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A polydiagnostic study of depressive disorders according to DSM-IV and 23 classical diagnostic systems

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Abstract The classification of mood disorders is one of the most highly debated topics in modern psychiatry. The introduction of DSM-III (and its followers) has set a new standard in this controversy but little empirical evidence is available as to how the various classical diagnostic categories of mood disorders by Kraepelin, Schneider, Leonhard, Hamilton, Kielholz, Winokur and others compare with this new standard. The Intensive Prospective Study arm of the Group for Longitudinal Affective Disorders Study has studied a broad spectrum of mood disorders in 23 participating centres from all over Japan with a polydiagnostic semistructured interview called Comprehensive Assessment List of Affective disorders. In this paper we examined how the various classical diagnostic systems of depressive disorders correspond to the DSM-IV diagnoses, and found the following: (1) The classical 'neurotic' or 'psychogenic' depressions are diagnosed as major depression and not as dysthymia in DSM-IV; although dysthymia was dubbed as 'depressive neurosis' in DSM-III, its criteria were not true to the traditional usage of the term. Viewed from the other side of the coin, DSM-IV can be said to stand in the unitary tradition. (2) Some of the classical diagnostic categories such as Schneider's depressive psychopathy and Klein's acute dysphoria as well as modern ones such as Akiskal's subaffective dysthymia and Angst's recurrent brief depression were rarely seen in traditional psychiatric treatment settings. (3) Comparisons of the unique diagnostic systems such as those by Leonhard, Winokur and Berner warrant further studies on their validity.

Key words depressive disorder, nosology, polydiagnosis.

INTRODUCTION

Throughout most of the 20th century, the classification of mood disorders has been one of the most highly debated topics in psychiatry. Innumerable classifications of depressive illnesses have been proposed. The complexity of these controversies are well illustrated by the fact that almost every classificatory format that is logically possible has been advocated and some more or less plausible evidence has been offered in its support.

The introduction of DSM-III[1] in 1980 (preceded by the Feighner criteria[2] and the Research Diagnostic Criteria[3]) has had deep influences on these controversies. The DSM-III brought all mood disorders together as a coherent group. Every category and subcategory was provided with an operational definition. The term manic-depressive and other ambiguous epithets such as psychotic, neurotic, endogenous and reactive, were all discarded. The two basic categories of DSM-III were designated as 'manic episode' and 'major depressive episode' and a fundamental

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distinction was drawn between unipolar and bipolar disorders. A major depressive episode was defined rather broadly, but could be subdivided in a number of alternative ways, for example, as with or without melancholia and with or without mood-congruent or mood-incongruent psychotic features. These frameworks have been adopted largely unchanged by DSM-III-R,[4] DSM-IV[5] and ICD-10[6] successively.

The question now arises, however, as to how the various classical classifications of mood disorders compare with those of the newer operational diagnostic criteria. How would Schneider's vital and reactive depression,[7] Leonhard's pure melancholia and pure depression[9] be diagnosed by DSM-IV? What about neurotic depression of the so-called Newcastle school,[10] Kielholz's psychogenic depression,[11] and Winokur's pure depression or depressive spectrum disease[12] To the best of the present authors' knowledge, these questions have not been sufficiently explored in the literature. In order to answer these questions, we need to either make an independent diagnostic interview for each of the many diagnostic systems with a broad spectrum of mood disorder patients, or develop operational diagnostic criteria for the various classical diagnoses, construct an exhaustive list of possible symptoms and, better still, a semi-structured interview to elicit these data and study a broad spectrum of mood disorder patients.

Since 1992, the Intensive Prospective Study (IPS) arm of the Group for Longitudinal Affective Disorders Study (GLADS) has been conducting a prospective, serial follow-up study of broadly defined mood disorder patients in 23 participating centres from all over Japan. One of the prominent features of this study is the use of the Comprehensive Assessment List of Affective disorders (COALA), a series of reliable semi-structured interviews which can derive polydiagnostic evaluations of 29 modern operational as well as classical diagnostic systems.[13] This paper therefore aims to examine how the classical diagnoses of depressive disorders compare with the modern operational diagnoses in the broadly defined spectrum of depressed patients.

METHODS

Subjects

The 23 participating centres of the IPS arm of the GLADS Project are listed in Table 1. The participating centres included: psychiatric departments of 13 university hospitals, six general hospitals, three mental hospitals and one community mental health centre within Japan. The representative sample of first-visit patients to these centres were selected according to the pre-set rules and were interviewed with a semi-structured interview called the Psychiatric Initial Screening for Affective disorders (PISA).[14] The details of these pre-set rules were left to individual centres as time and human resources varied in each centre; in some centres the PISA was administered to all the first-visit patients seen by the psychiatrists participating in the GLADS Project, in others it was administered to all the first-visit patients on a certain day of the week, or it was administered only to the first-visit patients who were first to attend on a certain day of the week. The inclusion and exclusion criteria for the IPS arm of the GLADS Project were as follows:

1. Depressive state (depressed mood or anhedonia for more than 4 days) or manic state (elevated, expansive or irritable mood for more than 4 days).
2. No antidepressant or antipsychotic medication for the preceding 3 months.
3. Aged 18 years or over.
4. No condition that would render the assessment of psychiatric status difficult, such as mental retardation, dementia or hearing impairment

Table 1. Twenty-three participating centres of the Intensive Prospective Study arm of the GLADS Project

Fukushima Medical College
Yamagata University School of Medicine
Yokohama City University School of Medicine
Gifu University School of Medicine
Nagoya City University Medical School
Aichi Medical University
Osaka Medical University
Kinki University School of Medicine
Tottori University Faculty of Medicine
School of Medicine, University of Tokushima
University of Occupational and Environmental Health
Oita Medical College
Faculty of Medicine, Kagoshima University
Konodai Hospital, National Center of Neurology and Psychiatry
National Hizen Hospital
Ebetsu Municipal Hospital
Ome Municipal Hospital
Saitama Prefectural Mental Health Center
Toyohashi Municipal Hospital
Toyokawa Municipal Hospital
Kawasaki Municipal Itoda Hospital
Tobu-Maruyama Hospital
Kachi Hospital

When a patient was deemed eligible according to the PISA interview, he/she was given full explanation regarding the purposes and procedures of the study. Only when the patient gave informed written consent, was he/she entered into the study.

Within 1 week from their first visit, the consenting patients were interviewed with the COALA (entry version).[15]

Instrument

The development of the PISA-COALA system, the rationale behind it and its inter-rater reliability has been extensively reported elsewhere.[13] To briefly recapitulate, the PISA collects data regarding the subject's baseline demographic characteristics, lists 33 symptoms corresponding to DSM-III-R diagnostic criteria of schizophrenia, mood disorders, anxiety disorders, somatoform disorders, dissociative disorders, organic mental disorders and substance use disorders, and ascertains that the subject meets the inclusion criteria. The median reliability coefficient for the psychopathological variables of the PISA was found to be a kappa of 0.85 (range: 0.71 to 1.0) among 107 pairs of conjoint interviews.[13]

The COALA consists of an entry version to be administered at intake, a follow-up version 1 to be administered monthly, a follow-up version 2 to be given every 6 months and a relapse version. The core interview schedule and diagnostic algorithms of the COALA derive from the Schedule for the Affective Disorders and Schizophrenia (SADS)[16] and the Composite Diagnostic Evaluation of Depressive Disorders (CODE-DD).[17] The COALA has further integrated some of the newer diagnostic systems, enabled severity ratings by way of the Hamilton Rating Scale for Depression, Petterson Mania Scale and Brief Psychiatric Rating Scale and covered psychosocial factors which may be influential in the pathogenesis and pathoplasty of mood disorders. The Entry version includes a semistructured interview for the assessment of 81 psychopathological variables, which are rated as 2–7 grades of severity, depending on the nature of the variable, for the worst 1 week of the current episode and for the last 1 week preceding the interview. Typically, for each psychopathological variable, its detailed definition, standard probe questions and listing of anchor points are explicated in this order. The median reliability coefficient for the psychopathological variables of the COALA was an ANOVA intraclass correlation coefficient (ICC) of 0.86 (range: – 0.01 to 1.0; there was only one variable which showed an ANOVA ICC of – 0.01, and the next smallest value was 0.43). The COALA Entry version also has sections for the life events during the past year, for past illnesses and for family history. The reliability of these sections have also been shown to be satisfactory.[13]

These psychopathological and related variables cover all the information relevant to the 29 diagnostic systems and are then combined through computer algorithms to derive various affective disorder diagnoses. The psychopathological variables which are rated in 2–7 grades of severity were dichotomised into present or absent, depending on the anchor points given to each variable. Typically, three grades correspond to 0 = absent, 1 = slight or doubtful, and 2 = present, so that only score 2 was rated as present. Five grades correspond to 0 = absent, 1 = very mild or doubtful, 2 = present and mild, 3 = present and moderate, and 4 = present and severe, so that scores of 2 or more were considered as present. In the case of seven grades, which correspond to 0 = absent, 1 = very mild, 2 = mild, 3 = moderate, 4 = moderately severe, 5 = severe and 6 = extremely severe, scores of 2 or more were rated as present. In addition to such representative operational diagnostic criteria sets as the Feighner criteria,[2] Research Diagnostic Criteria (RDC),[3] DSM-III-R,[4] DSM-IV,[5] ICD-10[6] and its Japanese Clinical Modification (JCM),[18] COALA can diagnose the patients according to 20 diagnostic schemata including those of Kraepelin,[19] Schneider,[7,8,20] Leonhard,[9] Vienna Research Criteria,[21] Lewis,[22] Hamilton and White,[23] Kiloh and Garside,[10] Pilowsky *et al.*,[24] Mendels and Cochrane,[25] Foulds,[26,27] Overall *et al.*,[28] Paykel,[29] Raskin and Crook,[30] CATEGO,[31] Robins and Guze,[32] Winokur,[12,33,34] Taylor and Abrams,[35] Klein,[36] Pollitt,[37] and Kielholz.[11] Furthermore, because our collaborative study aims to cover low-grade depressive states, we have incorporated the diagnostic criteria for recurrent brief depression of Angst,[38] subaffective dysthymia of Akiskal[39,40] and neurotic major depression of Zimmerman.[41] The median reliability coefficient for those diagnoses which had a base rate of at least 5% in our reliability study was a kappa of 0.75 (range: 0.39 to 1.0).[13]

Analyses

In this paper we would like to focus on the diagnostic systems that do not belong to the lineage of the RDC and the DSM, and examine how they correspond to the DSM-IV diagnoses.

RESULTS

During the study period between December 1992 and December 1995, 1968 patients were screened with the

PISA at the 23 centres participating in the IPS arm of the GLADS Project. Written informed consent from 126 eligible patients was obtained and these patients were entered into the study. Based on the semi-structured interview with the COALA Entry version, the diagnoses of these 126 subjects according to DSM-IV were as follows: major depressive disorder (n = 95), of which five presented with the so-called 'double depression' superimposed on pre-existing dysthymia, depressive disorder not otherwise specified (n=15), bipolar I disorder (n=7), of which four were currently depressed and three currently manic, bipolar II disorder (n=3), of which two were currently depressed and one hypomanic, schizoaffective disorder (n=1), substance-induced mood disorder (n=1), adjustment disorder (n=1), and bereavement (n=3).

In the following, we will concentrate on the 117 patients who were currently depressed, namely patients with sub-threshold depression (depressive disorder not otherwise specified or adjustment disorder: n=16), major depression not superimposed on dysthymia (n=90), bipolar depression (n=6) and double depression (n=5), and examine to which of the DSM-IV diagnoses the various diagnoses according to classical systems would correspond.

Table 2 lists those diagnostic systems which are said to be unitary, i.e. those which see only a quantitative difference in the broad spectrum of depressive disorders and do not approve of the endogenous/reactive or psychotic/neurotic dichotomy. Table 3, on the contrary, lists the so-called binary theories which see a qualitative difference between endogenous versus reactive depressions. According to any of these systems, most cases with endogenous depression would be diagnosed as major depression in DSM-IV as well as most cases with neurotic depression.

Many classical diagnostic systems acknowledge more than two subtypes of depression. For example, Schneider subclassified the spectrum of depressive disorders into four. He separated depression with past history of mania or hypomania as cyclothymia and distinguished, within the spectrum of unipolar depressive disorders, vital depression, reactive depression and depressive psychopathy. In our cohort, all cases which were diagnosed as cyclothymia according to Schneider were diagnosed as bipolar depression in DSM-IV, and all cases with vital depression were diagnosed as major depression. His reactive depression also corresponded mostly to DSM-VI major depression but there were some cases which would be diagnosed as subthreshold depression or double depression by DSM-IV. There was no cases which could be diagnosed as depressive psychopathy according to Schneider. Some authors, including Overall *et al.*,[28] Paykel[29] and Raskin and Crook[30], proposed more than three subtypes of depressive disorders on the basis of multivariate analyses of symptomatological data. Typically, they acknowledged one subtype which corresponds to the classical endogenous depression and two or more subtypes which fall under the rubric of neurotic depression. Not only most of the former but also most of the latter subtypes were diagnosed as major depression according to DSM-IV.

Several authors have proposed classification of depressive disorders quite unlike any other (Table 5). In the nosological system by Leonhard, who first

Table 2. Unitary diagnostic systems and DSM-IV

	Sub-threshold depression (n=16)	Major depression (n=90)	Bipolar depression (n=6)	Double depression (n=5)
Kraepelin (1896)				
Manic-depressive insanity	0	0	5	0
Mixed state, depressive excitement	0	0	0	0
Depressive state, paranoid melancholia	0	2	0	0
Depressive state, melancholia gravis	0	0	0	0
Depressive state, melancholia simplex	0	30	0	2
Lewis (1934)				
Possible melancholia	3	20	0	3
Probable melancholia	1	30	0	1
Definite melancholia	0	25	0	0

Table 3. Binary diagnostic systems and DSM-IV

	Sub-threshold depression ($n=16$)	Major depression ($n=90$)	Bipolar depression ($n=6$)	Double depression ($n=5$)
Kiloh & Garside (1963)				
Endogenous depression	2	75	0	1
Neurotic depression	1	4	0	1
Pollitt (1965)				
Physiological Type S depression	2	56	0	0
Psychological Type J depression	8	19	0	3
Mendels & Cochrane (1968)				
Possible endogenous depression	4	16	0	1
Probable endogenous depression	2	30	0	3
Definite endogenous depression	2	43	0	1
Pilowsky, Levine & Boulton (1969)				
Class B or Endogenous depression	3	72	0	3
Class A or Neurotic depression	2	10	0	1
Taylor & Abrams (1986)				
Minor depression	1	12	0	1
Endogenous depression	2	59	0	1

proposed the distinction between unipolar and bipolar disorders, all cases of manic-depressive disease are diagnosed as bipolar disorder by DSM-IV. Pure melancholia, which is accompanied by depressed mood, psychomotor inhibition and thought inhibitions, is most likely to be diagnosed as major depression in DSM-IV. Conversely, pure depression, which shows depressive changes only in mood, was not often observed in our cohort. There were, however, several cases of non-participatory depression.

Robins and Guze made a distinction between depressive disorders secondary to other psychiatric or medical diseases and primary depressive disorders.[32] This was of particular importance since, in the unitary theory of depression by Lewis, patients with secondary depression were excluded from the analyses from the beginning.[22] Robins and Guze's primary and secondary depressions were both likely to be diagnosed as major depression by DSM-IV.

Winokur[12,33,34] is known to have proposed subclassification of unipolar depression on the basis of family history. Pure depression refers to unipolar depression seen among the patients who have family history of depression but not of alcoholism or antisocial personality or mania. Depressive spectrum disease refers to one seen among the patients with family history of alcoholism or antisocial personality. Sporadic depression is seen among those who have no family history of depression, alcoholism, antisocial personality or mania. Most cases of DSM-IV major depression would be sporadic depression but several cases of pure depression or depressive spectrum disease were also seen among our cohort.

The Vienna Research Criteria[21] are unique in their emphasis on 'biorhythmic disturbances' and 'sleep disturbances'. Endogenomorphic–depressive axial syndrome requires depressed mood or lack of affective resonance or lack of drive in addition to these disturbances. These cases would be diagnosed as major depression or bipolar depression in DSM-IV. When irritability or hostile responses or hostile acting out is noted in addition to biorhythmic and sleep disturbances, endogenomorphic–dysphoric axial syndrome is diagnosed. A part of the cases of DSM-IV major depression belonged to this subgroup.

There was only one case in our cohort which was diagnosed as Akiskal's subaffective dysthymia and he received the diagnosis of major depression according to DSM-IV. No patient in our cohort was diagnosed as suffering from Angst's recurrent brief depression or from Zimmerman's neurotic major depression.

DISCUSSION

The strengths of the present study include the following. Firstly, it studied a very wide spectrum of mood disorders so that any patient who would be

Table 4. Pluralistic diagnostic systems and DSM-IV

	Sub-threshold depression ($n=16$)	Major depression ($n=90$)	Bipolar depression ($n=6$)	Double depression ($n=5$)
Schneider (1920)				
Cyclothymia	0	0	6	0
Reactive depression	4	18	0	2
Vital depression	0	46	0	1
Depressive psychopathy	0	0	0	0
Hamilton & White (1959)				
Retarded depression	1	33	0	1
Agitated depression	1	5	0	0
Overall, Hollister, Johnson & Pennington (1966)				
Type B or Hostile depression	1	1	0	0
Type C or Retarded depression	1	51	0	1
Type A or Anxious depression	0	8	0	0
Paykel (1971)				
Group 4A or Psychotic depression	3	64	0	1
Group 4B or Anxious depression	1	6	0	0
Group 4C or Hostile depression	0	2	0	0
Kielholz (1972)				
Somatogenic depression	0	2	0	0
Psychogenic reactive depression	3	43	2	2
Psychogenic neurotic depression	0	0	0	0
Endogenous cyclic depression	0	0	2	0
Endogenous periodic depression	0	8	0	0
Endogenous depression	2	22	0	1
Foulds (1973)				
Psychotic depression	1	11	0	0
Neurotic depression	6	54	0	5
Dysthymic depression	1	17	0	0
CATEGO (1974)				
Class D or Depressive psychosis	0	3	0	0
Class R or Retarded depression	6	73	0	2
Class N or Neurotic depression	0	4	0	0
Klein (1974)				
Endogenomorphic depression	3	68	0	3
Acute dysphoria	0	0	0	0
Chronic neurotic dysphoria	0	0	0	0
Raskin & Crook (1976)				
Type 3 or Endogenous depression	1	24	0	0
Type 2 or Neurotic depression	1	11	0	0
Type 4 or Poor premorbid personality depression	0	0	0	0
Type 1 or Agitated depression	0	9	0	0

diagnosed as depression in one diagnostic system but not in another is nonetheless likely to be included in our cohort. Moreover, this cohort is a representative subset of first-visit patients to various institutions reflecting the clinical variations from all over Japan. Thirdly, it employed a comprehensive semi-structured interview whose reliability has been ascertained. Fourthly, based on this comprehensive list of affective and related symptoms, computerized algorithms were prepared for many of the classical diagnostic schemes of clinical relevance.

The weaknesses of the present study includes its sample size. One hundred and twenty-six patients, of whom 117 were depressed at the time of the intake, may not be enough to allow a sufficient number of patients with rarer subtypes of depressive

Table 5. Other unique diagnostic systems and DSM-IV

	Sub-threshold depression ($n=16$)	Major depression ($n=90$)	Bipolar depression ($n=6$)	Double depression ($n=5$)
Leonhard (1959)				
Manic-depressive disease	0	0	6	0
Pure melancholia	1	54	0	1
Suspicious depression	0	0	0	0
Harried depression	0	0	0	0
Hypochondriacal depression	0	0	0	0
Self-torturing depression	0	0	0	0
Nonparticipatory depression	0	5	0	2
Robins & Guze (1972)				
Secondary depressive disorder	4	6	0	0
Primary depressive disorder	8	76	0	5
Winokur (1974)				
Pure depression	0	9	0	1
Depressive spectrum disease	0	7	0	1
Sporadic depression	2	57	0	3
Vienna Research Criteria (1983)				
Endogenomorphic-depressive axial syndrome	0	23	2	1
Endogenomorphic-dysphoric axial syndrome	0	12	0	0

disorders, such as Schneider's depressive psychopathy, Leonhard's pure depression and Klein's acute dysphoria. In addition, some may question the adequacy of the translation of classical diagnostic concepts into operationalized criteria. Admittedly our algorithms have only face validity and have not been formally tested for their concurrent validity in a study in which our algorithms would be compared with independent diagnostic interviews focusing on each of the classical diagnostic systems. This latter study would, however, require a formidable amount of work.

The theoretical importance and conceptual advantage of a polydiagnostic approach in psychiatric nosology has received increasing recognition recently. Berner *et al*.,[42] one of the first proponents of the polydiagnostic approach, argued that a diagnosis and diagnostic system has to be regarded as a hypothesis and that we accept different diagnostic conceptions until one of them is shown to be superior. They provided examples of such studies in the case of schizophrenia and endogenous depression but have not proceeded to produce polydiagnostic interview schedules or diagnostic algorithms. The List of Integrated Criteria for the Evaluation of Taxonomy for Depression (LICET-D) appears to have been the first attempt to provide an integrated criteria list of multiple diagnostic systems for affective disorders. It is a checklist with computerized algorithms that provides depressive diagnoses according to Feighner, RDC, DSM-III, VRC, Klein, Newcastle I Scale and Winokur.[43] Philipp and Maier in Germany developed a full-scale semistructured interview called the Polydiagnostic Interview (PODI) which allow Feighner, RDC, DSM-III, VRC and Taylor and Abrams criteria for major affective and psychotic disorders.[44] None of these studies, however, has incorporated classical diagnostic systems that were not originally proposed in the form of diagnostic criteria. In the USA, Ban developed the CODE-DD, the first standardized data collection system that enabled modern as well as classical diagnoses for unipolar depressive disorders.[17] Ban and his colleagues administered the CODE-DD to 230 patients with DSM-III-R major depression and found that DSM-III-R diagnosis of major depression is a broad concept which might be even broader than that of unipolar depression in most classical systems but that it does not cover some of the depressive diagnoses such as Schneider's vital depression and VRC endogenomorphic depressive–axial syndrome.[45,46]

One of the major findings of the present study is that the classical 'neurotic' or 'psychogenic' depressions were mostly re-diagnosed as major depression and not as dysthymia in DSM-IV. Although dysthymia was dubbed as 'depressive neurosis' in DSM-III, its diagnostic criteria were not true to the traditional usage of the term. In other words the

DSM-IV stands in the unitary tradition. There is actually ample reason not to maintain the endogenous-reactive dichotomy. Carey *et al.* attempted to prove that what they called 'endogenous' and 'neurotic' depressions were distinct illnesses. The supporting data they presented were clinical ratings from a series of 129 depressed inpatients, diagnosed clinically as 'endogenous' or 'neurotic', who were subjected to multiple regression analysis; the distribution of scores on the resulting function was bimodal rather than unimodal.[47] Taken in isolation, this was strong evidence for the validity of the distinctions in question. However, many other investigators have tried to obtain a bimodal distribution of scores on a discriminant function derived from consecutive series of depressions. Almost invariably they failed to obtain a bimodal distribution.[48–51] More recently, clustering techniques have been applied to depressive patients. Despite many differences in the patient populations and clinical ratings involved, and in the clustering programs employed, most of these have produced a cluster corresponding to endogenous depression or melancholia. However, none has produced a convincing second cluster corresponding to reactive or neurotic depression. Furthermore, 5-year follow-up data of the depressed patients in the NIMH Collaborative Program on the Psychobiology of Depression demonstrated little syndromal stability over successive depressive episodes.[52] And most importantly, the endogenous-reactive dichotomy is no longer believed to have treatment implications.[53,54]

Some diagnostic systems have introduced more than two subtypes of depressive disorders. Our results show that at least some of these, such as Schneider's depressive psychopathy and Klein's acute dysphoria, may be rather rare. Whether the other subtypes such as anxious depression, agitated depression and hostile depression possess any validity beyond a descriptive one could not be answered definitively by our present analysis, but, if we take DSM-IV as 'gold standard', then they cannot be said to have concurrent validity. Ban *et al*. also found that in most of the diagnostic systems providing more than two categories of unipolar depression, the majority of the patients with DSM-III-R major depression belonged to one diagnostic category only.[45] One might consider these findings in support of the contention that unipolar depressive illness represents a rather homogeneous, unitary diagnostic group.

The present study has also shown that some newly proposed diagnostic categories such as Angst's recurrent brief depression and Akiskal's subaffective dysthymia may also be rather infrequent at least in the traditional psychiatric treatment settings in Japan. This of course does not negate the importance of these diagnostic constructs, especially in view of the rather small sample size of our study, but it suggests that we may have to look elsewhere (such as in the community) in order to study these categories.

This paper has not addressed the relative validity of the competing diagnostic systems. In order to do this, we need to study external validators, such as familial aggregation, course, differential treatment response and laboratory tests, in conjunction with the polydiagnostic data. We have been collecting these data in the GLADS Project and such analyses are currently underway. We believe such a study would be especially worthwhile for those unique diagnostic systems such as Leonhard's, Winokur's and Vienna Research Criteria in comparison with the modern operational diagnostic criteria.

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