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Competing Definitions of Schizophrenia: What Can Be Learned From Polydiagnostic Studies?

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The contemporary diagnoses of schizophrenia (sz)—*Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*) and *International Classification of Diseases,10th Revision* (*ICD-10*)—are widely considered as important scientific achievements. However, these algorithms were not a product of explicit conceptual analyses and empirical studies but defined through consensus with the purpose of improving reliability. The validity status of current definitions and of their predecessors remains unclear. The so-called "polydiagnostic approach" applies different definitions of a disorder to the same patient sample in order to compare these definitions on potential validity indicators.

We reviewed 92 polydiagnostic sz studies published since the early 1970s. Different sz definitions show a considerable variation concerning frequency, concordance, reliability, outcome, and other validity measures. The *DSM-IV* and the *ICD-10* show moderate reliability but both definitions appear weak in terms of concurrent validity, eg, with respect to an aggregation of a priori important features. The first-rank symptoms of Schneider are not associated with family history of sz or with prediction of poor outcome. The introduction of long duration criteria and exclusion of affective syndromes tend to restrict the diagnosis to chronic stable patients. Patients fulfilling the majority of definitions (core sz patients) do not seem to constitute a strongly valid subgroup but rather a severely ill subgroup. Paradoxically, it seems that a century after the introduction of the sz concept, research is still badly needed, concerning conceptual and construct validity of sz, its essential psychopathological features, and phenotypic boundaries.

Key words: validation/diagnosis/polydiagnostic approach/concordance/schizophrenia concept/psychopathology/review

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Introduction

Schizophrenia (sz) remains an elusive entity, and the history of psychiatric research is replete with the attempts at formalizing its definition and hence to distinguish it from other disorders as well as the attempts at various internal subdivisions (eg, acute—chronic or poor premorbid—good premorbid subtypes). In fact, since the introduction of the concept, psychiatry has produced not less than 40 definitions of sz.

These historical permutations naturally sink gradually into oblivion with the most recent algorithms (such as *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* [*DSM-IV*] and *International Classification of Diseases, 10th Revision* [*ICD-10*]) acquiring the aura of important epistemological achievements with solid empirical foundations and insidiously reified into truly existing natural entities.[1, 2] Yet, it is important to realize that the operational diagnoses of today owe their shape not so much to their scientific foundations but to pragmatic needs and ensuing decisions to increase international consensus.

One possible investigative approach to the reliability and validity of sz definitions is to compare these definitions between themselves and with their historical predecessors. For example, to say that *ICD-10* is superior to *ICD-8*/*ICD-9* requires comparing these 2 algorithms with respect to some validating data of interest. The purpose of this study is to provide a review of such a polydiagnostic approach in sz research. This goal gains in urgency, given the ongoing contemplation of yet another change in the diagnostic systems.

The polydiagnostic approach[3–5] consists of applying different sets of criteria for a given diagnostic category to the same group of patients in order to assess the degree of concordance between the diagnoses and/or to compare their validity indicators.

Materials and Method

The Medline searches were performed for all clinical and epidemiological studies published since 1970 comparing at least 2 definitions of sz. The Medline search was supplemented by screening references of the individual

articles. Studies that did not indicate the numbers of patients with a given diagnosis were not included.

A preestablished scheme was used to record which and how many definitions were used, number of patients, the inclusion criteria, rating setting, the interrater reliability, the diagnostic concordance, follow-up assessments and their results, and other types of validation. Because the studies and hence the data were too heterogeneous, it was not possible to perform a systematic review, where the individual studies could enter into a meta-analytic approach.

Results

We have identified more than 100 articles published between 1972 and 2005, referring to 92 polydiagnostic studies. Twenty-six of these were follow-up studies. An overview of all studies appears in table 1.

Diagnostic Definitions

The polydiagnostic studies used approximately 40 different diagnostic definitions of sz and related disorders (2–23 in each study, median = 4). An overview of the definitions is shown in table 2. The formal criteria of these definitions differ; table 3 compares the criteria of some selected definitions.

Inclusion Criteria of the Individual Studies

58 studies (63%) dealt primarily with psychosis, the 11 of which (12%) with first-admission or recent onset psychosis. 34 studies (37%) included broad groups of patients and population subjects.

Psychopathological Ratings

The information about the details of psychopathological rating procedures was typically inadequate, except for listing the rating scales. 45% of the studies explicitly mentioned psychiatrists as raters, a further 13% used groups of raters with varying professional backgrounds, and 42% gave no information on the education of the interviewers.

In 26% of the cases, the rating was performed solely on the basis of hospital charts, in 39% exclusively on the basis of patient interviews, and in the remainder based on composite sources of information.

Reliability

The expectation of increased diagnostic reliability was what justified the introduction of operational definitions, and the *DSM-III* field studies did indeed present a high reliability level for sz (81%[6]), but the methodology was loose structured and no further field studies were presented for the later *DSM* revisions to clarify this issue. However, the diagnostic interrater reliability was assessed in less than half of the *polydiagnostic studies*, usually in the form of Cohen's kappa coefficients, which were, not surprisingly, somewhat better for the more recent (from Research Diagnostic Criteria [RDC] onward) operational definitions than for older definitions (Modestin et al,[7] Kirk and Kutchins,[8] cf. Kety et al[9] vs Kendler et al[10]), generally labeled "good" or even "excellent." Other forms of reliability checks (eg, test-retest) and other expressions of reliability (eg, symptom agreement) were rarely presented.

Before exploring the question of reliability, one should realize that there are 2 major, overlapping sources of a diagnostic disagreement: (1) *criterion variance*, which refers to the differences in the raters' use and *interpretation* of the *diagnostic criteria*, and (2) *information variance*, referring to the quality and quantity of the originally collected *psychopathological information*. The significance of *information variance* is illustrated by higher kappas found in rating live or videotaped interviews than in rating hospital charts[11] and by the fact that the reliability of rating case records remained only moderate even when using structured checklists.[12] Brockington[13] suggested that low interrater reliability for Feighner's and New Haven definitions in the Camberwell sample was caused by their complexity, which can be seen as an effect of *criterion variance*. As a rule, a diagnosis based on a few simple items becomes easily reliable compared with the diagnostic algorithms defined by many and interacting features.

Unfortunately, the structure of reliability was rarely discussed, and only a few studies allowed a more detailed reliability examination. In a unique study, Strakowski[14] showed that a lack of reliability between the clinical and the SCID-P (Structured Clinical Interview for DSM-II-R—Patient Version)–generated diagnoses could be partitioned into 58% caused by the information variance and 42% caused by the criterion variance. Unfortunately, such distinctions and explorations of the sources of variance are typically not performed nor discussed. Yet, if a creation or a revision of diagnostic criteria is motivated by reliability concerns, the emphasis should be focused on the criterion variance because the information variance is basically related to the comprehensiveness of the assessment.

Reliability is not an intrinsic property of the diagnostic definition. Needless to say, unreliability may be related to multiple factors, including skill and education of the interviewer. Reliability is higher in research settings but does not ensure reliability in clinical practice. Furthermore, reliability acquired through training on *clinical* samples cannot be unproblematically extrapolated to *population* studies where the majority of subjects do not suffer from any mental illness, or suffer from specific psychopathology but unaccompanied by dysfunction or distress, or where the subjects are prone to hide their symptoms. Moreover, the exact significance of quantifying reliability is not unequivocal. Thus, the magnitude of kappa coefficient may reflect differences in prevalence rates.[15] Kirk and Kutchins [8] demonstrated that a kappa

Table 1. The Polydiagnostic Studies

First author and year of publication	No. of Definitions of Schizophrenia (abbreviations of diagnostic definitions[a])	Sample (No. of patients included; diagnostic groups; design: follow-up [period: mean and/or range of years; no. {or %} of patients followed up]	Diagnostic Frequencies (%) (by all/by at least one definition; (range); *concordance: mean, (range)*	Validity (outcome: H = hospitalization, P = psychopathology, S = social function)
Shields 1972[60]	6 raters (clinical diagnoses)	57 twin pairs (24 MZ, 33 DZ); index twin: schizophrenia	-/-; (38–68); *Mean: 79.4%*	Twin concordance: highest in broadest criteria but best MZ:DZ discrimination with "middle-of-the-road" criteria
WHO-IPSS 1973,[36] 1979[104]	3 (ICD8, McKeon, Catego)	1202; Patients with functional psychosis of recent onset; multicenter design; follow-up (2 y; 75.5%)	25/-; (46–67); κ[b]: *ICD8/Catego: 0.68, ICD8/McKeon: 0.25*	Psychopathology: concordant patients more often males, single, no precipitating factors, hallucinations, delusions, flatness of affect, less depressed, higher cross-centee stability
Strauss1974[105]	3 (DSM2, FRS, Langfeldt)	142; Psychotic inpatients; follow-up (2 y, *N* = 111)	-/-; Follow-up: (26–77); —	Outcome (H, P, S): no significant differences
Hawk 1975[106]	3 (DSM2, FRS, Langfeldt)	131; Psychotic inpatients; follow-up (5 y, *N* = 80)	Follow-up patients: 76/76; (24–76); —	Outcome (H, P, S): no significant differences between different groups of schizophrenics
Taylor 1975[107]	2 (Feig, Taylor)	111; First-admission psychosis (clinical diagnosis of schizophrenia: *N* = 89)	The 89 patients: 6/18; (11–12); κ = *–0.27*	Differentiation by the single criteria of Feig: no major differences between clinical schizophrenia and mania
Newmark 1976[108]	4 (Bleu, FRS, Newmark, Yusin)	335; Inpatients (DSM2 schizophrenia: *N* = 108)	-/-; (21–47); *Significant differences*	Correspondence with DSM2 diagnosis: Bleu lowest correspondence
Strauss 1977[19]	8 (DSM2, Feig, Flex, FRS, NHSI, RDC)	272; First-admission, functional psychiatric disorder	-/45; (1–25); —	—
Brockington (Camberwell sample) 1978[13]	9; (Catego, Feig, Flex6, Forrest, FRS, Langfeldt, NHSI, Taylor)	119; First admission, possibly functional psychosis	25/-; At least 1 of 4 definitions: 53; (3–38); κ = *0.29; (0.04–0.67)*	—
Brockington (Netherne sample) 1978[13] Kendell 1979[45]	7 (Catego, Flex, FRS, Langfeldt, NHSI, RDC)	134; Inpatients with ICD8 functional psychosis; follow-up (6.5 y, *N* = 118)	Outcome diagnoses: 10/-; At least 1 of 6 definitions: 63; (18–36); κ = *0.59; (0.37–0.79)*	Outcome (H, P, S): Prediction of symptomatic outcome more successful than of social outcome
Koehler 1978[109]	2 (Feig, Taylor)	116; First-admitted patients with schizophrenia without FRS	18/31; (20–29); *Feig vs Taylor:* κ = *0.52*	—
Overall 1979[41]	6 sets of research diagnostic criteria (CDC, Feig, Flex, RDC, SI, TAC)	166; Schizophrenia patients	-/-; (27–92); *Disagreement*	Agreement with clinical diagnosis of schizophrenia: 27–92%. No definition superior to another
Bland 1979,[42] 1980[110]	3; (Feig, FRS, NHSI)	43; First-admission schizophrenia; follow-up (14 y, *N* = all)	-/-; (88–98); —	Outcome (P, S): related to Feig, not to FRS

Table 1. Continued

First author and year of publication)	No. of Definitions of Schizophrenia (abbreviations of diagnostic definitions[a])	Sample (No. of patients included; diagnostic groups; design: follow-up [period: mean and/or range of years; no. {or %} of patients followed up]	Diagnostic Frequencies (%) (by all/by at least one definition; (range); concordance: mean, (range)	Validity (outcome: H = hospitalization, P = psychopathology, S = social function)
Stephens 1980[46]	7 (Bland, DSM2, Feig, Flex, FRS, NHSI, RDC)	120; Predominantly schizophrenia patients; follow-up (9.8 y, *N* = 82)	-/-; (39–89); *RDC vs all except DSM2:* κ^b *(0.24–0.37)*	Outcome (H, P, S): not predicted by FRS (among others)
Helzer 1981[47]	4 (Catego [broad], DSM3, Feig, RDC)	134; Inpatients with functional psychosis (= Brockington's Netherne sample 1978); follow-up (6.5 y [5–8.3]; *N* = 125)	Outcome diagnoses: -/-; (14–42); κ *(0.24–0.84)*	Outcome (H, P, S): DSM3 and Feig identified poor outcome patients
Singerman 1981[43]	3 (DSM3, Feig, RDC)	216; Psychiatric patients and nonpatients	-/-; (12–19); κ *(0.38–0.59)*	—
Berner 1982[3]	8 (Bleu, Feig, FRS, RDC, VRC—no raw data on: Catego, ICD9, Taylor)	100; Functional psychosis	-/-; 5 Definitions: (21–59); *33–86%*	—
Endicott 1982[111]	10 (DSM3, Feig, Flex, NHSI, RDC, Taylor)	168; Inpatients	1/27; (4–26); *Dramatic differences*	—
Stephens 1982[31]	9 (Astrup, DSM1, DSM3, Feig, Flex, FRS, NHSI, RDC, Taylor)	283; Psychotic inpatients; follow-up (5–16 y, *N* = all)	7/97; (37–88); κ *(0–0.69)*	Outcome (P, H): predicted by DSM3 but not FRS
Klein 1982[32]	7 (DSM3, Feig,[c] Flex, FRS, RDC, Taylor)	46; Patients with DSM2 and NHSI schizophrenia	7/87; (24–63); κ *(–21– 0.84)*	Premorbid adjustment and chronicity (retrospective): FRS had better premorbid adjustment
Asnis 1982[65]	6 (Flex, Feig, NHSI, RDC, Taylor)	47; Chronic, hospitalized patients with RDC schizophrenia	64/100; (64–100); *4 Definitions:* κ^b *(0.08–0.47)*	Outcome (H, P, S): better prognosis for non-Taylor; Family history of schizophrenia spectrum disorders: no significant differences
Silverstein 1982[21]	3 (DSM2, DSM3, RDC)	252; Inpatients	-/-; (24–41); —	—
Young 1982[112]	4 (Flex, FRS, RDC, Taylor)	196; Inpatients (not only mild symptoms)	5/52; (19–30); *Significant agreement*	Latent class analysis: blunted affect and absence of affective syndromes related to latent class schizophrenia
Helmes 1983[11]	13 (Bleu, DSM3, Edwards, Feig, Flex, Kraep, Langfeldt, MBleu, Newmark, Willis, Yusin)	31; Outpatients with chronic schizophrenia (a subsample of Cernovsky 1985); retrospective design (10.8 y, *N* = all)	-/-; (Flex 80, Feig 91); —	—
Schanda 1984[49]	5 (DSM3, FRS, ICD9, RDC, VRC)	90; Patients with delusional syndromes; follow-up (6–9 y, *N* = 84)	-/-; (8–51); —	Outcome (course prognosis: episodic or chronic; P): DSM3, ICD9, and RDC: more chronic course. Affective symptomatology: high prognostic value

Table 1. Continued

First author and year of publication)	No. of Definitions of Schizophrenia (abbreviations of diagnostic definitions[a])	Sample (No. of patients included; diagnostic groups; design: follow-up [period: mean and/or range of years; no. {or %} of patients followed up]	Diagnostic Frequencies (%) (by all/by at least one definition; (range); concordance: mean, (range)	Validity (outcome: H = hospitalization, P = psychopathology, S = social function)
McGlashan 1984[44]	4 (DSM3, Feig, NHSI, RDC)	400; residentially treated inpatients; follow-up (2–15 y, *N* = 330)	-/-; (28–55); vs *"established use":* κ *(0.49–0.56)*	Diagnostic stability: Feig most stable. Outcome (P, S): all definitions had predictive validity; Feig had the poorest outcome
McGuffin 1984[62]	6 (Feig, Flex, FRS, RDC, Taylor, Tsuang + diagnostician judgments)	60 twin pairs: 26 MZ, 34 DZ; index twin probands schizophrenic	-/-; (13–45); —	Probandwise concordance: MZ concordance 11–58% (lowest Flex(6), highest Tsuang hebephrenic). MZ correlation in liability: 0.59–0.93. Estimated morbid risk: 0.19–0.65%.
Westermeyer 1984[51]	2 (DSM2, DSM3)	153; Patients with DSM2 schizophrenia (43% first admission); follow-up (median 2.3 y, *N* = all)	41/100; (41–100); —	Outcome (H, P, S): sex the most powerful predictor of overall outcome in DSM2, but not in DSM3
Lewine 1984,[20] Burbach 1984[113]	6 (Feig, Flex, FRS, NHSI, Taylor, RDC)	387; Inpatients; patients with only mild symptoms excluded	-/-; (2–60); κ = *0.24; (0.02–0.47)*	Sex ratio: more stringently defined schizophrenia yielded a significantly greater male to female ratio
Rosen 1984[114]	4 (Flex, FRS, Langfeldt, RDC)	46; Drug-free male inpatients with RDC or Feig schizophrenia	-/100; (74–100) Flex not included; —	Presence of positive and negative symptoms: positive correlation within RDC paranoid and undifferentiated subtypes
Kendler 1984,[24] Gruenberg 1985[100]	4 (DSM3, ICD9, RDC, Tsuang)	187; Inpatients with Feig schizophrenic; follow-up (short-term: 2.5 y, *N* = 172; long-term: 24 y, *N* = 175)	100/100; 100; *Subtypes:* κ *(0.21–1.00)*	Outcome (H, P, S): paranoid subtype best outcome; Tsuang more successful at predicting outcome
Cernovsky 1985,[28] Landmark 1986,[29] 1990,[30] Helmes 2003[115]	13 (Bleu, DSM3, Edwards, Feig, Flex, FRS, Kraep, Langfeldt, Mbleu, Newmark, Willis, Yusin)	120; Schizophrenia outpatients on depot injections; Helmes: a subgroup of 107 patients with schizophrenia by most systems	24/100; (35–93); *Phi (0.08–0.72)*	Intercorrelation with social and anamnestic variables: Kraep correlated with social adjustment; Feig longer prodrome. Correspondence of a symptom "triad" with the other definitions (phi): 0.24–0.64; Helmes: Cluster analysis of symptoms: no unambiguous solution for no. of clusters, limited support for historical subtypes

Table 1. Continued

First author and year of publication)	No. of Definitions of Schizophrenia (abbreviations of diagnostic definitions[a])	Sample (No. of patients included; diagnostic groups; design: follow-up [period: mean and/or range of years; no. {or %} of patients followed up]	Diagnostic Frequencies (%) (by all/by at least one definition; (range); concordance: mean, (range)	Validity (outcome: H = hospitalization, P = psychopathology, S = social function)
Kulhara 1986[35]	6 (Catego, DSM3, Feig, FRS, ICD9, RDC)	112; patients with ICD9 schizophrenia	17/100; (43–100); *All except ICD9:* κ *(0–0.64)*	Subtypes: 15 of 17 patients meeting all criteria had paranoid schizophrenia
Ben-Tovim 1986[75]	2 (DSM3, ICD9)	Villages in Botswana (N = 2625); demographic design	-/-; —; —	1-y prevalence (age adjusted): DSM3 43 and ICD9 53 per 10 000
Berner 1984,[77] 1986,[26] Lenz 1986,[27] 1991,[116] Katschnig 1988[76]	8 (Bleu and FRS vs DSM3, Feig, ICD9, RDC, Taylor, VRC)	200; First-admission patients with ICD9 functional psychosis; follow-up (7 y, N = 186)	-/-; (21–61); —	Sex ratio and age of onset: More males and earlier onset in narrow definitions. Male patients lower age of onset; Probability of diagnosis: Bleu symptoms considered more significant than FRS symptoms for schizophrenia by all systems. Duration of hospital stay: correlated with formal thought disorder; Diagnostic stability of ICD9, RDC, and DSM3
Coryell 1987[117]	3 (DSM3, Feig, RDC)	98; Inpatients with nonmanic psychoses; follow-up (0.5 y, N = all)	-/-; (20–37); *53–86%*	Outcome (P, S): family history of major depression: DSM3 not different from affective patients
Cooper 1987[66]	2 (DSM3, ICD9)	Patients with broad ICD9 schizophrenia in a catchment area; demographic design	-/-; —; —	Annual incidence rates (by sex and age): 8–20 per 100 000. Male-to-female ratio: 2.2–2.4
Tandon 1987[118]	2 (FRS, RDC)	294; Inpatients	12/25; (19–20); κ^b = *0.47*	Predictive value of FRS: 90%. Specificity of FRS for schizophrenia vs major depression = 97%
Jorgensen 1987[119]	2 (DSM3, ICD8)	129; Mothers with a clinical diagnosis of schizophrenia (The Copenhagen High-risk Study)	81/94; (84–91); κ^b = *0.42*	—
Modestin 1987[50]	5 (Bleu, DSM3, Flex, FRS, RDC)	52; Schizophrenia patients admitted with acute psychotic decompensation	-/100; (22–77); κ^b *(–0.07–0.34)*	Presence of basic symptoms (FCQ): no significant differences
Levav 1987[69]	3 (DSM3, NHSI, RDC)	509; First admissions	-/-; (32–44); —	Yearly incidence rates: 24–32 per 100 000
Fenton 1988[120]	2 (DSM3, DSM3R)	532; Inpatients in long-term residential setting; follow-up (15 y (2–32), N = 146 of 164 schizophrenics)	31/34; (31–34); —	Outcome (H, P, S): no differences in outcome

Table 1. Continued

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Hwu 1988[121]	2 (DSM3, ICD9)	137; Inpatients with functional psychiatric disorder; follow-up (7 y, *N* = 127)	32/63; (36–46); κ^b = *0.50*	Diagnostic stability high. Outcome (P, S): ICD9 more favorable than ICD3
Gerbaldo 1989[122]	5 (DSM3, FC, Feig, ICD9, RDC)	100; Inpatients with endogenous psychosis	-/-; (30–66); *Against FC:* κ^b *(0.37–0.86)*	Comparison with FC process psychoses: most FC process psychoses were schizophrenia by other definitions
Goodman 1989[123]	3 (DSM2, DSM3R, Tsuang-paranoid)	78; discharged DSM2-schizophrenia patients (37 paranoid); follow-up (2 y, *N* = all)	DSM3: 62%; paranoid subtypes: 9/40; (17–29); —	Outcome (H): more inpatient days for DSM2 paranoids and DSM3R nonparanoids
Möller 1989[124]	3 (DSM3, ICD8, RDC)	183; Inpatients with ICD8 functional psychoses retrospectively rediagnosed; follow-up (5–8 y)	Follow-up: -/-; (43–57); *Against ICD8:* κ *(0.20–0.63)*	Outcome (H, P, S): DSM3 schizophrenia poorest GAS outcome
US Soviet study 1989[125]	3 (DSM3R, USSR chart, USSR current)	27; USSR forensic psychiatric patients	15/89; (15–89); κ^b *(0.04–0.52)*	—
Leboyer 1990[25]	4 (DSM3, DSM3R, ICD10, Tsuang)	104; DSM3R schizophrenia members of 49 families; follow-up (13.7 y [1–44], *N* = all)	100/100; 100; Subtypes: κ *(0.57–0.96)*	Subtype stability: fairly good by all, highest for patients with hebephrenia
Ni Nuallain 1990[73]	2 (Catego, ICD8)	689 patient sample with ICD8 schizophrenia diagnoses; demographic design	14/100; (14–100); —	1-y prevalence: Catego S-class: 10 and ICD8: 73 per 10 000
Keks 1990,[57] 1992[58]	11 (Bleu, Cloninger, DSM3, Feig, Flex, FRS, Kraepelin, Langfeldt, Mbleu, RDC, Taylor)	44; Acutely psychotic men (and 28 healthy controls)	7/100; (36–70); —	Basal PRL concentration: lower in RDC, DSM3, and others. Haloperidol reaction on PRL: lower by all definitions except FRS and Bleu.
Copolov 1990,[37] McGorry 1992[33]	12 (Bleu, Cloninger, DSM3, Feig, Flex, FRS, Kraep, Langfeldt, Mbleu, RDC, Taylor)	176; Recent onset functional psychosis	-/-; 8 Definitions: (20–73); κ *(–0.27–0.67)*	Clusters created by explorative multidimensional scaling: (for men) one cluster formed by definitions excluding, and another cluster by definitions permitting affective symptoms. Sex ratio: sex difference by Flex
Peralta 1991[53]	3 (Bleu, FRS)	86; RDC schizophrenia	49/100; (51–63); —	Association with basic symptoms (FCQ): higher in FRS than in Bleu

Table 1. Continued

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Wetterberg 1991[126]	8 (DSM3, DSM3R, Feig, Flex, FRS, Pichot, RDC, Taylor)	51; Patients with psychiatric symptomatology (single-pedigree study)	-/-; (61–100); —	—
Jablensky (WHO 10-country study) 1992[127]	3 (ICD9, Catego SPO, Catego S+)	1379; Patients with psychotic symptoms or behavior; follow-up (2 y)	50/98; (53–92); κ[b] *(0.06–0.42)*	Cross-center Catego and ICD subtype variations
Dollfus 1992[128]	11 (Catego, DSM3R, Feig, Flex, FRS, ICD9, Langfeldt, NHSI, RDC, Taylor, VRC)	51; Nonorganic and nonaffective DSM3R psychosis (present or past)	-/-; (22–78); —	Presence of symptoms: DSM3R, ICD9, and others included patients with negative and depressive symptoms. Phase of illness: ICD9, FRS, and others included more patients with acute symptoms.
Peralta 1992[34]	21 (Bleu, Catego, Cloninger, DSM3, Edwards, Feig, Flex, FRS, Guze, Kraep, Langfeldt, MBleu, Newmark, Pull, RDC, Taylor, VRC, Willis, Yusin)	118; Inpatients with schizophrenia	16/100; (36–88); *4 Definitions:* κ *(0.13–0.66)*	Association with basic symptoms (FCQ): positively with FRS but negatively with DSM3R
Farmer 1992[129]	11 (Crow, DSM3, DSM3R, Farmer, Feig, Flex, FRS, Pull, RDC, Taylor, Tsuang)	397; Psychotic inpatients	-/-; 8 Definitions: (29–74); —	—
Iacono 1992[68]	5 (DSM3, Feig, Flex, ICD9, RDC)	175; First-episode cases in a large city	-/-; (17–65); —	Incidence rates: 7.4–15.0 per 100 000; Male to female risk ratio: 2.64–3.47
Hiller 1993[12]	2 (DSM3R, ICD10)	100; Inpatients with ICD8 endogenous psychosis	-/-; (30–44); —	—
Keks 1993[59]	11 (Bleu, MBleu, Cloninger, DSM3, Feig, Flex, FRS, Kraep, Langfeldt, RDC, Taylor)	26; Acutely admitted schizophrenia patients	4/100; (23–62); —	α_2-adrenergic receptor sensitivity by measuring growth hormone response to clonidine: lower only by Bleu, Cloninger, FRS, Langfeldt, MBleu, and Taylor
Castle 1993[67]	5 (DSM3, DSM3R, Feig[67,], ICD9, RDC)	470; First-contact nonaffective psychosis	-/100; (29–100); —	Incidence rates: 6.0–25.2 per 100 000; Male to female incidence rate ratio: 0.5–2.5 (< 45 y: >1; > 45 y: <1)
Strik 1993[130]	2 (DSM3R, Leonhard)	18; Remitted schizophrenia inpatients (+18 controls)	61/100; (61–100); —	P300 amplitudes: Leonhard: significantly lower amplitude than controls

Table 1. Continued

First author and year of publication)	No. of Definitions of Schizophrenia (abbreviations of diagnostic definitions[a])	Sample (No. of patients included; diagnostic groups; design: follow-up [period: mean and/or range of years; no. {or %} of patients followed up]	Diagnostic Frequencies (%) (by all/by at least one definition; (range); concordance: mean, (range)	Validity (outcome: H = hospitalization, P = psychopathology, S = social function)
Deister 1993,[131] 1994[23]	4 (Andreasen, DSM3R, FRS, ICD10)	148; Patients with narrowly defined schizophrenia; follow-up (23 y (10–50), *N* = 144)	Follow-up patients: 2/100; (22–100); —	Long-term outcome (H, P, S): 93% persisting alterations. Highest discrimination for DSM3R. FRS had no prognostic value; Subtypes: paranoid and positive subtypes best outcome
Kety 1994,[9] Kendler 1994[10]	2 Kety: Kraep-Bleu- DSM2; Kendler: DSM3	76 index and 76 control adoptees and their biological and adoptive relatives (national sample); index adoptees originally diagnosed within a Kraep-Bleu-DSM2 schizophrenia spectrum	-/-; (41–62); —	Prevalence of schizophrenia spectrum disorders in biological vs control relatives: significantly higher by both definitions. Higher, though insignificantly, by DSM2 than by DSM3
Dollfus 1994[132]	14 (Bleu, Catego, DSM3R, Feig, Flex, FRS, ICD9, ICD10, Langfeldt, NHSI, Pull, RDC, Taylor, VRC)	15; Patients (11 in an acute phase of illness, 14 hospitalized)	-/-; —; —	Concordance between diagnoses by medical examiner and by computer: excellent (κ = 0.63–1)
Wciórka 1995,[133] 1995[134]	5 (Bleu, DSM3, FRS, ICD10, VRC)	167 Inpatients with delusional syndrome; follow-up (8.7 y, *N* = 107)	11/93; (26–83); —	Outcome (H, P, S): DSM3 connected with higher intensity of residual symptoms
Almeida 1995[135]	11 (Catego, DSM3R, DSM4, Feig, Flex, FRS, ICD10, Langfeldt, NHSI, RDC, Taylor)	47, Patients with ICD9 late paraphrenia (+33 controls)	-/100; Probable or definite: (46–100); κ *(0.02–0.57)*	—
Davies 1995[136]	(1) 2 (Feig, non-Feig-ICD10) and (2) 5 (DSM3, DSM3R, Feig, ICD10, RDC)	45; Mothers with schizophrenia (past/present) admitted to a mother-baby unit	-/-; (36–82); —	Admission with acute post partum illness episode: in 43% of non-Feig ICD10, but none of Feig schizophrenics.
Craddock 1996[137]	2 (DSM3R, RDC)	100; 50 Patients from affective and 50 from schizophrenic families	-/-; (26–27); κ *(0.72–0.80)*	Agreement between OPCRIT diagnoses and consensus best-estimate lifetime diagnoses: good to excellent agreement (κ = 0.93–0.97)
Harvey 1996[72]	2 (DSM3R, Feig)	980; Prevalence survey. Demographic design	37/62; (44–55); κ = *0.72*	Prevalence: 29–31 per 10 000
Hill 1996,[138] Roberts 1998[139]	6 (DSM3R, DSM4,* Feig, FRS, ICD10, RDC) *Roberts	83; Subjects with antemortem DSM3R schizophrenia, rediagnosed postmortem; 57% suicide	5 Definitions: 21/69; 6 definitions: (42–70); *5 definitions:* κ *(0.32–0.64)*	Validation of antemortem diagnoses of schizophrenia by polydiagnostic reassessment: disagreement

Table 1. Continued

First author and year of publication)	No. of Definitions of Schizophrenia (abbreviations of diagnostic definitions[a])	Sample (No. of patients included; diagnostic groups; design: follow-up [period: mean and/or range of years; no. {or %} of patients followed up]	Diagnostic Frequencies (%) (by all/by at least one definition; (range); concordance: mean, (range)	Validity (outcome: H = hospitalization, P = psychopathology, S = social function)
Faraone 1996,[18] Nurnberger 1994[140]	2 (DSM3R, RDC)	260; Patients with schizophrenia, schizoaffective and affective psychosis (intrasite study: 179, intersite study: 81)	-/-; (9–19); —	Latent class analysis: Excellent sensitivity and specificity of both definitions. Confusability estimates: DSM3R schizoaffective subtypes often confused with schizophrenia
Williams 1996[141]	12 (Crow, DSM3, DSM3R, Farmer, Feig, ICD10, NHSI, Pull, RDC, Taylor, Tsuang)	30; A range of diagnoses including nonpsychotic	13/70; (30–70); —	—
Lindström 1997[71]	4 (DSM3, DSM3R, DSM4, ICD10)	Long-term DSM3R functional psychosis in a catchment area; demographic design	-/-; —; —	1-y prevalence of schizophrenia: 49–55 per 10 000
Mason 1997,[48] Harrison 1996[142]	4 (Catego, DSM3R, ICD9, ICD10)	99; First-contact patients; follow-up (13 y, *N* = all)	-/-; Onset: (31–68); κ *(0.13–0.77)*	Diagnostic stability: DSM3R and ICD10: high specificity. Outcome (P, S): significant only for DSM3R and ICD10. Effect of duration criteria: a 6-month criterion improved predictive validity.
Jeffreys 1997[143]	2 (DSM3R, Feig)	Patient samples from 2 censuses of people with a broad clinical diagnosis of schizophrenia	283 Patient sample: 36/62; (39–60); κ = *0.63*	Point prevalence (age 15+): broad schizophrenia: 59, DSM3R: 35, and Feig: 34 per 10 000
Kendler 1998[55]	2 (DSM3R, Kendler)	343; Patients with broadly defined schizophrenia and affective illness (+ matched controls)	-/-; DSM3R: 37; Latent classes: schizophrenia 26, Hebephrenia 3; —	Latent class analysis, risk of illness in relatives: highest risk for schizophrenia in relatives of hebephrenia class patients
Maslowski 1998[144]	12 (Bleu, Catego, Dongier, DSM3R, Edwards, Flex, FRS, Kraep, Langfeldt, MBleu)	113; Schizophrenia patients, 57 colored and 56 black individuals	-/-; —; —	Diagnostic consensus: core symptoms remained the same between 2 ethnic groups but qualitative differences
Wciórka 1998[145]	2 (DSM4, ICD10)	105; Schizophrenia patients hospitalized in acute phase	83/100; (86–97); *83%*	Comparison of diagnostic and symptomatological profiles: minor differences
Cardno 1999,[63] 2002[64]	4 (DSM3R, FRS, ICD10, RDC)	224 twin pairs (106 MZ); twins with lifetime history of psychosis	-/-; Twin 1: (42–48); —	Twin concordance rate: 0.41–0.43 (FRS: 0.21); lifetime morbid risk: 0.75–0.84; heritability estimates: 0.83–0.87 (FRS: 0.71)
Amin 1999[40]	2 (DSM3R, ICD10)	168; First-contact psychotic patients; follow-up (3 y, *N* = 161)	-/-; (25–34); —	Positive predictive value: 82–83%; concordance between onset and follow-up diagnosis: κ = 0.46–0.54

Table 1. Continued

First author and year of publication)	No. of Definitions of Schizophrenia (abbreviations of diagnostic definitions[a])	Sample (No. of patients included; diagnostic groups; design: follow-up [period: mean and/or range of years; no. {or %} of patients followed up]	Diagnostic Frequencies (%) (by all/by at least one definition; (range); concordance: mean, (range)	Validity (outcome: H = hospitalization, P = psychopathology, S = social function)
Pfuhlmann 1999[146]	3 (ICD10, DSM3R, Leonhard)	22 MZ and 25 DZ twin pairs; twins hospitalized with ICD9 and DSM3R schizophrenia spectrum psychoses	-/-; (6–32); —	Twin concordance: Leonard systematic schizophrenia: absent in MZ and all DZ patients discordant—therefore impossible to calculate concordance rates
Azevedo 1999[147]	2 (DSM3R, ICD10)	140; Subjects from bipolar and schizophrenia pedigrees (100), and schizophrenia patients (40)	-/-; (46–47); —	Agreement between OPCRIT diagnoses and consensus best-estimate lifetime diagnoses: excellent (κ = 0.81–0.83)
Peralta 1999,[148] 2003[149]	1999: 2 (DSM3R, Feig); 2003: 2 (DSM4, ICD10)	660; Inpatients with psychotic symptoms; iIndex episode and lifetime psychopathology ratings	-/-; (53–64), Feig not included; *Good to excellent*	1999: Prevalence of FRS: FRS did not increase likelihood of DSM3R and Feig schizophrenia; 2003: Latent class analysis: concordance of between ICD10 and a schizophrenia lifetime class: κ 0.43; between ICD10 and a schizophrenia index episode class: κ 0.61
Allardyce 2000[70]	3 (DSM4, ICD10)	Incidence rates of schizophrenia over time in SW Scotland; demographic design	-/-; —; —	Incidence rates over time (20-y period): falling rate of clinical, but not of OPCRIT diagnoses
Forrester 2001[22]	5 (DSM3R, Feig, ICD10, RDC)	204; Patients discharged with an ICD9 diagnosis of functional psychosis; Follow-up (8.2 y (5 admissions), *N* = all)	-/-; First admission: (18–29); fifth admission: (30–50); —	Diagnostic stability:1–2 admission 70–84%; 1–5 admission 58–96%; ICD9 highest and ICD10 lowest
Jansson 2002[39]	8 (DSM3, DSM4, Feig, Flex, ICD9, ICD10, RDC, VRC)	155; First admissions (one third clinically psychotic)	Excluding simple schizophrenia: 9/70; (24–57); κ *(0.24–0.82)*	Concurrent validity: ICD9 was associated with family history of schizophrenia and "trait" formal thought disorder (unlike ICD10)
Häfner 2003[150]	2 (Catego, ICD9)	232; First-illness episodes of a broad ICD9 schizophrenia; follow-up (5 y, *N* = 112)	-/-; (73–87); —	Sex ratio: differences nonsignificant
Modestin 2003,[7] Bleuler 1978[97]	6 (DSM3R, DSM4, FRS, ICD10, MBleu, RDC)	205; Schizophrenia inpatients from M. Bleuler's long-term study (*N* = 208); follow-up (10 to >20 y; 202 rediagnosed patients)	-/-; (69–92); κ *(0.06–0.99)*	Outcome (course prognosis): with the modern definitions the proportion of patients with undulating course and recovery slightly decreased. Correspondence with MBleu as project diagnosis: κ = 0.06–0.24

Table 1. Continued

Author (first author and year of publication)	No. of Definitions of Schizophrenia (abbreviations of diagnostic definitions[a])	Sample (No. of patients included; diagnostic groups; design: follow-up [period: mean and/or range of years; no. {or %} of patients followed up]	Diagnostic Frequencies (%) (by all/by at least one definition; (range); concordance: mean, (range)	Validity (outcome: H = hospitalization, P = psychopathology, S = social function)
Jäger 2004[151]	2 (DSM4, ICD10)	218; Inpatients with functional psychosis; follow-up (15 y, *N* = 201)	23/29; (23–29); κ = *0.86*	Outcome (P, S): no marked differences in outcome; incomplete delimitation of transient/episodic psychoses from schizophrenia
Barrett 2005[74]	3 (DSM4, ICD10, RDC)	Cases with psychotic disorder in a catchment area (in Sarawak)	-/-; —; —	Prevalence rates of treated schizophrenia: 18–35 per 10 000; age corrected (to age 55) 42–83 per 10 000
Jakobsen 2005,[152] 2006[38]	7 (DSM3, DSM3R, DSM4, Feig, FRS, ICD10, R'DC)	100; Patients with chronic functional psychosis	-/-; (69–98); κ *(–0.10–0.89)*	Cooccurrence of affective and psychotic symptoms: the elimination of OPCRIT item 52 increased the concordance of schizophrenia spectrum disorders
Peralta 2005[56]	23 (Bleu, Catego, Cloninger, DSM3R, DSM4, Edwards, Feig, Flex(6), FRS, Guze, ICD10, Kraep, Langfeldt, MBleu, Newmark, NHSI, Pull, RDC, Taylor, VRC, Willis, Yusin)	660; Patients with psychotic symptoms (= Peralta 1999,[148] 2003[149])	-/-; (29–87); *Concordance poor*	Factor analysis, 3 factors had substantial interpretation: a general schizophrenia factor, a Schneiderian factor, and a Bleulerian factor
Stompe 2005[153]	4 (Bleu, *DSM4*, *ICD10*, Leonard)	220; Consecutively admitted patients with schizophrenia	100/100; 100; —	Subtype prevalence: variation of subtype frequencies, especially catatonic and hebephrenic subtypes

Note. DSM, Diagnostic and Statistical Manual of Mental Disorders; *ICD*, *International Classification of Diseases.*
[a]The diagnostic abbreviations are explained in table 2. As some systems give rise to more than one definition (eg, Flex(5) and Flex(6)), the total number of definitions may be greater than the number of abbreviations.
[b]Calculated from article data.
[c]As modified by Tsuang.[154]

Table 2. Diagnostic Abbreviations

Andreasen	Negative and positive schizophrenia, Andreasen and Olsen[155]
Astrup	Astrup et al[156]
Bland	Bland and Orn[42]
Bleu	Eugen Bleuler[84]
Catego	Catego (narrow or nuclear schizophrenia = S+, broad = S+, P+, S?, P?, and O?), Wing et al[157]
CDC	Composite Diagnostic Checklist Criteria[41]
Cloninger	Cloninger et al[158]
Crow	Crow[159]
Dongier	Acute delusional psychosis, M. Dongier[160]
DSM2	*DSM-II*, APA[161]
DSM3	*DSM-III*, APA[6]
DSM3R	*DSM-III-R*, APA[162]
DSM4	*DSM-IV*, APA[163]
Edwards	"North America," Edwards[161, 164]
Farmer	Farmer et al[165]
FC	Frankfurt Classification System[166]
Feig	St Louis Criteria, Feighner et al[88]
Flex	Flexible system, IPSS, WHO[167]
Forrest	Forrest and Hay[168]
FRS	First-rank symptoms, Schneider[87]
Guze	Guze et al[169]
ICD8	*ICD-8*, WHO[170]
ICD9	*ICD-9*, WHO[171]
ICD10	*ICD-10*, WHO[172]
Kendler	Latent classes[55]
Kraep	Kraepelin[85]
Langfeldt	Langfeldt[173]
Leonhard	Leonhard[174]
Mbleu	Manfred Bleuler[175]
McKeon	McKeon cluster, IPSS, WHO[36]
Newmark	Newmark et al[176]
NHSI	New Haven Schizophrenia Index[177]
Pichot	Delusional Attack[178]
Pull	Critères empiriques français[179, 180]
RDC	*Research Diagnostic Criteria*, Spitzer et al[181–183]
SI	The Schizophrenic Index[184]
TAC	Texas Actuarial Checklist[185]
Taylor	Taylor and Abrams[107, 186]
Tsuang	Tsuang and Winokur [187]
USSR	Snezhnevsky[186,] Holland and Shakhmatova-Pavlova[189]
VRC	Vienna Research Criteria, Berner et al[4]
Willis	"Great Britain," Willis and Bannister[161, 190]
Yusin	Yusin et al[191]

Note. DSM, Diagnostic and Statistical Manual of Mental Disorders; *ICD*, *International Classification of Diseases*.

of the same magnitude may be presented by different adjectives (eg, good or excellent), depending on the agenda of the individual study. Finally, the conventional wisdom of low reliability precluding validity[16] is not invariably true. Some authors demonstrated that diagnostic validity is possible even in the case of low reliability, if the sensitivity is low and specificity is high.[17, 18]

Frequencies of Specific Diagnoses

Variation in frequencies between definitions. The studies demonstrated a wide range in the proportions of patients fulfilling the criteria for the individual definitions of sz (eg, Strauss and Gift[19]: 1–25%; Lewine et al[20]: 2–60%). Such differences in the frequency and hence in the inclusiveness of the definitions reflect the variation in the diagnostic criteria. The influence of the duration criteria and the exclusion of affective syndromes were illustrated by a shift from *DSM-II* (having no such criteria) to the criteria of RDC and *DSM-III*.[21] *DSM-II* sz was often repartitioned as affective, schizoaffective, and schizophreniform disorders.

A *DSM-IV* and *ICD-10* reanalysis of the Burghölzi sz sample, originally diagnosed by Eugen and Manfred Bleuler, showed that the sz diagnosis was retained in nearly in all cases as the contemporary spectrum diagnoses (sz, schizoaffective disorder, schizotypal personality disorder).[7]

Interstudy variation. There was a striking interstudy variation in the proportion of patients fulfilling a given diagnosis of sz. Differences in study design and inclusion criteria were primarily responsible for this variation. The number of studies allowing an assessment of frequencies of the contemporary definitions was limited. Across 12 studies, the proportion of *DSM-III-R* sz varied from 24 to 100%, lowest in a group of patients with "functional psychosis[22]" and highest in patients with "narrowly defined schizophrenia.[23]" Corresponding figures are found for *ICD-10* sz.

The samples composed of the patients selected because of their sz diagnosis were (tautologically) frequently diagnosed as having sz by all applied definitions.[24, 25] Selection of chronic sz patients resulted in frequent sz diagnosis even by Feighner's conservative definition.[11] In fact, a comparison of different samples of patients demonstrated that the proportion of Feighner sz increased with chronicity, whereas it was not the case for the frequencies of Schneider's first-rank symptom (FRS)—Berner et al[26] and Lenz et al[27] vs Cernovsky et al[28] and Landmark et al.[29, 30]

Diagnostic Concordance (47 studies)

Substantial differences in concordance between the sz definitions were demonstrated in studies comparing the various preoperational definitions.[31–34] Yet, between related systems, there was a considerable concordance.[7, 31] Some diagnostic concentricity was seen between related definitions. Thus, in one study, almost all Feighner cases fulfilled also *DSM-III* criteria.[33] Cases fulfilling most of the definitions of sz and, consequently, yielding the highest concordance were often named "core schizophrenia" cases. In one study,[35] such cases were found to suffer from paranoid sz. The concordant group of the IPSS

Table 3. Comparison of the Diagnostic Criteria of Selected Schizophrenia Definitions

Name of Schizophrenia Definition/Diagnostic System	Author/Year	Operational Criteria	Duration Criteria		Exclusion of Affective Disorder	Symptom Criteria					
			Illness	Psychosis		First-Rank Symptoms	Bizarre Delusions	Formal Thought Disorder	Autism	Blunted/ Inadequate affect	Disturbance Self or of Personality
Schizophrenia	Bleuler 1908/1911[84]	–	–	–	–	–	–	+	+	BI	+
St Louis diagnostic criteria	Feighner 1972[88]	+	6 mo	–	+	–	–	+	–	–	–
New Haven Schizophrenia Index	Astrachan 1972[177]	+	–	–	–	–	–	+	+	BI	–
Flexible system	Carpenter WHO-IPSS 1973[167]	+	–	–	–	–	+	+	–	BI	–
Present State Examination/ Catego S+	Wing 1974[157]	+	–	–	–	+	–	–	–	–	–
Research Diagnostic Criteria	Spitzer 1975,[181, 182] 1978[183]	+	–	2 wk	+	+	+	+	–	B	–
ICD-9	WHO 1978[171]	–	–	–	–	+	–	+	+	BI	+
DSM-III	APA 1980[6]	+	6 mo	Active phase	+	+	+	+	–	BI	–
Vienna Research Criteria	Berner 1983[4]	+	–	–	–	–	–	+	–	B	–
DSM-IIIR	APA 1987[162]	+	6 mo	Active phase	+	+	+	+	–	BI	–
ICD-10	WHO 1993[172]	+	–	1 mo	+	+	+	+	–	BI	-
DSM-IV	APA 1994[163]	+	6 mo	1 mo	+	+	+	+	–	B	–

Note. +, present; –, not present, *DSM*, *Diagnostic and Statistical Manual of Mental Disorders*; *ICD*, *International Classification of Diseases*.

patients was characterized by a higher percentage of males and of single patients, a psychopathological profile with more hallucinations, delusions, and flatness of affect, fewer depressive symptoms, precipitating factors, and previous inpatient treatments.[36] Uniforming the patient sample tended to increase the concordance between the definitions.

Restricting the sample to a group of patients with illness duration longer than 6 months increased the concordance kappa between definitions having different duration criteria.[35] In one study, the concordance was increased by widening the sample to all first admissions and by eliminating the 3 strictest definitions.[13] Definitions excluding affective symptoms were demonstrated to form a cluster with a higher kappa than the cluster formed by the definitions that permit them.[37] In a sample of chronic psychotic patients, the elimination of the OPCRIT item 52, "co-occurrence of psychotic and affective symptoms," increased the agreement of the sz spectrum disorders.[38] Among all studies of the present review comparing diagnostic concordance kappas ($N = 34$), values above 0.80 were found exclusively in those that included chronic psychotic patients but not in first-onset psychotic patients and mixed groups of patients (Fisher exact test: $P < .005$).

Validation

78 studies (85%) presented validation data. The most frequently occurring measure of validation was the predictive power of diagnostic definitions. However, true concurrent validation—be it through neurobiological markers or other relevant measures that do not enter into the diagnostic definition such as family history of mental illness, psychometric measures of formal thought disorder, or subjective sense of self-dissolution[39]—was rare.

Outcome

24 studies (28%) compared the outcome of different sz definitions. The majority of the outcome periods were longer than 5 years. The outcome variables investigated were the prediction of the course of illness, the number of readmissions, symptomatology levels, diagnostic stability, and of social and functional outcome.

Diagnostic stability as a measure of outcome (6 studies) was usually calculated as positive predictive value. Several studies showed high stability of the operational definitions, such as *DSM-III-R* and *ICD-10*.[40]

Conservative definitions were found to be predictors of poor outcome, but tautologically, the notion of conservatism is often dependent on the chronicity of course. This applied first of all to Feighner's criteria.[41–44] Broad definitions such as The New Haven Schizophrenia Index, on the other hand, did not predict the outcome.[13, 31, 42, 45, 46] Such diagnoses embrace favorable as well as poor outcome cases; conservative diagnoses only include the latter group. The duration criteria of the diagnostic algorithm influence the predictive validity. Thus, the 6-month duration criterion has been demonstrated to increase predictive validity in terms of diagnostic stability.[12, 47, 48] Elimination of affective components in sz tended to result in an aggregation of chronic, nonepisodic, and therefore stable forms of illness.[49, 50]

Schneider's FRS, playing a central part in the contemporary sz definitions, resulted in a relatively inclusive sz concept that did not predict the outcome.[13, 23, 27, 31, 45, 46] In comparing *DSM-II* and *DSM-III*, the former was found to be more inclusive and indicative of a more favorable outcome. The *DSM-III* appeared to exclude many females with favorable outcome.[51]

Psychopathological Validation

In a few studies, concurrent validity was established by relating sz definitions with traditional sz symptoms or traits such as Bleuler's fundamental symptoms, Schneider's FRS, Huber's basic symptoms, and premorbid adjustment.

ICD-9 sz when compared with *ICD-10* was associated with formal thought disorder[39] and with self-disorders and basic symptoms (L.B.J and J.P, unpublished data from the same study).

In a comparison of 6 definitions of sz, Bleulerian fundamental symptoms were found to be more important for the diagnosis than Schneiderian FRS.[26] In one study, Schneider sz was associated with better premorbid adjustment than non-Schneider sz.[32] The significance of basic symptoms assessed by Frankfurt Complaint Questionnaire (FCQ)[52] seemed more ambiguous,[34, 50, 53] probably, because of the methodological shortcomings of the FCQ.

Cluster, Latent Class, and Factor Analyses

In the IPSS,[36] a McKeon cluster analysis of the present state examination (PSE) data resulted in 10 clusters. Some *ICD-8* sz subtypes tended to be concentrated in certain clusters. Some clusters were common to all centers, others only in a small number of them. Three clusters were selected to make up a sz definition for further analyses together with de *ICD-8* and Catego-S diagnoses.

Latent class analysis[54] was carried out in a handful of studies. In an attempt to explain test-retest reliability findings, Faraone[18] estimated the sensitivity and specificity of RDC and *DSM-III-R* diagnoses to latent classes. Sz according to both systems had high kappas and excellent sensitivity and specificity. Kendler[55] compared classes generated by a handful of OPCRIT items collected in the Roscommon Family Study with *DSM-III-R* diagnoses. The classes which emerged resembled well-known diagnostic categories such as classic (Kraepelinian) sz, hebephrenia, and schizophreniform disorder. Eighty-four percent of cases classified as classic sz were also so diagnosed by the *DSM-III-R*. The classes were validated against the familial risk of illness. The risk for sz and

sz spectrum was significantly increased in relatives of all probands classes except major depression and, especially, marked in the relatives of hebephrenia-class patients (sz 16.1%, sz spectrum 45.5%).

Factor analysis of diagnostic variables of 23 sz definitions applied by Peralta[56] to 660 psychotic patients yielded 3 interpretable factors (a general sz factor, a Schneiderian factor, and a Bleulerian factor) explaining 58% of the variance, which was found to support a dimensional approach to sz.

Biological Parameters

Only a few studies related biological findings to multiple diagnoses. Assuming that the prolactin-releasing potency of a drug corresponds to its antipsychotic potency, Keks[57, 58] found prolactin concentration to be lower in patients fulfilling criteria precluding affective syndromes.

In measuring the growth hormone response to the injection of clonidine as an expression of α_2-adrenergic receptor sensitivity, Keks[59] found that most of the definitions associated with blunted response did not preclude affective symptomatology.

Heritability

Heritability served as a measure of validation in a few studies.

Twin studies. Gottesman and Shields, examining twin concordance as an expression of heritability, found both monozygotic (MZ) and dizygotic (DZ) concordance highest using the broadest definitions (among nonoperational diagnoses of 6 clinicians) but the best MZ:DZ discrimination using "middle-of-the-road" criteria.[60, 61] However, the emphasis on maximizing MZ:DZ concordance ratio is only meaningful on the prior assumption of polyfactorial transmission.

Conservative definitions such as Feighner's were among those with the highest MZ twin concordance whereas FRS were among those with the lowest.[62] MZ twins diagnosed by the operational definitions had higher concordance and correlation in liability compared with FRS-diagnosed twins.[62–64]

Adoption studies. In a sample of biological and adoptive relatives of index adoptees with sz and of control adoptees, significant differences were found in the prevalence of sz spectrum disorders in biological vs control relatives of index probands both by a Kraepelin-Bleuler-*DSM-II* definition[9] and by *DSM-III*.[10] The percentage of spectrum disorders was higher, though insignificantly, among the relatives of the former than of the latter.

Family history. Few polydiagnostic studies compared the familial rates of sz. Comparing 4 definitions, Asnis[65] failed to find significant differences between the familial rates of sz spectrum disorders. In a first-admission sample, *ICD-9* sz was found to be significantly associated with family history of sz, whereas *ICD-10* was not associated at all.[39] Moreover, partitioning of *ICD-10* sz[39] revealed that sz selectively aggregated in the relatives probands diagnosed by the criterion 2 (an assortment of Bleulerian and second rank symptoms). Kendler's latent class analysis study,[55] mentioned above, showed a dramatically increased risk for sz in the relatives of the hebephrenia-class probands.

Demography

Incidence. Four studies calculated the incidence rates of sz to be within a range from 6 to 32 per 100 000 inhabitants.[66–69] The rates varied within each study between the diagnostic definitions. Thus, *ICD-9* sz was found to be broader than *DSM-III* and *DSM-III-R*, and Feighner's definition was the most restrictive.

Examining the alleged decline in the incidence of sz, Allardyce[70] found a falling rate of clinical diagnosis over time (20 years) but not the OPCRIT-generated *ICD-10* and *DSM-IV* sz, suggesting that changes in the diagnostic habits have operated to bias the reported rates.

Prevalence. Lindstrom[71] calculated the 1-year prevalence of sz by 4 contemporary diagnostic definitions to be within the range of 40–47 per 10 000. The prevalence found by Harvey[72] was 29–31 per 10 000. The 1-year prevalence of the PSE S-class estimated by Ni Nuallain[73] was as low as 10 per 10 000 as compared with the 73 of *ICD-8* because of the failure of the S-class to identify patients who presented with exclusively negative symptoms. The combination of PSE and lifetime syndrome checklist data increased the PSE S-class prevalence to 39 per 10 000. Among the Iban of Sarawak, Barrett[74] found rates of treated sz between 18 and 35 per 10 000—age corrected (to age 55) between 42 and 83 per 10 000, and in rural Botswana, Ben-Tovim[75] found the age-adjusted 1-year prevalence of *DSM-III* sz to be 43 per 10 000 and of *ICD-9* 53 per 10 000.

Gender distribution. 40 studies inform about the gender distribution. The mean numbers of male and female patients in these particular studies were 95 and 86 (nonsignificant). Some studies allowed for a comparison of incidence rates, frequencies, and lifetime courses. The highest ratio of male to female incidence rate was produced by the narrow Feighner definition.[67, 68] Other studies failed to demonstrate the incident sex ratio differences between broad and narrow definitions.[66, 76] Conservative definitions yielded a significantly greater male to female prevalence ratio.[20, 51, 67, 77] Patients excluded by the narrow definition were typically favorable-outcome females.[51] Castle[67] found the male-to-female ratio to be

higher than 1 in patients with onset below age 45 and lower than 1 above age 45 in sz definitions requiring a 6-month duration.

Age of onset. Male patients had a lower age of onset in nearly all definitions,[76] but narrow definitions seemed to be associated with onset before age 25 in a greater part of the patients than the broad ones.[77]

Discussion

The polydiagnostic studies of the past 4 decades reflect an evolution away from prototypically anchored diagnostic concepts of sz to polythetically oriented definitions, based on the so-called operational criteria. It is, however, necessary to point out that all studies reviewed here—as polydiagnostic comparisons—necessitated a certain operationalization of the examined definitions.

The principal finding of our review is that the degree of concordance between different definitions of sz varies considerably, depending, of course, on the similarity of the criteria. The number of sz cases in a given sample may vary by more than factor 3 when diagnosed by 2 different systems. This is far from trivial and not only because of psychopathological considerations. In fact, etiological research is very frequently performed through comparisons of "schizophrenias" with "nonschizophrenias," ie, the sample is simply dichotomized into szs and the remainder of the sample. Such procedure may attenuate or otherwise obscure differences of interest because the "nonschizophrenia" group may contain spectrum cases as well as sz cases defined so by other sets of criteria.

The polydiagnostic studies do not provide sufficient validity data to justify claiming a clear superiority of any particular definition over others. In many studies, the percentage of sz cases so diagnosed by all diagnostic algorithms is remarkably low. This subgroup—usually called "core schizophrenia"—appears to us more as a product of severity and impenetrable interactions between the single criteria rather than as being reflective of a class with a *particularly strong validity*.

What is conspicuously lacking in the polydiagnostic studies is a serious and systematic reflection on the *conceptual validity* of sz, ie, *what we take this illness to be* in the very first place.[78] Empirical phases of validation do not happen in a void but are preceded and constrained by the original typifications of what we take sz to be.[78–83] There are several possibilities: eg, is it an illness mainly defined by *trait-like* intersubjective displacement, subjective orientation with changes of the worldview (as described by Bleuler's generic term of autism[84, 81]), compromised unity of consciousness and self-dissolution (Kraepelin[85, 86]), characteristic psychotic symptoms (a view unjustly ascribed to Schneider[87]), a deteriorating or unremitting course (Feighner[88]), simply a multidimensional construct,[56, 89] or something else (eg, schizotaxia[90, 91])?

The issue of affective symptoms represents a special concern in the discussions of conceptual and construct validity. The exclusion of affective components from the picture of sz, despite their clinical reality as ubiquitous symptoms in all stages of sz, has also necessitated a creation of a rather convoluted category of schizoaffective psychosis.[92] This evacuation of affective symptoms from sz appears as quite arbitrary, and yet as shown by Keks,[57–59] a stratification of sz by presence or absence of affective symptoms may be biologically meaningful. The subdivisions of sz on the basis of biological findings obtained in polydiagnostic studies are in agreement with Bleuler's claim that we deal with a group of szs rather than a single disease.[84] Such a view gains currently provisional support from genetic studies. Thus, in a family study by Hallmayer et al, a mathematically identified subtype of sz, characterized by pervasive neurocognitive deficit, had a distinct genetic profile.[93]

Empirical validity is a multidimensional concept comprising pathogenetic and etiologic knowledge (or hypotheses), course, treatment response, etc. Although we have knowledge of a variety of etiologically relevant risk factors in sz, this knowledge has no substantive form, which could permit assessment of causal validity in a polydiagnostic context. Genetic data[39] suggest that it is the Bleulerian dimension of fundamental symptoms that is associated with familial aggregation of sz. No molecular genetic studies have so far been included in the polydiagnostic designs.

Predictive validity—exploring outcome and stability of course—is examined in approximately half of the studies. Unfortunately, it is a rather equivocal type of validity. Prediction of course may serve as a validity criterion with an independent a priori assumption that, say, an unremitting course or chronic social dysfunction is *constitutive of a given diagnostic entity*. The recent duration criteria lead to an automatic exclusion of favorable outcome, acute psychosis. Diagnostic stability in the sense of basically unchanged psychopathological picture as a measure of validity is at odds with the well-replicated findings that 20–30% of patients with sz recover from psychosis (cf. Modestin et al,[7] Hafner and an der Heiden,[94] Ciompi and Muller,[95] Huber et al,[96] and Bleuler[97]). Psychopathological stability would be relevant as a validating criterion if one were interested in the persistence of the trait features of the illness, indicating structural alterations of consciousness.[81] Therefore, definitions based on trait-like features (eg, Bleuler's fundamental symptoms) appear to be more stable than those based on fluctuating psychotic features (eg, FRS). In the latter case, diagnostic stability means chronic, productive psychosis. The FRS are particularly poor predictors of outcome.[13, 23, 27, 31, 45, 46] Conservative definitions with *inbuilt* chronicity (deviant preonset personality) such as Feighner's are more likely to predict uniformly poor outcome. Unfortunately, only few studies made an attempt to examine differential validity of sz by other means than outcome prediction.

A dominating concern of contemporary psychiatry is the quest for reliability of diagnostic categories. The very rise of "operational" definitions in the 1970s was stimulated by the demonstration of alarming US-UK diagnostic disagreements.[98, 99]

The operational definitions seem to have modestly increased the interrater reliability (eg, Gruenberg et al[100]; Kety et al[9] vs Kendler et al[10]). However, reliability is easy to achieve but "it becomes vacuous when it is a primary goal, un-associated with other concerns.[101]" In the quest for reliability, many domains of psychopathology of sz, once considered as taxonomically and pathogenetically crucial (eg, the notion of autism or formal thought disorder) have been either strongly simplified (converting the "fundamental" schizophrenic symptoms into behaviorally defined "negative symptoms[86, 102]") or deleted altogether from the psychiatric idiom (eg, the notion of self or subjectivity[103]).

In conclusion, this review highlights certain steps that seem to us as urgently needed in sz research. There is a need for integrating the rapidly expanding technological means with explicit reflection constrained by phenomenological familiarity with sz. Empirical studies should increasingly lose their exploratory nature and become instead designed to answer more specific and explicit questions.

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