted the patients 6 months after their entry into the study. Our method of outcome assessment resembled the Longitudinal Interval Follow-up Evaluation used in the NIMH Collaborative Study (Keller et al. 1987). In the 30–90 min phone interview, raters determined the type and amount of treatment received following discharge from index hospitalization. The HRS, BDI, and GAS were completed for the week before the 6-month follow-up interview. The patients indicated whether they had returned to their normal self at the time of hospital discharge, and each week of the follow-up was similarly rated. The interviewers also rated the presence or absence of the eight DSM-III part B criteria symptoms for major depressive disorder for each postdischarge week. To make the weekly usual self and symptom ratings the interviewers inquired about change points, dates when definite improvement or worsening took place. Each week was assigned a symptom rating on a 4-point scale. A week without depressive symptoms was assigned a score of 1. The presence of one or two criterion depression symptoms resulted in a score of 2. A score of 3 reflected the presence of three or four criterion symptoms and the presence of five or more symptoms was scored 4. Following the convention adopted by the Collaborative Study, sustained recovery was defined as a period of at least 8 consecutive weeks in which the patient had no more than two depressive symptoms. We also defined sustained recovery more narrowly, requiring an 8-week period with no depressive symptoms. Finally, in order to make use of the most outcome data possible, we determined the mean symptom rating across all weeks of the follow-up for each period, and calculated the mean of these values for each diagnostic group.

We evaluated the reliability of our follow-up procedure in two ways (Zimmerman and Coryell 1986). 21 patients were interviewed once per month after their discharge from the hospital until their scheduled 6-month follow-up interview. The monthly interviews followed the above-described format for the 6-month interview. Audio tapes of these interviews were rated to assess reliability in an observer-rater paradigm. An independent rater interviewed the patients 6 months after their index admission and assessed symptomatology for the entire postdischarge period. Thus, we examined the test-retest reliability of follow-up assessments by comparing information obtained from the monthly interviews with the data collected at the 6-month interview. Ratings of audio tapes of the monthly interviews achieved excellent reliability. Fair to excellent agreement was also found between the monthly and 6-month interviews, with the highest agreement for ratings of treatment received and the lowest agreement for sustained recovery ratings.

Results

The majority of the 184 patients were female (70.6%), married (45.6%) or single (26.6%), and had previously been hospitalized at least once (78.8%). Based on the FH-RDC low thresholds for diagnoses, 56 (30.4%) patients had FPDD, 64 (34.8%) had DSD, and 64 (34.8%) had SDD. Three patients could not be classified with the high threshold diagnoses because information was missing regarding the treatment received by the ill relatives. Based on the high diagnostic thresholds the prevalence of SDD increased to 56.9% ($n = 103$), whereas the number of patients with FPDD ($n = 44$, 24.3%) and DSD ($n = 34$, 18.8%) decreased.

Consistent with our previous studies of the validity of the familial subtypes the high theshold diagnoses were stronger predictors of outcome; therefore, we only present the results for these diagnoses.

Hospital Course

Discharge ratings were not completed in the 34 (18.5%) patients whose hospital stay lasted a week or less. More DSD than FPDD and SDD patients were discharged within a week of admission (Table 1). All three groups differed significantly in the frequency with which ECT was prescribed; FPDD patients were the most likely to receive ECT and DSD patients the least likely. The data in Table 1 also indicate that the FPDD patients had a more favorable hospital course than the other two groups. This was not due to the greater likelihood that they received ECT since the

Table 1. Hospital course of familial subtypes of primary unipolar depression with high thresholds used to diagnose relatives[a]

	Sporadic depressive disease (SDD)	Familial pure depressive disease (FPDD)	Depressive spectrum disease (DSD)	3-Group comparison	SDD vs FPDD	DSD vs FPDD	DSD vs SDD
n	85	40	22				
Days hospitalized	27.7 ± 18.1	36.5 ± 21.8	20.6 ± 14.2	0.001	0.05	0.001	0.05
% Discharged during 1st week	17.3	9.1	35.3	0.05	–	0.01	0.05
% Treated with electroconvulsive therapy (ECT)	34.0	52.3	14.7	0.001	0.05	0.001	0.05
Admission Hamilton Rating Scale (HRS)	24.4 ± 5.4	22.9 ± 5.7	22.3 ± 5.0	–	–	–	–
Discharge HRS	10.5 ± 8.0	6.9 ± 5.5	10.0 ± 5.9	0.05	0.01	–	–
% Change HRS[b]	56.8	69.8	54.7	–	0.05	0.05	–
Admission Beck Depression Inventory (BDI)	31.2 ± 10.7	27.7 ± 11.1	28.7 ± 10.1	–	–	–	–
Discharge BDI	12.4 ± 11.3	8.3 ± 7.8	12.2 ± 8.0	–	0.05	–	–
% Change BDI[b]	58.3	66.8	56.6	–	–	–	–
Admission Global Assessment Scale (GAS)	37.1 ± 7.9	36.9 ± 8.2	38.3 ± 6.2	–	–	–	–
Discharge GAS	57.6 ± 12.1	62.9 ± 7.3	60.0 ± 8.5	0.05	0.01	–	–

[a] All values are means ± SD unless otherwise indicated.
Sample sizes and all rating scale values are for patients with both admission and discharge assessments. Values for days hospitalized and % discharged during 1st week of hospitalization are based on all patients in the study (103 SDD, 44 FPDD, 34 DSD)

[b] % Change calculated as $\frac{\text{admission score} - \text{discharge score}}{\text{admission score}}$

Table 2. Hospital course of familial subtypes of primary unipolar depression with high thresholds used to diagnose relatives in patients who were and were not treated with ECT[a]

	SDD	FPDD	DSD	3-Group comparison	SDD vs FPDD	DSD vs FPDD	DSD vs SDD
NonECT patients, *n*	50	17	17				
Days hospitalized	19.5 ± 13.5	23.3 ± 16.2	16.9 ± 11.2	–	–	–	–
Admission HRS	23.9 ± 5.7	24.9 ± 5.9	21.4 ± 5.1	–	–	–	–
Discharge HRS	12.0 ± 8.1	7.5 ± 5.8	10.6 ± 5.2	–	0.05	–	–
% Change HRS	49.9	68.6	50.2	–	0.05	0.05	–
Admission BDI	30.0 ± 10.7	28.7 ± 12.1	27.1 ± 9.6	–	–	–	–
Discharge BDI	14.3 ± 11.2	7.8 ± 6.7	12.1 ± 5.4	–	0.01	–	–
% Change BDI	51.4	68.8	53.8	–	–	–	–
Admission GAS	38.9 ± 8.2	36.1 ± 7.1	39.1 ± 6.7	–	–	–	–
Discharge GAS	57.0 ± 11.8	64.1 ± 8.4	59.2 ± 7.4	–	0.05	–	–
ECT patients, *n*	35	23	5				
Days hospitalized	43.7 ± 14.9	48.6 ± 19.3	41.6 ± 11.9	–	–	–	–
Admission HRS	25.2 ± 5.0	21.5 ± 5.1	25.2 ± 3.8	0.05	0.01	–	–
Discharge HRS	8.5 ± 7.3	6.4 ± 5.3	8.0 ± 8.1	–	–	–	–
% Change HRS	66.8	70.6	70.0	–	–	–	–
Admission BDI	33.0 ± 10.6	27.0 ± 10.5	34.2 ± 11.0	–	0.05	–	–
Discharge BDI	9.5 ± 10.9	8.7 ± 8.6	12.4 ± 14.2	–	–	–	–
% Change BDI	70.2	65.3	64.9	–	–	–	–
Admission GAS	34.4 ± 6.7	37.6 ± 9.0	35.6 ± 3.0	–	–	–	–
Discharge GAS	58.6 ± 12.8	62.0 ± 6.5	62.6 ± 12.3	–	–	–	–

[a] All values are means ± SD unless otherwise indicated.
Sample sizes and all rating scale values are for patients with both admission and discharge assessments. Values for days hospitalized are based on all patients in the study (nonECT patients: 68 SDD, 21 FPDD, 29 DSD; ECT patients: 35 SDD, 23 FPDD, 5 DSD)

[b] % Change calculated as $\frac{\text{admission score} - \text{discharge score}}{\text{admission score}}$

Table 3. Outcome at 6-month follow-up of familial subtypes of primary unipolar depression using high thresholds to diagnose relatives

	SDD ($n = 91$)	FPDD ($n = 38$)	DSD ($n = 29$)	3-Group comparison	SDD vs FPDD	DSD vs FPDD	DSD vs SDD
Outpatient visits, $\bar{x} \pm$ SD	9.2 ± 8.5	8.6 ± 7.6	11.0 ± 8.0	–	–	–	–
Rehospitalized, %	30.8	31.6	20.7	–	–	–	–
Adequate dose of AD meds[a], %	67.8	73.0	69.0	–	–	–	–
Sustained recovery, %							
– no depressive symptoms	26.6	47.2	34.5	–	0.05	–	–
– 1 or 2 depressive symptoms	55.3	83.3	58.6	0.05	0.01	0.05	–
– back to normal self	53.2	58.3	58.6	–	–	–	–
Mean weekly follow-up symptom score, $\bar{x} \pm$ SD	2.6 ± 1.0	2.1 ± 1.0	2.6 ± 1.0	0.05	0.05	–	–
Follow-up HRS, $\bar{x} \pm$ SD	9.8 ± 8.6	6.3 ± 6.7	9.3 ± 9.4	–	0.05	–	–
Follow-up BDI, $\bar{x} \pm$ SD	13.4 ± 12.4	10.8 ± 13.6	15.6 ± 13.3	–	–	–	–
Follow-up GAS, $\bar{x} \pm$ SD	60.6 ± 17.5	63.0 ± 16.5	61.2 ± 17.9	–	–	–	–

[a] An adequate dose of antidepressant medication (AD meds) was defined as a minimum of 8 consecutive weeks during which the patient received at least 100 mg/day of imipramine or an equivalent TCA, 900 mg/day of lithium, or 30 mg/day of phenelzine or an equivalent MAOI

differences between groups was greater for the patients not treated with ECT (Table 2). In fact, ECT response was not associated with familial subtyping based on the high diagnostic thresholds, although the sample of DSD patients was too small to draw firm conclusions (Table 3). Significantly more FPDD patients improved (FPDD vs DSD, 80.0% vs 50.0%, $\chi^2 = 6.01$, $P < 0.05$; FPDD vs SDD, 80.0% vs 60.0%, $\chi^2 = 4.88$, $P < 0.05$), and recovered by the time of discharge (FPDD vs DSD, 57.5% vs 36.4%, $\chi^2 = 2.54$, nonsignificant; FPDD vs SDD, 57.5% vs 36.5%, $\chi^2 = 4.90$, $P < 0.05$).

Outcome at 6-Month Follow-up

We successfully traced 88.6% of the patients for the 6-month follow-up interview. The FPDD patients generally had a better 6-month course, and these differences were not accounted for by differences in the amount of treatment received after discharge. Of interest, although the FPDD patients reported less symptoms that the other groups they were no more likely to indicate that they had returned to their normal self during the follow-up interval (Table 3).

Discussion

The only other large-scale follow-up study of the familial subtypes was the chart review study by Van-Valkenburg et al. (1977) who found that more FPDD than DSD patients were rehospitalized and had subsequent episodes of depression during the follow-up interval. In subsequent publications summarizing the development of familial subtyping Winokur (1983) noted that these results were contrary to the expected poorer outcome for DSD patients who were presumably returning to a more chaotic environment than FPDD patients. Interestingly, we also found a similar trend for FPDD patients to be more frequently rehospitalized during the follow-up interval. However, our follow-up study, which was based on personal interview rather than chart review, also found that FPDD patients were characterized by higher rates of recovery during the follow-up interval and lower levels of symptoms at the 6-month cross-sectional assessment. This suggests that FPDD patients less frequently relapsed, but when they did manifest depressive symptoms they were more likely to be rehospitalized. Perhaps this is because they have a more favorable experience with hospitalizations. They were less likely to be discharged almost immediately after admission, and hospital treatment was more likely to relieve their symptoms.

In previous reports we found that compared to patients with DSD, patients with FPDD more frequently had abnormal results on the dexamethasone suppression test, experienced fewer life events, had fewer marital separations and divorces, had better social support, less frequently made a nonserious suicide attempt, and had a more characteristic endogenous symptom profile. Some of the results of the present study are also consistent with the hypothesis that DSD is a variant of neurotic depression whereas FPDD is analogous to the endogenous subtype. Despite

equal levels of depressive symptoms, DSD patients were less frequently treated with ECT and more frequently rapidly discharged from hospital. We suspected that DSD patients were often hospitalized because of suicidal crises, and discharged when these crises resolved, and additional analyses supported this hypothesis. The DSD patients who were rapidly discharged were significantly more likely to have made a nonserious suicide attempt before admission than the DSD patients who remained in the hospital for a longer period of time (50.0% vs 19.6%, $\chi^2 = 5.93$, $P < 0.05$). The DSD patients who were not discharged soon after admission did not improve as much as FPDD patients. Also, FPDD improved more than SDD patients and these differences were maintained during the 6-month follow-up. Similar to other reports, the use of higher diagnostic thresholds augmented the differences between groups.

The generally positive findings of the present study are in contrast to the negative results from our study examining the prognostic validity of DSM-III melancholic and RDC endogenous subtyping (Zimmerman et al. 1987b). Our collection of studies examining the prognostic validity of different methods of subtyping depression suggests that classifications based on historical features such as the presence of a preexisting axis I disorder (primary vs secondary), preexisting personality disorder (neurotic vs nonneurotic), or specific family history (familial subtypes) have significant prognostic value (Coryell et al. 1985; Zimmerman et al. 1986b, 1987b), whereas classifications based on state variables such as cross-sectional symptoms or admission dexamethasone suppression test results fail to predict course (Zimmerman et al. 1987a, b). Evidence is accumulating that a longitudinal perspective is superior to a cross-sectional one in subclassifying depression.

References

Andreasen NC, Endicott J, Spitzer RL, Winokur G (1977) The family history method using diagnostic criteria. Arch Gen Psychiatry 34:1229–1235

Beck AT, Rush AJ, Shaw BF, Emery G (1979) Cognitive therapy for depression. Guilford Press, New York

Coryell W, Zimmerman M, Pfohl B (1985) Short-term prognosis in primary and secondary major depression. J Affect Dis 9:265–270

Endicott J, Spitzer RJ, Fleiss JL, Cohen J (1976) The Global Assessment Scale: A procedure for measuring overall severity of psychiatric disturbance. Arch Gen Psychiatry 33: 766–771

Feighner JP, Robins E, Guze SB, Woodruff RA, Winokur G, Munoz R (1972) Diagnostic criteria for use in psychiatric research. Arch Gen Psychiatry 26:57–63

Hamilton M (1967) Development of a rating scale for primary depressive illness. Br J Social Clin Psychology 6:278–296

Katz MM, Secunda R, Hirschfeld RM, Koslow S (1979) NIMH clinical research collaborative branch program on the psychobiology of depression. Arch Gen Psychiatry 36:765–771

Keller MB, Lavori PW, Friedman B, Nielsen E, Endicott J, McDonald-Scott P, Andreasen NC (1987) The longitudinal interval follow-up evaluation. Arch Gen Psychiatry 44: 540–548

VanValkenburg C, Lowry M, Winokur G, Cadoret R (1977) Depression spectrum disease versus pure depressive disease. J Nerv Ment Dis 165:341–347

Winokur G (1979) Unipolar depression: Is it divisible into autonomous subtypes? Arch Gen Psychiatry 36:47–52

Winokur G (1983) The validity of familial subtypes of depression. McLean Hospital Journal 8:17–37

Winokur G, Behar D, VanValkenburg C, Lowry M (1978) Is a familial definition of depression both feasible and valid? J Nerv Ment Dis 166:764–768

Zimmerman M, Coryell W (1986) Reliability of follow-up assessments of depressed inpatients. Arch Gen Psychiatry 43:468–470

Zimmerman M, Coryell W, Pfohl BM (1985a) The importance of diagnostic thresholds in familial classification: The dexamethasone suppression test and familial subtypes of depression. Arch Gen Psychiatry 42:300–304

Zimmerman M, Coryell W, Pfohl BM (1985b) The treatment validity of DSM-III melancholic subtyping. Psychiatry Res 16:37–43

Zimmerman M, Coryell W, Pfohl B (1986a) Validity of familial subtypes of primary unipolar depression. Arch Gen Psychiatry 43:1090–1096

Zimmerman M, Coryell W, Pfohl B, Corenthal C, Stangl D (1986b) ECT response in depressed patients with and without a DSM-III personality disorder. Am J Psychiatry 143:1030–1032

Zimmerman M, Coryell W, Pfohl B (1987a) Prognostic validity of the dexamethasone suppression test: results of a six-month prospective follow-up. Am J Psychiatry 144:212–214

Zimmerman M, Coryell W, Stangl D, Pfohl B (1987b) Validity of an operational definition for neurotic unipolar major depression. J Affect Dis 12:29–40

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