Epidemiological and Clinical Characterization Following a First Psychotic Episode in Major Depressive Disorder: Comparisons With Schizophrenia and Bipolar I Disorder in the Cavan-Monaghan First Episode Psychosis Study (CAMFEPS)

Olabisi Owoeye[1,2], Tara Kingston[1,2], Paul J. Scully[1,2], Patrizia Baldwin[1,2], David Browne[1,2], Anthony Kinsella[2], Vincent Russell[1,3], Eadbhard O'Callaghan[†,4], and John L. Waddington[*,1,2]

[1]Cavan-Monaghan Mental Health Service, Cavan General Hospital & St Davnet's Hospital, Monaghan, Ireland; [2]Molecular & Cellular Therapeutics, Royal College of Surgeons in Ireland, Dublin, Ireland; [3]Department of Psychiatry, Royal College of Surgeons in Ireland, Beaumont Hospital, Dublin, Ireland; [4]DETECT Early Psychosis Service, Dublin, Ireland

[†]Deceased.

[*]To whom correspondence should be addressed; Molecular & Cellular Therapeutics, Royal College of Surgeons in Ireland, St Stephen's Green, Dublin 2, Ireland; tel: +353-1-402-2129, fax: +353-1-402-2453, e-mail: jwadding@rcsi.ie

While recent research on psychotic illness has focussed on the nosological, clinical, and biological relationships between schizophrenia and bipolar disorder, little attention has been directed to the most common other psychotic diagnosis, major depressive disorder with psychotic features (MDDP). As this diagnostic category captures the confluence between dimensions of psychotic and affective psychopathology, it is of unappreciated heuristic potential to inform on the nature of psychotic illness. Therefore, the epidemiology and clinical characteristics of MDDP were compared with those of schizophrenia and bipolar disorder within the Cavan-Monaghan First Episode Psychosis Study (*n* = 370). Epidemiologically, the first psychotic episode of MDDP (*n* = 77) was uniformly distributed across the adult life span, while schizophrenia (*n* = 73) and bipolar disorder (*n* = 73) were primarily disorders of young adulthood; the incidence of MDDP, like bipolar disorder, did not differ between the sexes, while the incidence of schizophrenia was more common in males than in females. Clinically, MDDP was characterized by negative symptoms, executive dysfunction, neurological soft signs (NSS), premorbid intellectual function, premorbid adjustment, and quality of life similar to those for schizophrenia, while bipolar disorder was characterized by less prominent negative symptoms, executive dysfunction and NSS, and better quality of life. These findings suggest that what we currently categorize as MDDP may be more closely aligned with other psychotic diagnoses than has been considered previously. They indicate that differences in how psychosis is manifested vis-à-vis depression and mania may be quantitative rather than qualitative and occur within a dimensional space, rather than validating categorical distinctions.

Key words: psychotic illness/major depressive disorder with psychotic features/schizophrenia/bipolar disorder/psychopathological dimensions/diagnostic categories

Introduction

Though the psychosis phenotype can occur in myriad human circumstances, our understanding derives primarily from studies in schizophrenia; thus, despite recent advances, we remain in considerable ignorance.[1–3] The explanatory challenge, with historical antecedents in the classical conundrum as to the relationship between *dementia praecox* and *manic-depressive psychosis* (the *Kraepelinian dichotomy*),[4–6] has contemporary resonance in categorical vs dimensional concepts of psychosis and if/how these should be reflected in Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) and International Classification of Disease-11[7,8]: do current psychotic diagnoses reflect not discrete entities but, rather, domains defined by certain psychopathological dimensions and functional characteristics, the boundaries of which are likely arbitrary and in continuity with other domains of mental illness, through to the limits of "normal" human experience.[9–11]

While a primary focus of much recent research has been on the nosological, clinical, and biological relationships between schizophrenia and bipolar disorder,[12–15] the most common psychotic diagnosis other than schizophrenia and bipolar I disorder is major depressive disorder with the DSM-IV[16] specifier "severe, with psychotic features" (MDDP). Though it reflects the confluence between dimensions of psychotic and affective psychopathology,

MDDP, also known as psychotic depression,[17] has been surprisingly overlooked in this context (this *theme*).[18] While psychotic features occur in only a minority of patients with major depressive disorder,[19–22] contemporary evidence suggests that MDDP is not related solely to severity of illness[21] and may be better conceptualized as a distinct clinical syndrome.[23]

In contrast, while the DSM-IV specifier "severe, with psychotic features" is available also for bipolar I disorder, psychosis has long been[24,25] and continues to be[15] conceptualized as integral thereto; psychotic features are evident clinically in the majority of patients with bipolar disorder (eg, 73% of 246 cases),[26] with contemporary evidence suggesting this categorical distinction to be arbitrary and not related solely to severity of illness, such that bipolar disorder may be better conceptualized by a continuum of psychosis.[27,28] This would be analogous to the situation whereby depression occurs so commonly in schizophrenia[20,29] as to not require a DSM-IV specifier "with depressive features"; rather, schizophrenia may be better conceptualized by a continuum of depression that is "an integral part of psychosis."[30]

Following review of psychotic depression[17] and of first-episode studies that have vs have not included MDDP,[31] further first-episode studies of MDDP have evolved. For example, 2 recent studies, both of which imposed an arbitrary upper age cutoff, have compared first-episode MDDP with schizophrenia and bipolar disorder: one[32] focussed on psychopathology and indicated commonalities in symptom profiles that differed in severity; the other[33] focussed on neuropsychology and indicated commonalities in cognitive profiles that differed in severity and pervasiveness. In the face of historical and contemporary challenges, understanding of psychotic illness and the categorical vs dimensional debate would be greatly enhanced by studying first-episode psychosis, ascertained on an epidemiological basis across the whole adult life span and via all routes to care, in the absence of a priori diagnostic restriction. Application of contemporary diagnostic algorithms as post hoc assessment, rather than as a criterion for inclusion/exclusion, would resolve all 12 DSM-IV psychotic diagnoses and allow systematic comparisons between selected diagnostic categories across several levels of enquiry. The Cavan-Monaghan First Episode psychosis Study (CAMFEPS)[31,34] adopts such methodology. To illuminate the extent to which features of MDDP associated with the psychosis domain align themselves with those of schizophrenia and bipolar I disorder, we describe here comparisons between these 3 diagnostic categories at the level of epidemiology and clinical features, in terms of psychopathology, neuropsychology, neurology, premorbid adjustment, and quality of life. Other articles in this *theme* make similar comparisons at the level of clinical and molecular genetics,[35] structural and functional neuroimaging,[36] and treatment.[37]

Materials and Methods

Study Setting

CAMFEPS is a prospective study, operating since 1995, that seeks to identify "all" incident cases presenting with a first episode of any psychotic disorder in 2 rural counties in Ireland, Cavan and Monaghan, as described previously in detail.[31,34] Study protocols were approved by the Research Ethics Committees of the North Eastern Health Board, the Health Service Executive Dublin North East Area, St Patrick's Hospital, Dublin, St John of God Hospital, Co, Dublin, and the Central Mental Hospital, Dublin, to include (*a*) subjects giving written informed consent to formal assessment and (*b*) obtaining diagnostic and demographic information from case notes and treating health professionals for subjects from whom informed consent for assessment was not obtained.

Cavan and Monaghan are 2 contiguous rural counties with a population of 109 139 (55 821 males and 53 318 females) at the 2002 census; the region consists of towns, villages, and remote areas, in the absence of any major urban areas, and is of substantial ethnic and social homogeneity, with the great majority of the population being white Irish.[38] CAMFEPS is based within Cavan-Monaghan Mental Health Service, which operates a community-based service model with a focus on home treatment, general practice liaison, and services based in small local clinics. It involves 2 community mental health teams, a specialist service for the elderly and a community rehabilitation team; central to the delivery of health services in this model is the use of home-based treatment as an alternative to hospital admission.[39] All cases from this catchment area who present to services in other parts of the country are returned to Cavan-Monaghan Mental Health Service as soon as is practicable.

Study Outline

CAMFEPS involves the following ascertainment procedures[31,34]: cases resident in the Cavan-Monaghan Mental Health Service catchment area are identified from (*a*) all treatment teams in the catchment areas, (*b*) cases from the catchment areas who choose to avail of private mental health care in St Patrick's Hospital, Dublin, or St John of God Hospital, Co, Dublin, which together account for >98% of all national private psychiatric admissions,[40] and (*c*) cases from the catchment areas having admission to the national forensic service at the Central Mental Hospital, Dublin.

The primary criterion for entry into the study is a first lifetime episode of any DSM-IV psychotic illness, to include a first manic episode (with or without the specifier "severe with psychotic features"), at age 16 or above, with no upper age limit. DSM-IV diagnosis is made at study entry and again at 6 months thereafter; there are no exclusion criteria other than a previously treated

psychotic episode; hence, all psychotic diagnoses included in DSM-IV are incepted into the study.

Study Assessments

At entry into the study, cases are first evaluated using the Structured Clinical Interview for DSM-IV (SCID) Axis I Disorders.[41] At 6 months thereafter, all clinical information, to include case notes and discussions with the treating teams, are reviewed to confirm or update the initial DSM-IV diagnosis.[31,34] For individuals who died between study entry and 6 months, the most proximal diagnosis was carried forward. For individuals from whom informed consent to assessment was not obtained, the Research Ethics Committees approved a protocol for accessing basic demographics, clinical records, and treating teams to allow DSM-IV diagnosis; these demographics and diagnoses are then entered into the anonymized data set. For individuals giving informed consent to evaluation, the following instruments were applied as soon as was practicable over the first few weeks following initial presentation:

1. Psychopathology was assessed using the Positive and Negative Syndrome Scale (PANSS),[42] to resolve scores for positive and negative symptoms.
2. Neuropsychology was assessed using the Mini-Mental State Examination (MMSE),[43] to screen for marked cognitive impairment in a population that extends naturalistically through to the 10th decade; the National Adult Reading Test (NART),[44] to estimate level of intellectual functioning prior to the onset of psychotic symptoms; and the Executive Interview (EXIT),[45] to access executive functioning in this population that included older cases unable to perform more incisive instruments.
3. Neurology was assessed using the Neurological Evaluation Scale (NES)[46] and the Condensed Neurological Examination (CNE),[47] to evaluate neurological soft signs (NSS); the Simpson-Angus Scale (SAS),[48] to evaluate extrapyramidal movement disorder; and the Abnormal Involuntary Movement Scale (AIMS),[49] to evaluate involuntary movement disorder.
4. Premorbid adjustment was assessed using the Premorbid Adjustment Scale (PAS),[50] applied over childhood (PAS-1, age up to 11 years) and adolescence (PAS-2, age 12–15 years), with the late adolescent period (PAS-3, age 16–18 years) suspended because of potential confounding with the onset of psychosis.
5. Quality of life was assessed using the Quality of Life Scale (QLS),[51] to evaluate interpersonal relations, instrumental role, intrapsychic foundations, and common objects and activities.

Data Analysis

Incidence is expressed as the annual number of cases per 100 000 of population aged ≥ 15 years, with 95% CI for incidence rates and rate ratios (RR) between the genders. These analyses were performed using Stata Release 7. Demographic and assessment data are expressed as means with SD and medians with interquartile ranges (IQR) and analyzed using ANOVA followed by Student's *t* test (2 tailed); because differences in age between some study groups were encountered (see "Results" section), ANOVAs were repeated using ANCOVA for age. These analyses were performed using SPSS version 15.

Results

Overview

Over its first 13 years of operation, between May 1995 and April 2008, CAMFEPS identified 370 cases of any DSM-IV psychotic disorder (214 males, 156 females). Annual incidence across all psychotic diagnoses [33.5 (95% CI: 30.1–37.0)/100 000 aged ≥ 15] was higher in males [39.0 (34.0–45.0)] than in females [28.0 (23.8–32.8); RR = 1.39 (95% CI: 1.13–1.71), $P < .01$]. Mean age at first presentation across all psychotic diagnoses [38.4 (SD 19.5) {median 32 (IQR 29)} range 16–92] was 7 years younger in males [35.6 (SD 18.5) {median 28 (IQR 24)} range 16–87] than in females [42.3 (SD 20.2) {median 37 (IQR 31)} range 16–92, $P < .001$].

Diagnostic Composition

Among the above study cohort, the number of cases who received at 6 months post-presentation one of the 3 DSM-IV diagnoses here at issue were as follows (70% by direct SCID interviews, 30% by SCID-based evaluation of all clinical documentation and direct interviews with treating teams; males [M] and females [F]):

1. schizophrenia, 73 (54 M, 19 F);
2. bipolar disorder, 73 (38 M, 35 F): 54 (26 M, 28 F) with the specifier "severe, with psychotic features"; 19 (12 M, 7 F) without this specifier;
3. major depressive disorder, severe, with psychotic features, 77 (36 M, 41 F).

The other DSM-IV psychotic diagnoses encountered, each smaller in number and hence not considered further here, were as follows: schizophreniform disorder, 21 (12 M, 9 F); schizoaffective disorder, 19 (11 M, 8 F); brief psychotic disorder, 20 (6 M, 14 F); delusional disorder, 22 (11 M, 11 F); substance-induced psychotic disorder, 20 (18 M, 2 F); psychotic disorder due to a general medical condition, 11 (8 M, 3 F); substance-induced mood disorder, with manic features, 6 (4 M, 2 F); mood disorder due to a general medical condition, with manic features, 3 (1 M, 2 F); and psychotic disorder not otherwise specified, 23 (14 M, 9 F).

MDDP: Comparative Epidemiology

Incidence for each of these diagnoses was indistinguishable. While each diagnosis could occur at any age across

the adult life span, from the teens through to the eighth or ninth decade, schizophrenia and bipolar disorder first presented most commonly in young adulthood (schizophrenia: median < mean; bipolar disorder: median < mean); in contrast, MDDP first presented most commonly in middle age ($P < .001$ vs schizophrenia and bipolar disorder; median > mean; table 1).

For schizophrenia, incidence was 3-fold higher in males than in females (RR = 2.95 [1.73–5.04], $P < .001$), with mean age at first presentation being 9 years younger in males than in females ($P < .05$). In contrast, both incidence and age at first presentation for MDDP and for bipolar disorder were indistinguishable between the sexes; there was no difference in age at first presentation between the 74% of bipolar patients with vs the 26% of those without the specifier "severe, with psychotic features," for either sex (tables 1 and 2).

MDDP: Comparative Clinical Characteristics

For schizophrenia, cases completing PANSS assessment (44 M, 10 F) were younger at first presentation (27.9 [11.3]) than those not completing assessment (10 M, 9 F; 39.5 [19.1], $P < .01$). For MDDP, cases completing PANSS assessment (19 M, 18 F) were younger at first presentation (40.6 [18.9]) than those not completing assessment (17 M, 23 F; 61.0 [20.4], $P < .01$). For bipolar disorder, cases completing PANSS assessment (20 M, 25 F) did not differ in age at first presentation (33.9 [14.5]) from those (18 M, 10 F) not completing assessment (30.6 [13.1]). Those completing and not completing PANSS assessments did not differ in gender distribution. Similar profiles were seen in relation to those completing vs not completing other assessments. These differences between cases completing vs not completing assessment may reflect (*a*) general willingness to engage that diminishes with age, to a lesser extent in those with manic as opposed to depressive psychopathology, interacting with (*b*) feasibility of engagement in a dispersed, rural environment that, for the great majority of cases, involves a domestic or community setting rather than an inpatient facility (see "Study Setting" section).

Psychopathology. Setting schizophrenia as the reference category, PANSS-positive symptom scores did not differ in MDDP or bipolar disorder (table 3); here and below, there were no effects of sex or diagnosis × sex interactions unless otherwise stated. PANSS-negative symptom scores were slightly lower in MDDP and substantially lower in bipolar disorder ($F_{2,130} = 29.32$, $P < .001$). These findings were essentially unaltered on ANCOVA for age; PANSS subscale scores were each unrelated to age.

Bipolar patients with the specifier "severe, with psychotic features" differed from those without this specifier only in evidencing higher PANSS-positive symptom scores ($F_{1,41} = 4.32$, $P < .05$); PANSS-negative symptom scores were indistinguishable.

Table 1. Number of Cases and Age at First Presentation by Diagnosis at 6 Months

Diagnostic Group	Number of Cases and Age Parameters		
	Total	Males	Females
Schizophrenia	73 30.9 (14.5) {25 (17)} [16–79]	54 28.6 (13.3)* {23 (13)} [16–77]	19 37.4 (16.3) {35 (27)} [16–79]
Major depressive disorder with psychotic features	77 51.2 (22.0) {57 (41)} [16–87]	36 49.6 (23.0) {57 (45)} [16–87]	41 52.6 (21.4) {57 (40)} [17–83]
Bipolar disorder	73 32.6 (14.0) {28 (22)} [16–80]	38 31.2 (13.3) {24 (22)} [18–70]	35 34.2 (14.7) {29 (27)} [16–80]
Bipolar disorder without psychotic features	19 34.8 (14.4) {30 (26)} [18–70]	12 34.7 (16.6) {32.5 (27)} [18–70]	7 35.0 (10.7) {30 (22)} [27–52]
Bipolar disorder with psychotic features	54 31.9 (13.9) {24 (22)} [16–80]	26 29.6 (11.5) {24 (14)} [18–55]	28 34.0 (15.7) {27 (27)} [16–80]

Note: Data are number of cases and mean age (SD) {median (interquartile range)} [absolute range].
*$P < .05$ vs females.

Table 2. Incidence by Diagnosis at 6 Months

Diagnostic Group	Incidence		
	Total	Males	Females
Schizophrenia	6.4 (5.0–8.1)	9.6* (7.2–12.5)	3.2 (1.9–5.1)
Major depressive disorder with psychotic features	6.9 (5.5–8.7)	6.5 (4.5–9.0)	7.4 (5.3–10.0)
Bipolar disorder	6.6 (5.2–8.3)	6.9 (4.8–9.4)	6.3 (4.4–8.7)

Note: Data are incidence/100 000 of population aged >15 (95% CI).
*$P < .01$ vs females.

Table 3. Clinical Features by Diagnosis at 6 Months

Clinical Feature	Diagnosis				
	Schizophrenia	Major Depressive Disorder With Psychotic Features	Bipolar Disorder	Bipolar Disorder Without Psychotic Features	Bipolar Disorder With Psychotic Features
Psychopathology					
PANSS positive	17.4 (6.4) [54]	14.7 (6.5) [37]	16.3 (8.1) [45]	10.9 (5.0) [7]	17.3 (8.3)* [38]
PANSS negative	21.7 (7.4) [54]	17.3 (8.3)** [37]	9.5 (4.0)*** [45]	8.0 (1.5) [7]	9.7 (4.3) [38]
Neuropsychology					
MMSE	28.1 (2.2) [51]	27.4 (2.6) [36]	28.1 (2.1) [39]	28.6 (2.2) [7]	27.9 (2.1) [38]
NART	22.6 (11.5) [46]	23.0 (8.9) [30]	26.5 (9.8) [36]	28.1 (14.3) [7]	26.1 (8.7) [29]
EXIT	8.4 (4.5) [46]	9.9 (4.2) [33]	6.9 (5.3)**** [39]	4.8 (2.1) [6]	7.3 (5.6) [33]
Neurology					
NES	14.2 (8.1) [47]	18.7 (11.0) [30]	10.3 (8.0)** [34]	6.3 (7.7) [6]	11.1 (7.9) [28]
SAS	3.9 (3.4) [50]	4.1 (3.7) [33]	2.7 (3.6) [43]	0.9 (0.9) [7]	3.1 (3.8) [36]
AIMS	1.3 (2.5) [51]	0.9 (1.4) [33]	0.7 (2.0) [44]	0.0 (0.0) [7]	0.8 (2.2) [37]
Premorbid adjustment					
PAS-total	23.3 (7.0) [42]	26.2 (10.9) [25]	19.9 (8.2)**** [30]	20.7 (5.6) [6]	19.7 (8.8) [24]
PAS-1	10.6 (3.1) [42]	12.6 (4.4)** [25]	9.5 (4.0) [30]	9.8 (2.2) [6]	9.4 (4.3) [24]
PAS-2	12.7 (4.8) [42]	13.6 (6.8) [25]	10.4 (4.3) [30]	10.8 (3.3) [6]	10.3 (4.6) [24]
Quality of life					
QLS-total	65.5 (20.6) [45]	76.1 (28.0) [28]	100.3 (22.3)*** [37]	104.6 (16.1) [7]	99.3 (23.6) [30]

Note: PANSS, Positive and Negative Syndrome Scale; MMSE, Mini-Mental State Examination; NART, National Adult Reading Test; EXIT, Executive Interview; NES, Neurological Evaluation Scale; SAS, Simpson-Angus Scale; AIMS, Abnormal Involuntary Movement Scale; PAS, Premorbid Adjustment Scale; QLS, Quality of Life Scale.
Data are mean (SD) [number of cases].
*$P < .05$ vs bipolar disorder without psychotic features, **$P < .05$, ***$P < .001$ vs schizophrenia, and ****$P < .05$ vs major depressive disorder with psychotic features.

Neuropsychology. MMSE and NART scores were similar in schizophrenia, MDDP, and bipolar disorder (table 3). While EXIT scores in MDDP did not differ from those in schizophrenia, scores were lower (less dysfunction) in bipolar disorder than in MDDP ($F_{2,112} = 3.60$, $P < .05$). These findings were essentially unaltered on ANCOVA for age; as expected, MMSE scores decreased with age ($F_{1,119} = 10.35$, $P < .01$) and EXIT scores increased with age ($F_{1,111} = 3.07$, $P < .05$), while NART error scores were unrelated to age.

Bipolar patients with the specifier "severe, with psychotic features" did not differ from those without this specifier in terms of MMSE, EXIT, or NART error scores; among bipolar patients, males evidenced slightly higher NART scores ($F_{1,32} = 8.63$, $P < .05$).

Neurology. NES scores were similar in schizophrenia and MDDP but were lower in bipolar disorder ($F_{2,105} = 6.66$, $P < .001$; table 3); a numerically similar profile for CNE scores failed to attain statistical significance. Each of SAS and AIMS scores were low and did not differ between the diagnoses. These findings were essentially unaltered on ANCOVA for age; as expected, NES scores ($F_{1,104} = 14.56$, $P < .001$) increased with age, while low SAS and AIMS scores were unrelated to age.

Bipolar patients with the specifier "severe, with psychotic features" did not differ from those without this specifier in terms of NES, CNE, SAS, or AIMS scores.

Premorbid Adjustment. PAS-total scores were similar in schizophrenia and MDDP but slightly lower in bipolar disorder ($F_{2,91}$ = 3.64, P < .05; table 3). However, ANCOVA for age revealed PAS-total scores to be higher in MDDP ($F_{2,90}$ = 4.20, P < .05). This effect of diagnosis on PAS-total derived primarily from PAS-1 (age up to 11 years), for which scores were higher in MDDP on both ANOVA ($F_{2,91}$ = 4.48, P < .05) and ANCOVA for age ($F_{2,91}$ = 4.82, P < .01). As expected, PAS-total, PAS-1, and PAS-2 scores were each unrelated to age.

Bipolar patients with the specifier "severe, with psychotic features" did not differ from those without this specifier in terms of PAS-total, PSA-1, or PAS-2 scores; among bipolar patients, males evidenced slightly higher PAS-2 scores ($F_{1,26}$ = 6.33, P < .05).

Quality of Life. QLS-total scores were similar in schizophrenia and MDDP but were higher in bipolar disorder ($F_{2,104}$ = 17.76, P < .001; table 3); this effect of diagnosis on QLS-total was evident for interpersonal relations, instrumental role, intrapsychic foundations, and common objects and activities. These findings were essentially unaltered on ANCOVA for age; QLS scores were unrelated to age.

Bipolar patients with the specifier "severe, with psychotic features" did not differ from those without this specifier in terms of QLS scores.

Discussion

MDDP is here compared with schizophrenia and bipolar disorder using data from CAMFEPS,[31,34] a study of first-episode psychosis that involves a defined catchment area, all routes to care (ie, public, private, and forensic), all modes of initial care provision (ie, inpatient, outpatient, and community/home-based), full diagnostic scope (ie, all 12 DSM-IV psychotic diagnoses), no arbitrary upper age cutoff (ie, cases incepted throughout the adult life span), and Research Ethics Committee approvals to include diagnostic and demographic information on those cases from whom informed consent for assessment was not obtained.

Epidemiology

Schizophrenia was, as expected, primarily a disorder of young adulthood, which was considerably more common in males than in females, in accordance with evidence that more restrictive diagnostic criteria result in increasing male preponderance[52,53]; first presentation with psychosis was at a younger age in males than in females, in accordance with a long-standing literature.[54–56] Bipolar

disorder was also, as expected, primarily a disorder of young adulthood; however, in contrast to schizophrenia, neither incidence nor age at first manic episode differed between males and females, as noted previously.[57,58] While the number of cases with each diagnosis did not allow further exploration of age-at-onset distributions, CAMFEPS is contributing cases to large, collaborative data sets that have sufficient statistical power to conduct such analyses.[56]

In contrast to both schizophrenia and bipolar disorder, age at first psychotic episode in MDDP was much more evenly distributed across the life span. Furthermore, in contrast to schizophrenia, but in a manner similar to bipolar disorder, age at first psychotic episode in MDDP did not differ between males and females. These findings could not be readily related to previous first-episode studies comparing MDDP with other psychotic diagnoses due to several methodological differences, including mode of case ascertainment, pooling of MDDP and bipolar disorder into an "affective psychosis" group, absence of either a bipolar or a schizophrenia group, inclusion only of bipolar cases "with psychotic features", and, particularly, application of an arbitrary upper age cutoff.[32,59–62] The present findings elaborate previous studies[54–56] in indicating that age at onset of psychosis appears meaningfully higher in epidemiological than in nonepidemiological studies. Thus, early intervention programs focussing on late adolescence and early adulthood may fail to include an important population of first-episode patients, particularly those with MDDP.

Clinical Features—Similarities Between Diagnoses

At the first psychotic episode, MDDP, schizophrenia, and bipolar disorder were indistinguishable as follows:

1. Severity of positive psychotic symptoms.
2. Absence of gross, nonspecific cognitive impairment.
3. Level of intellectual function prior to the first psychotic episode. While reduced premorbid intellectual function has been widely reported in schizophrenia,[63] studies in bipolar disorder are more equivocal.[64] Findings in 2 studies of first-episode MDDP[33,65] are similar to those reported here.
4. Absence of movement disorder, as would be expected for first-episode cases having minimal exposure to primarily second-generation antipsychotics and other drugs.

Clinical Features—Differences Between Diagnoses

At the first psychotic episode, MDDP, schizophrenia, and bipolar disorder were distinguishable as described subsequently.

Negative Symptoms. They, evident in schizophrenia even at the first psychotic episode,[62] were slightly less

prominent in MDDP and considerably less evident in bipolar disorder. A single previous study reported both negative symptom and depression scores to be indistinguishable between MDDP and schizophrenia.[65] In addition to long-standing debate regarding the ability of the PANSS to differentiate primary and enduring from secondary and possibly transient negative symptoms, a further debate endures on the extent to which negative symptom scores may be confounded with depressive symptoms[66]; given a lack of consensus on the relationship between PANSS-negative symptom scores and those for instruments such as the Calgary Depression Scale for Schizophrenia,[66–68] the severity of negative symptoms in MDDP may not be independent of severity of depression. However, a variant perspective would note that symptoms such as anhedonia are considered a "core" clinical feature of both schizophrenia and depression,[16] with a neurobiology that appears to transcend these diagnostic categories.[16,69] Few negative symptoms at the first manic episode would be expected,[62,70] due in part to some psychopathological psychometric incompatibility between negative and manic features over the early, florid phase of illness.

Executive Dysfunction and NSS. Both executive dysfunction and NSS, widely reported in schizophrenia,[33,71] were similar in MDDP. Two previous studies have reported executive dysfunction in MDDP to be similar to[33] or slightly less severe than[65] in schizophrenia; we are not aware of any comparable findings for NSS. Executive dysfunction and NSS were less severe in bipolar disorder, as noted for executive dysfunction in some but not all previous studies.[28,33,72]

Premorbid Adjustment. This, widely reported to be impaired in schizophrenia both before and during adolescence,[73] was slightly more impaired in MDDP, particularly up to age 11; we are not aware of any comparable finding. As PAS assessments involve retrospective data, we cannot exclude that this finding might be influenced by differences in age between cases with MDDP and those with schizophrenia. While previous studies in bipolar disorder have been less conclusive, they suggest poor premorbid adjustment to a lesser extent than is commonly reported in schizophrenia, particularly over adolescence[74]; the present findings were numerically similar but failed to attain statistical significance.

Quality of Life. This, widely reported as compromised in schizophrenia from the first episode,[75] was similar in MDDP; we are not aware of any comparable finding. Quality of life was less compromised in bipolar disorder. On a lifetime basis, similar findings have been noted, with depressive symptoms being the strongest predictor of compromise.[76]

Clinical Features in Bipolar Disorder in Relation to Psychosis Specifier

At the first episode, bipolar patients with the specifier "severe, with psychotic features" showed greater severity of positive psychotic symptoms than bipolar patients without this specifier. In contrast, these 2 groups were indistinguishable in terms of negative symptoms, premorbid intellectual functioning, executive dysfunction, NSS, movement disorder, premorbid adjustment, and quality of life. On a lifetime basis, previous studies have noted these 2 groups to be distinguished by positive symptoms, only modestly by cognitive impairment, and not by negative symptoms, premorbid intellectual function, or premorbid adjustment.[70,74,77,78]

Strengths

The strengths of CAMFEPS are as follows: (*a*) The methodologies employed to ensure the closest approximation to epidemiological completeness for all DSM-IV psychotic diagnoses. (*b*) Inception of cases across the whole adult life span and via all routes to care, in the absence of a priori diagnostic restriction. (*c*) The breadth of assessments informative on psychosis, to allow comparisons to be made between MDDP, schizophrenia and bipolar disorder. (*d*) While the data presented here are cross-sectional, the study is prospective in design, to allow comparisons between diagnostic categories on a longitudinal basis.

Limitations

The limitations of CAMFEPS include those common to most studies of first-episode psychosis: (*a*) Despite the methodologies employed, an unknown number of cases may still have been missed. (*b*) As clinical assessments relate primarily to features of psychotic illness, future studies should include more incisive instruments for the evaluation of depressive and manic psychopathology, together with a broader range of neuropsychological assessments. (*c*) Though assessments were made as soon as practicable after presentation, subjects had usually received some exposure to second-generation antipsychotics and other medications; this may have influenced psychopathological and neurological ratings. (*d*) Assessments were unavailable for a minority of cases; as attrition related particularly to older cases with MDDP, this reduces generalizability of the findings across the life span but accentuates comparability between MDDP, schizophrenia, and bipolar disorder for those cases that first present in young adulthood. (*e*) Comparisons between MDDP, schizophrenia, and bipolar disorder are made in the absence of a comparison group having major depressive disorder without psychotic features and a healthy control group.

A particular issue relates to the long-term stability of the 3 diagnostic categories of MDDP, schizophrenia,

and bipolar disorder. Recent studies continue to indicate that while the majority of subjects with each diagnosis retain that diagnosis over follow-up periods of between 2 and 10 years, MDDP shows somewhat less prospective consistency than schizophrenia and bipolar disorder.[61,79,80] On 6-year follow-up of the first 202 subjects in CAMFEPS,[34] prospective diagnostic consistencies were 88% for schizophrenia and 76% for bipolar disorder, with consistency for MDDP among the first 40 of the 77 cases in the current cohort depending upon the unknown diagnostic outcome for 7 cases who died between 6-month and 6-year assessments (no deaths for schizophrenia; 2 deaths for bipolar disorder): if each of these 7 were to have evolved to diagnoses other than MDDP, prospective consistency would be 55%; if each were to have retained their initial diagnosis of MDDP, as did the majority of such cases, prospective consistency would be 73%, a value similar to that for bipolar disorder. The most common transitions were as follows: from MDDP to bipolar disorder > schizoaffective disorder > schizophrenia; from schizophrenia to schizoaffective disorder > bipolar disorder; from bipolar disorder to schizoaffective disorder > schizophrenia. While instability applies to all psychiatric diagnoses and should not exclude any DSM-IV diagnostic category from evaluation vis-à-vis other conceptually related diagnoses, future studies of MDDP should include longer term evaluation of its diagnostic (in)stability.

Overview and Conclusions

Though some quantitative differences were identified for MDDP vis-à-vis schizophrenia and bipolar disorder, it is important that the epidemiological and clinical "signatures" for these diagnostic categories at a population level are not misinterpreted as validating a diagnosis of MDDP, or indeed of schizophrenia or bipolar disorder, at the level of an individual patient. It is apparent that a first episode of each diagnosis can occur in an individual of either sex and at any age over the adult life span, and with a wide range of positive and negative symptoms, executive dysfunction, neurological dysfunction, or quality of life, on a background of a similarly wide range of premorbid intellectual function and adjustment.

Current theory favors not the replacement of the categorical approach to diagnosis of psychotic illness but rather its supplementation by a dimensional perspective[9,81,82]; these dimensions include positive psychotic symptoms, negative symptoms, mania, depression, and cognitive impairment.[9] These findings from CAMFEPS sustain and elaborate this proposition. The psychotic diagnoses of MDDP, schizophrenia, and bipolar disorder were each characterized by similar severity of psychotic symptoms. Relative to schizophrenia, MDDP was characterized by similar scores for negative symptoms, executive dysfunction, NSS, premorbid intellectual function and adjustment, and quality of life. These findings

suggest that what we currently categorize as MDDP and schizophrenia may be more closely aligned than has been considered previously; they indicate that subtleties in how psychosis is manifested vis-à-vis depression may be occurring within this dimensional space rather than underpinning these categorical distinctions. Bipolar disorder was characterized by less prominent negative symptoms, executive dysfunction, NSS, and better quality of life, with little difference between categories with vs without the specifier "severe, with psychotic features" other than in quantity of psychotic symptoms. These findings elaborate an increasing evidence base[5,9,11–15,76] that what we currently categorize as schizophrenia and bipolar disorder are closely aligned along a continuum of impairment (schizophrenia > bipolar disorder); they indicate that psychosis and mania may be related constructs within the same dimensional space rather than underpinning these categorical distinctions.

To further clarify these issues, future studies should extend this approach to the yet broader range of psychotic diagnoses and psychopathological dimensions encompassed by DSM-5, particularly schizoaffective disorder, delusional disorder, brief psychotic disorder, and psychotic disorder not otherwise specified; because CAMFEPS accumulates additional cases, it will accrue sufficient power to address these challenges. The coordinated application on a longitudinal basis of epidemiological, clinical, biological, and treatment approaches, in representative patient and ultrahigh risk/prodromal populations, is most likely to achieve this objective.

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