Psychological Medicine (2013), **43**, 2523–2533. © Cambridge University Press 2013
doi:10.1017/S003329171300041X

ORIGINAL ARTICLE

Diagnostic trajectory, interplay and convergence/divergence across all 12 DSM-IV psychotic diagnoses: 6-year follow-up of the Cavan-Monaghan First Episode Psychosis Study (CAMFEPS)

T. Kingston[1,2], P. J. Scully[1], D. J. Browne[1], P. A. Baldwin[1], A. Kinsella[2,3], V. Russell[1,4], E. O'Callaghan[3]† and J. L. Waddington[1,2]*

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

Background. The boundaries of psychotic illness and the extent to which operational diagnostic categories are distinct in the long term remain poorly understood. Clarification of these issues requires prospective evaluation of diagnostic trajectory, interplay and convergence/divergence across psychotic illness, without *a priori* diagnostic or other restrictions.

Method. The Cavan-Monaghan First Episode Psychosis Study (CAMFEPS), conducted using methods to attain the closest approximation to epidemiological completeness, incepts all 12 DSM-IV psychotic diagnoses. In this study we applied methodologies to achieve diagnostic reassessments on follow-up, at a mean of 6.4 years after first presentation, for 196 (97%) of the first 202 cases, with quantification of prospective and retrospective consistency.

Results. Over 6 years, the 12 initial psychotic diagnoses were characterized by numerous transitions but only limited convergence towards a smaller number of more stable diagnostic nodes. In particular, for initial brief psychotic disorder (BrP), in 85% of cases this was the harbinger of long-term evolution to serious psychotic illness of diagnostic diversity; for initial major depressive disorder with psychotic features (MDDP), in 18% of cases this was associated with mortality of diverse causality; and for initial psychotic disorder not otherwise specified (PNOS), 31% of cases continued to defy DSM-IV criteria.

Conclusions. CAMFEPS methodology revealed, on an individual case basis, a diversity of stabilities in, and transitions between, all 12 DSM-IV psychotic diagnoses over 6 years; thus, psychotic illness showed longitudinal disrespect to current nosology and may be better accommodated by a dimensional model. In particular, a first episode of BrP or MDDP may benefit from more vigorous, sustained interventions.

Received 29 August 2012; Revised 31 January 2013; Accepted 5 February 2013; First published online 12 March 2013

Key words: Diagnostic categories, first-episode psychosis, psychopathological dimensions, psychotic illness, 6-year follow-up.

Introduction

Despite the large body of research that has been carried out on psychotic illness, fundamental questions remain unanswered (Tandon *et al.* 2008; MacDonald & Schulz, 2009). Among these challenges, we are still seeking to define the boundaries of psychosis and the extent to which those aspects of psychotic illness that we resolve into separate diagnostic categories are in fact distinct in any fundamental way. This is exemplified by (i) classical debate regarding the relationship between 'non-affective psychosis' (typified by schizophrenia) and 'affective psychosis' [typified by manic-depressive psychosis (now bipolar disorder) and psychotic depression] (Jablensky, 1999; Demjaha *et al.* 2009; Fischer & Carpenter, 2009; Craddock & Owen, 2010) and (ii) the broader, contemporary debate regarding a dimensional rather than a categorical concept of psychosis; current psychotic diagnoses may reflect not discrete entities but, rather, domains defined by certain psychopathological and functional characteristics, the boundaries of which are probably notional and in continuity with other domains of mental illness, through to the limits of 'normal' human behavior (Tandon *et al.* 2009; van Os & Kapur, 2009; Waddington *et al.* 2012).

* Address for correspondence: Professor J. L. Waddington, Molecular and Cellular Therapeutics, Royal College of Surgeons in Ireland, Dublin 2, Ireland.
(Email: jwadding@rcsi.ie)
† Deceased.

DSM-IV (APA, 1994) defines 12 diagnostic categories that involve psychotic symptoms: schizophrenia (SZ); schizo-affective disorder (SA); schizophreniform disorder (SF); delusional disorder (DD); brief psychotic disorder (BrP); bipolar I disorder (BD); major depressive disorder, with psychotic features (MDDP); substance-induced psychotic disorder (SIP); substance-induced mood disorder, with manic features (SIM); psychotic disorder due to a general medical condition (PGMC); mood disorder due to a general medical condition, with manic features (MGMC); and psychotic disorder not otherwise specified (PNOS). However, although these diagnoses differ operationally in terms of etiological assumptions and characteristics such as duration of illness and extent of affective symptoms, they all share the presence of psychotic symptoms at some point during the course of illness. Early in the course of psychotic illness, the maelstrom of symptoms can lead to considerable diagnostic fluidity (Malla & Payne, 2005). Thereafter, long-term (in)stability of diagnosis may yield important information as to their import: do initial diagnoses remain stable, diverge, or converge to a smaller number of more highly populated categories that might be considered fundamental diagnostic nodes?

One essential strategy for addressing the challenges raised by this categorical approach has yet to be applied in the numerous follow-up studies of first-episode cohorts to date (Bromet *et al.* 2005; Menezes *et al.* 2006), primarily due to attendant methodological difficulties: to study prospectively the 'totality' of first-episode psychosis (FEP), ascertained on an epidemiological basis across the whole adult lifespan and through all routes to care, in the absence of *a priori* diagnostic restriction; longitudinal application of contemporary diagnostic algorithms as *post-hoc* assessment, rather than as a criterion for inclusion/exclusion, would then allow the epidemiological, clinical and pathobiological characteristics of resultant diagnoses to be compared systematically. Described here are (i) procedures that attain 97% follow-up, at a mean interval of 6 years, of 202 subjects constituting an epidemiological cohort of FEP, and (ii) the diagnostic trajectory, interplay and extent of convergence/divergence across each of the 12 DSM-IV psychotic diagnoses over this interval.

Method

Study setting

Subjects were participants in the Cavan-Monaghan First Episode Psychosis Study (CAMFEPS). This is a prospective study, operating since 1995, of 'all' incident cases presenting with a first episode of any psychotic disorder in two rural counties in Ireland, Cavan and Monaghan, as described previously in detail (Scully *et al.* 2002; Baldwin *et al.* 2005). Cavan and Monaghan are two contiguous rural counties with a population of 109139 (55821 males and 53318 females) at the 2002 census; the region consists of remote areas, villages and towns, in the absence of any major urban areas, and is of substantial ethnic and social homogeneity, with the vast majority of the population being white Irish (Central Statistics Office, 2003).

The study is based within the 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 two 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 (McCauley *et al.* 2003). All cases from this catchment area who present to services in other parts of the country are returned to the Cavan-Monaghan Mental Health Service as soon as is practicable.

Study cohort

In outline, CAMFEPS involves the following ascertainment procedures (Baldwin *et al.* 2005): 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 (Daly *et al.* 2004), and (*c*) cases from the catchment areas having admission to the national forensic service at the Central Mental Hospital, Dublin; the small number of cases missed initially and identified subsequently are incorporated retrospectively. The primary criterion for entry to the study is a first lifetime episode of any psychotic illness, to include a first manic episode, at age $\geqslant$16 years, with no upper age limit. DSM-IV diagnosis is made at first presentation, together with psychopathological and cognitive assessments that are outlined elsewhere (Owoeye *et al.* 2010). At 6 months thereafter, as described previously (Baldwin *et al.* 2005), all clinical information, that is case-notes and discussions with the treating teams, is reviewed to confirm or update, by DSM-IV criteria, the initial diagnosis. There are no exclusion criteria other than a previously treated psychotic episode. Thus, all psychotic diagnoses included in DSM-IV are

https://doi.org/10.1017/S003329171300041X Published online by Cambridge University Press

incepted into the study (i.e. SZ, SA, SF, DD, BrP, BD, MDDP, SIP, SIM, PGMC, MGMC and PNOS). We additionally encountered simple deteriorative disorder (SDD) (see DSM-IV Appendix B: Criteria Sets and Axes Provided for Further Study), which encompasses schizophrenia-like deterioration in functioning with primarily negative symptoms and transient psychotic symptoms that do not reach the threshold for diagnosis of a psychotic disorder. This disorder, having a long history as 'simple schizophrenia' and retained in ICD-9, was included here on the basis of it conforming in considerable part to classical concepts of the 'clinical core' of schizophrenia (Black & Boffeli, 1989; Parnas, 2011).

Follow-up

This study is a follow-up of the 202 cases having their first presentation over the first 8 years of CAMFEPS, between May 1995 and April 2003 (Baldwin *et al.* 2005). Follow-up was undertaken between July 2005 and June 2007. Study protocols were approved by the Research Ethics Committees of the North Eastern Health Board (and, following restructuring, of 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, clinical and demographic information from case-notes and treating health professionals for subjects declining formal assessment. Given that, for some subjects, more than a decade had elapsed since onset of what might have been a single episode of psychosis at a vulnerable time of their lives, it was felt that initial contact should be made in a sensitive manner; thus, one of the key tenets determining the mode of re-establishing contact with patients to seek their participation was that this should be made initially by a health professional with whom they had previous clinical contact.

Once name and date of birth had been identified for each subject, a search of the electronic records of Cavan-Monaghan Mental Health Service was performed to identify those still in contact with the service and their point of contact. For those who were no longer in contact with the service, a search of their medical records was performed to gather information on address, general (family) practitioner (GP) and past key workers. A notice was placed on the front page of each subject's medical records, identifying them as a potential candidate for the study and requesting mental health professionals to (i) ask if they would be willing to participate, and then (ii) contact the investigator with the outcome of the request. Where medical records were missing, as many details as possible were gleaned from the CAMFEPS dataset to facilitate tracing.

Contact was then made with individual clinical teams to establish, for those subjects still in contact with the service, their next appointment; community psychiatric nurses (CPNs) were extremely important in this process, as the quality of the relationships established by CPNs with subjects greatly facilitated the process of tracing and obtaining consent to participate. For those who declined to participate, information was obtained on the basis of an interview with their mental health professional and this process pertained to any other key worker identified (GP or psychiatrist outside of the Cavan-Monaghan Mental Health Service), as long as they had had regular contact with the subject within the past year.

For those subjects who were no longer under the care of a mental health service (approximately 50% of participants), telephone contact was made with their GP to establish whether they still attended and, if not, who was their new GP. The relevant GPs were then asked to inform the subjects about the study and ask if they would be willing to participate. If the subjects were willing to participate, they were informed that the investigator would make contact with them to arrange an appointment for assessment.

A small number of subjects had been incepted through private psychiatric hospitals or the national forensic service; follow-up involved contacting their treating consultant psychiatrist, who was requested to ask the subject if they were willing to participate and be contacted by the investigator.

Where the subject had moved out of the catchment area and was now being treated by another mental health service, similar procedures were followed as for primary care, substituting consultant psychiatrist for GP.

In instances where there was difficulty in identifying a current address for a subject, other community agencies were used, such as Medical Card Offices, Community Welfare Officers and police. Once an address was identified, all GPs in the area were contacted to establish the GP currently providing care; this GP then initiated contact with the subject on behalf of the investigator.

The Births, Marriages and Deaths Offices for Cavan and Monaghan were contacted with a list of names of all subjects who were thought by health-care professionals to be deceased, or who had not been traced successfully through the above means. The Officer provided death certificates for all subjects who were deceased; from these, date and cause of death were noted and included in the dataset.

https://doi.org/10.1017/S003329171300041X Published online by Cambridge University Press

Follow-up assessment

For subjects giving informed consent to reassessment at follow-up, each was interviewed, either in their own home, in a community clinic, in hospital or elsewhere at their convenience. The Structured Clinical Interview for DSM-IV (SCID-IV; First *et al.* 2002) was conducted by the first author (T.K.), who was blind to diagnosis at 6 months, to establish current DSM-IV diagnosis; additional assessments included psychopathology, functioning, quality of life and service engagement, to be described elsewhere. For subjects declining reassessment, DSM-IV diagnosis was made on the basis of all available information gathered from case-notes and their current key worker, whether a mental health professional or a GP.

Additional demographic information ascertained at follow-up included whether deceased, with cause of death, marital status, living status and any co-morbidity. The investigator was a Clinical Research fellow who conducted all follow-up assessments without reference to assessments at onset and 6 months.

Diagnostic consistency was determined as prospective consistency (PC; the percentage of subjects with each diagnosis at 6 months who retained that diagnosis at 6 years) and retrospective consistency (RC; the percentage of subjects with each diagnosis at 6 years who had received that diagnosis at 6 months). Data were analyzed using SPSS version 15 (SPSS Inc., USA).

Results

Demographics

We sought to follow up all 202 cases incepted into CAMFEPS over its first 8 years [mean age at first presentation 36.0 (S.D.=18.1) years; 121 male, mean age 32.4 (S.D.=15.7) years; 81 female, mean age 41.5 (S.D.=20.2) years]. Of these, 196 [97%; mean age at follow-up 42.6 (S.D.=18.6) years; 115 male, mean age 38.9 (S.D.=16.3) years; 81 female, mean age 48.0 (S.D.=20.3) years] were followed up at a mean of 6.4 (S.D.=2.3, range 2.6–11.9) years after first presentation, for which '6-year follow-up' is used hereafter as convenient shorthand. It was not possible to obtain follow-up data for six cases [3%, all male; mean age at first presentation 29.3 (S.D.=9.2) years]: for two, no record of the case was identifiable; two had moved out of the country and were untraceable; and for two, their records were in a private hospital and could not be accessed. Their diagnoses at first presentation were: one each of SZ, SA, BD, MDDP, DD and PNOS.

Of the 196 cases for whom follow-up data and DSM-IV diagnoses were obtained [179 (91%) through the SCID; 17 (9%) through all available sources of clinical information, that is case-notes and discussions with the treating teams (Baldwin *et al.* 2005)], 13 (seven male, six female) were found to be deceased: for four cases death was by suicide [all male, mean age at death 58.5 (S.D.=16.8) years; diagnoses at first presentation: two SZ; two MDDP); for one case death was the result of a road traffic accident (female, age at death 27 years; diagnosis at first presentation: MDDP); and for eight cases deaths were the result of typical natural causes [five cardiovascular, three pneumonia; three male, five female; mean age at death 74.0 (S.D.=11.4) years; diagnoses at first presentation: one SF, one BD, four MDDP and one SIP].

Diagnostic interplay from 6 months to 6-year follow-up

Data on diagnostic shifts between first presentation and 6-month assessments, together with the incidence of individual psychotic diagnoses at 6 months, have been presented previously in detail (Baldwin *et al.* 2005). Demographics for each psychotic diagnosis at the 6-month assessment are given in Table 1. For these 196 cases, details of stability of, or transitions from, diagnoses at 6 months to other categories at 6 years are summarized in Table 3. Diagnosis of SF at both 6 months and 6 years refers to no recurrence of psychosis since the first episode. One case with a diagnosis of SF at 6 months died subsequently of natural causes. Diagnosis of BrP at 6 years refers to no recurrence of psychosis since the first episode. One case with a diagnosis of MDDP at 6 months subsequently experienced a hypomanic episode and then a further depressive episode with psychotic features; this resulted in a diagnosis at 6 years of bipolar II disorder, depressed, with psychotic features. Seven cases with a diagnosis of MDDP at 6 months died subsequently (four natural causes, one road traffic accident, two suicide); an 80-year-old female with a diagnosis of PNOS at 6 months received a diagnosis of Alzheimer's disease (ALZ) at 6 years.

Trajectories to 'convergence' at 6-year follow-up

Demographics for each psychotic diagnosis at the 6-year follow-up are given in Table 2. For these 196 cases, specifics of stability of, or transitions to, diagnoses at 6 years from other categories at 6 months are summarized in Table 3. Two cases with a diagnosis of SF at 6 years involve no recurrence of psychosis between the first episode and 6 months but re-emergence of SF at 6 years. One case with a diagnosis of DD at 6 years involved a first episode of BrP with no recurrence of psychosis at 6 months but emergence of DD at 6 years. One case with a diagnosis of BrP at 6 years involved a first episode of substance-induced

https://doi.org/10.1017/S003329171300041X Published online by Cambridge University Press

Table 1. *Demographics for each psychotic diagnosis at 6 months following first presentation*

	Males			Females			
		Age (years)			Age (years)		
Diagnosis	*n*	Mean	S.D.	*n*	Mean	S.D.	PC (%)
SZ	34	28.1	14.2	8	33.6	13.9	88
SA	6	27.3	7.9	5	22.8	4.6	82
SF	5	35.6	12.1	6	54.2	29.1	27
DD	6	38.8	8.0	4	43.0	21.5	20
BrP	2	41.5	–	8	35.3	9.3	20
BD	17	32.0	15.6	17	34.6	16.9	76
MDDP	17	42.9	22.9	23	48.3	20.9	55
SIP	11	29.6	15.2	0	–	–	36
SIM	4	36.0	18.9	2	46.5	–	50
PGMC	2	44.0	–	2	57.5	–	50
MGMC	0	–	–	1	69	–	–
PNOS	8	22.1	3.7	5	45.6	28.4	31
SDD	1	23	–	0	–	–	–
Suicide	2	47.5	–	0	–	–	–
Total	115	32.5	16.0	81	41.5	20.2	59

SZ, Schizophrenia; SA, schizo-affective disorder; SF, schizophreniform disorder; DD, delusional disorder; BrP, brief psychotic disorder; BD, bipolar I disorder; MDDP, major depressive disorder, with psychotic features; SIP, substance-induced psychotic disorder; SIM, substance-induced mood disorder, with manic features; PGMC, psychotic disorder due to a general medical condition; MGMC, mood disorder due to a general medical condition, with manic features; PNOS, psychotic disorder not otherwise specified; SDD, simple deteriorative disorder; PC, prospective consistency to 6 years; S.D., standard deviation.

psychosis with no recurrence of psychosis at 6 months until the emergence of BrP at 6 years. One case involved a first episode of substance-induced mood disorder with psychotic features, with no recurrence of psychosis after 6 months until the emergence of BrP at 6 years.

Discussion

CAMFEPS was initiated in 1995 (Baldwin *et al.* 2005) using methodology that seeks the closest approximation to epidemiological completeness for FEP. To our knowledge, no other study has included each of the defined catchment areas, all routes to care (i.e. public, private or forensic), all modes of care (i.e. in-patient, out-patient or home-based), full diagnostic scope (i.e. all 12 DSM-IV psychotic diagnoses), no arbitrary upper-age cut-off (i.e. cases incepted throughout the adult lifespan) and Research Ethics Committee approvals to include demographic and diagnostic information on those cases declining formal assessment.

In the present study, we have continued this methodological approach to seek the closest approximation to epidemiological completeness of follow-up at 6 years following the first psychotic episode. The purpose of the study was to determine, for the 202 cases incepted over the first 8 years of CAMFEPS, the extent to which each of the 12 DSM-IV psychotic diagnoses, made following the first 6 months of illness, remain stable, converge to a smaller number of accumulating diagnoses or diverge. These methods for case ascertainment and assessment at long-term follow-up allowed us to obtain diagnoses for 97% of the initial cohort, with 91% of these being through a face-to-face SCID and 9% through case records and/or current key worker information, whether a mental health professional or GP. We consider each of the 12 DSM-IV psychotic diagnoses in turn, beginning with the most populous categories. It should be emphasized that interpretation vis-à-vis previous studies is rendered problematic by none having adopted the current methodological approach in a comparable (i.e. rural) setting.

At follow-up, SZ was a generally stable and accumulating diagnosis (PC>RC), primarily from SF, DD and PNOS; this is in accordance with both the classical literature (van Os & Kapur, 2009) and prospective

https://doi.org/10.1017/S003329171300041X Published online by Cambridge University Press

Table 2. *Demographics for each psychotic diagnosis at 6-year follow-up*

	Males			Females			
		Age (years)			Age (years)		
Diagnosis	*n*	Mean	S.D.	*n*	Mean	S.D.	RC (%)
SZ	42	30.1	14.1	18	35.6	17.4	62
SA	16	28.9	11.1	11	28.9	13.2	33
SF	1	25	–	2	81.5	–	100
DD	2	31.0	–	1	31	–	67
BrP	2	17.0	–	2	40.5	–	50
BD	18	33.2	15.9	17	36.6	15.8	74
BD2DP	0	–	–	1	57	–	–
MDDP	13	40.4	19.5	14	45.7	18.6	82
SIP	8	27.0	10.7	0	–	–	50
SIM	3	21.7	4.0	3	38.0	19.3	50
PGMC	1	44	–	2	69.0	–	67
MGMC	0	–	–	1	69	–	–
ALZ	0	–	–	1	80	–	–
PNOS	2	18.5	–	2	27.5	–	100
SDD	0	–	–	0	–	–	–
RIP	3	63.0	15.1	6	64.2	25.3	–
Suicide	4	55.0	19.2	–	–	–	–
Total	115	32.5	16.0	81	41.5	20.2	59

SZ, Schizophrenia; SA, schizo-affective disorder; SF, schizophreniform disorder; DD, delusional disorder; BrP, brief psychotic disorder; BD, bipolar I disorder; BD2DP, bipolar II disorder, depressed, with psychotic features; MDDP, major depressive disorder, with psychotic features; SIP, substance-induced psychotic disorder; SIM, substance-induced mood disorder, with manic features; PGMC, psychotic disorder due to a general medical condition; MGMC, mood disorder due to a general medical condition, with manic features; ALZ, Alzheimer's disease; PNOS, psychotic disorder not otherwise specified; SDD, simple deteriorative disorder; RIP, deceased other than suicide; RC, retrospective consistency from 6 months; S.D., standard deviation.

first-episode studies (Bromet *et al.* 2005, 2011; Addington *et al.* 2006; Chang *et al.* 2009). In a 'sister' cohort, conducted in an urban population in Ireland, the incidence of SZ was higher than in the present rural cohort but showed similar long-term diagnostic stability; thus, importantly, the excess of SZ associated with urbanicity does not seem to be attributable to variations in diagnostic stability (Whitty *et al.* 2005; Kelly *et al.* 2010). The small number of cases evolving to BD or MDDP over time indicates that vigilance should be maintained in monitoring for and treating affective symptoms over the long-term course of an illness that seems essentially psychotic at onset.

Despite SA having generated so much controversy historically (Maier, 2006; Cheniaux *et al.* 2008) and being a 'longstanding problem that plagues psychiatric nosology' (Mahli *et al.* 2008), we have not been able to identify any contemporary, prospective studies of FEP that have ascertained and followed up meaningful numbers of cases of SA, these being more commonly pooled pragmatically into a category of 'schizophrenia spectrum' psychoses (Addington *et al.* 2006; Chang *et al.* 2009; Bromet *et al.* 2011). Here, we find SA to also be a generally stable and accumulating diagnosis (PC>RC), but with a profile of accumulation, that is from BD/MDDP, distinct from that seen in SZ. This differential accumulation from 'feeder' diagnoses would indicate that SA might be more correctly characterized as a psychotic mood disorder (Lake & Hurwitz, 2006).

Over the past several years BD has been increasingly included in prospective studies of FEP, with affective psychosis having previously been more commonly a reason for exclusion (Menezes *et al.* 2006). We found BD to be a generally stable diagnosis, in accordance with both the classical literature (Müller-Oerlinghausen *et al.* 2002) and more recent prospective first-episode studies (Schimmelmann *et al.* 2005;

https://doi.org/10.1017/S003329171300041X Published online by Cambridge University Press

Table 3. *Summary of diagnostic transitions over illness trajectory from 6-month assessment to 6-year follow-up*

	Diagnosis at follow-up																
Diagnosis at 6 months	SZ	SA	SF	DD	BrP	BD	BD2DP	MDDP	SIP	SIM	PGMC	MGMC	ALZ	PNOS	RIP	Suicide	Total at 6 months
SZ	37	3	0	0	0	1	0	0	1	0	0	0	0	0	0	0	42
SA	1	9	0	0	0	0	0	1	0	0	0	0	0	0	0	0	11
SF	5	0	3	0	0	0	0	0	2	0	0	0	0	0	1	0	11
DD	5	1	0	2	0	0	0	1	0	0	1	0	0	0	0	0	10
BrP	2	1	0	1	2	2	0	2	0	0	0	0	0	0	0	0	10
BD	2	3	0	0	0	26	0	0	0	1	0	0`	0	0	2	0	34
MDDP	2	3	0	0	0	4	1	22	1	0	0	0	0	0	5	2	40
SIP	1	2	0	0	1	1	0	0	4	1	0	0	0	0	1	0	11
SIM	0	1	0	0	1	1	0	0	0	3	0	0	0	0	0	0	6
PGMC	1	1	0	0	0	0	0	0	0	0	2	0	0	0	0	0	4
MGMC	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	1
PNOS	3	3	0	0	0	0	0	1	0	1	0	0	1	4	0	0	13
SDD	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Suicide	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	2
Total at follow-up	60	27	3	3	4	35	1	27	8	6	3	1	1	4	9	4	196

SZ, Schizophrenia; SA, schizo-affective disorder; SF, schizophreniform disorder; DD, delusional disorder; BrP, brief psychotic disorder; BD, bipolar I disorder; BD2DP, bipolar II disorder, depressed, with psychotic features; MDDP, major depressive disorder, with psychotic features; SIP, substance-induced psychotic disorder; SIM, substance-induced mood disorder, with manic features; PGMC, psychotic disorder due to a general medical condition; MGMC, mood disorder due to a general medical condition, with manic features; ALZ, Alzheimer's disease; PNOS, psychotic disorder not otherwise specified; SDD, simple deteriorative disorder; RIP, deceased other than suicide.

Chang *et al.* 2009). However, transitions to BD (PC= RC) were less frequent than for SZ and SA (see also Ruggero *et al.* 2010) and were commonly from MDDP due to the emergence of at least one manic episode (Ketter *et al.* 2004). Transitions from BD were more frequent than for SZ and SA, and were most commonly to SA (Conus *et al.* 2010).

Among those psychotic diagnoses occurring at the first episode, MDDP has received the least systematic study; even more so than for BD, MDDP has been a common reason for exclusion from FEP studies (Menezes *et al.* 2006). We find MDDP to be a less stable and more complex diagnosis (PC<RC) than SZ, SA or BD (Ruggero *et al.* 2011; Tohen *et al.* 2012). Emergence of psychosis in the context of MDD reflects most robustly the intersection of affective and psychotic psychopathological dimensions (Demjaha *et al.* 2009; Linscott & van Os, 2010; Waddington *et al.* 2012). Here, MDDP was characterized in the long term by three primary trajectories: (i) for the majority, an enduring diagnosis of MDDP; thus, these affective and psychotic dimensions continued to intersect rather than converge on an affective psychotic diagnosis; (ii) for a minority, enduring psychosis, with transition to more portentous psychotic diagnoses, particularly those having an affective dimension (BD>SA>SZ); however, these transitions occurred less often than reported recently in an FEP study that adopted a different methodological approach (Bromet *et al.* 2011); and (iii) for a minority, death due to suicide, accidental death or natural causes. Although explanations for this high rate of mortality over follow-up are likely to include the older age and increased risk for suicide among cases of MDDP, it suggests scope for further attention to both mental and physical health in this group to reduce such long-term adversities.

Long-term transition of SF primarily to SZ (PC<RC) was in accordance with both classical (Strakowski, 1994) and contemporary (Marchesi *et al.* 2007) literature, due in the main to enduring psychosis that ultimately attains the DSM-IV duration-of-illness criterion for SZ; however, we did not encounter previously described transitions to BD or MDDP (Marchesi *et al.* 2007). For a smaller number of cases, follow-up of SF clarified the role of substance abuse and led to subsequent diagnosis of SIP; for only a small minority of cases was SF a benign initial diagnosis without long-term import.

The literature regarding BrP is confounded by studies of ICD-10 F23, 'acute and transient psychotic disorders', which encompasses a wide variety of clinical concepts that overlap with, but extend far beyond, BrP and indeed SF (Castagnini & Berrios, 2009; Chang *et al.* 2009). We have been able to identify only one contemporary, prospective study of FEP that has ascertained and followed up subjects with DSM-IV BrP; this involved five cases assessed over 1 year, one of whom evolved to schizophrenia (Addington *et al.* 2006). In the present study, all cases of BrP at presentation, occurring primarily among women, were by definition characterized initially by the rapid remission of psychosis; thereafter, the large majority remained well over the subsequent 6 months, with a small minority experiencing transition to BD or MDDP during this period (Baldwin *et al.* 2005). However, among those cases of BrP remaining well at 6 months, by 6 years the large majority had experienced deterioration to SZ, SA, DD, BD or MDDP. The case of SDD showed a similar course, as noted previously (Serra-Mestres *et al.* 2000).

Thus, over the duration of CAMFEPS to date, 85% of cases of BrP have experienced rapid remission, followed only in the longer term by the emergence of a more portentous psychotic diagnosis. BrP may be a far from benign occurrence that is, in reality, the harbinger of long-term evolution to serious psychotic illness, the diagnostic diversity of which may further challenge categorical nosology and favor a dimensional model. The emergence of BrP, with its defining rapid remission, may be a transient exacerbation over some arbitrary threshold of what is currently conceptualized subclinically as 'attenuated psychotic symptoms' or 'brief, limited, intermittent psychotic symptoms', which can confer 'ultra high risk' for subsequent psychotic illness (Nelson *et al.* 2011). This arbitrary threshold may be a position along a dimension that extends from the breadth of psychotic ideation in the 'normal' population through to clinical psychosis (van Os *et al.* 2009; Demjaha *et al.* 2009; Linscott & van Os, 2010; Waddington *et al.* 2012); BrP may straddle the upper boundary along a dimension of 'ultra high risk' for psychotic illness that then transitions to variable diagnostic categories with overlapping dimensions of psychopathology. Irrespective of these theoretical considerations, BrP may require more vigorous, sustained intervention than is currently appreciated, so as to reduce risk for such long-term sequelae.

The trajectory of DD was similar to that of SF in most commonly evolving to SZ, as noted previously (Whitty *et al.* 2005; Chang *et al.* 2009); one case of BrP at first presentation evolved to DD over follow-up. As with BrP and SF, for only a minority of cases was DD a benign initial diagnosis without long-term import. This trajectory suggests that treatment at first presentation and thereafter should take into account the likelihood of DD being the harbinger of long-term evolution to more serious psychotic illness and possibly benefiting from more vigorous, sustained intervention.

https://doi.org/10.1017/S003329171300041X Published online by Cambridge University Press

Contemporary studies have reported varying findings as to the stability of SIP *versus* evolution to a primary psychotic diagnosis over varying periods of follow-up (Whitty *et al.* 2005; Addington *et al.* 2006; Caton *et al.* 2007; Bromet *et al.* 2011). Here, SIP occurred only in men and was due to abuse of a wide range of individual or combined substances. Over the 6-year follow-up, similar proportions of SIP retained that diagnosis, or evolved to SZ/SA. Thus, it is important in the early treatment of SIP to note that simple abstinence from the putative causative agent may not be adequate for achieving freedom from future psychotic episodes. We have been unable to identify any other study that has specifically ascertained and systematically followed up subjects with DSM-IV SIM. Here, SIM occurred in both men and women due to substances of either abuse or pharmacotherapy [primarily antidepressant-induced mania (Goldberg & Truman, 2003; Daray *et al.* 2010) and corticosteroid-induced mania (Brown & Suppes, 1998; Kenna *et al.* 2011)]. Over follow-up, similar proportions of SIM retained that diagnosis or evolved to SA/BD.

We have been unable to identify any other study that has ascertained and followed up subjects with DSM-IV PGMC and MGMC. Here, similar proportions of PGMC retained that diagnosis or evolved to SZ/SA. The single case of MGMC retained that diagnosis at 6 years.

The primary limitation of the present study is that, despite the methodologies used, an unknown number of cases still may have been missed and information on cases declining formal assessment is less complete. Additionally, the total number of cases identified results in the least common diagnostic categories having small numbers. Furthermore, contemporary studies have reported varying findings regarding the long-term diagnostic outcome of PNOS over differing periods of follow-up, with evolution to SZ being most common (Whitty *et al.* 2005; Addington *et al.* 2006; Chang *et al.* 2009). Here, over 6 years the most common diagnostic transition from PNOS was to SZ/SA as the long-term course of psychotic illness became clearer. For one elderly female, diagnosis at 6 years was Alzheimer's disease; her atypical psychosis at 6 months may have been an early manifestation of Alzheimer's neuropathology, attesting the challenges of distinguishing in such circumstances between DSM-IV diagnoses of PNOS *versus* dementia of the Alzheimer type, with delusions (Ropacki & Jeste, 2005). However, even with all the assessments available at the first episode, 6 months and 6 years, supplemented by all available information from case records and health professionals, almost one-third of cases diagnosed initially as PNOS continued to defy the SCID/DSM-IV algorithm and endured as PNOS.

Conclusions

CAMFEPS methodology reveals limited diagnostic convergence, primarily to SZ/SA (from 27% to 44% of the cohort), and elaborates the diversity of stabilities in, and transitions between, all 12 DSM-IV psychotic diagnoses over 6 years; thus, the present findings indicate that psychosis is manifested within a dimensional space, with diagnostic outcomes that can show longitudinal disrespect to current categories. The extent to which psychosis might be better described dimensionally (van Os & Kapur, 2009; Waddington *et al.* 2012), as typified by MDDP, may be further clarified by systematic, comparative evaluation of pre-morbid characteristics and, prospectively, of psychopathology, neuropsychology and functional outcome in relation to treatments across these 12 DSM-IV psychotic diagnoses. In particular, the findings suggest that first-episode diagnoses of BrP, MDDP and DD may benefit from more vigorous, sustained interventions to reduce risk for potentially adverse outcomes in the long term.

Acknowledgments

The CAMFEPS was supported by the Stanley Medical Research Institute and Cavan-Monaghan Mental Health Service. We thank J. Quinn and M. Morgan for their contributions to data collection and the staff of Cavan-Monaghan Mental Health Service, particularly M. Maguire and T. McEnteggart, its associated GPs, St Patrick's Hospital, Dublin, St John of God Hospital, Co. Dublin, and the Central Mental Hospital, Dublin, for their kind assistance.

Declaration of Interest

None.

References

Addington J, Chaves AC, Addington D (2006). Diagnostic stability over one year in first-episode psychosis. *Schizophrenia Research* **86**, 71–75.

APA (1994). *Diagnostic and Statistical Manual of Mental Disorders*, 4th edn. American Psychiatric Association: Washington, DC.

Baldwin P, Browne D, Scully PJ, Quinn JF, Morgan MG, Kinsella A, Owens MJ, Russell V, O'Callaghan E, Waddington JL (2005). Epidemiology of first-episode psychosis: illustrating the challenges across diagnostic boundaries through the Cavan-Monaghan study at 8 years. *Schizophrenia Bulletin* **31**, 624–638.

Black DW, Boffeli TJ (1989). Simple schizophrenia: past, present, and future. *American Journal of Psychiatry* **146**, 1267–1273.

https://doi.org/10.1017/S003329171300041X Published online by Cambridge University Press

Bromet E, Naz B, Fochtmann LJ, Carlson GA, Tanenberg-Karant M (2005). Long-term diagnostic stability and outcome in recent first-episode cohort studies of schizophrenia. *Schizophrenia Bulletin* **31**, 639–649.

Bromet E, Kotov R, Fochtmann JL, Carlson GA, Tanenberg-Karant M, Ruggero C, Chang SW (2011). Diagnostic shifts during the decade following first admission for psychosis. *American Journal of Psychiatry* **168**, 1186–1194.

Brown ES, Suppes T (1998). Mood symptoms during corticosteroid therapy: a review. *Harvard Review of Psychiatry* **5**, 239–246.

Castagnini A, Berrios GE (2009). Acute and transient psychotic disorders (ICD-10 F23): a review from a European perspective. *European Archives of Psychiatry and Clinical Neuroscience* **259**, 433–443.

Caton CL, Hasin DS, Shrout PE, Drake RE, Dominguez B, First MB, Samet S, Schanzer B (2007). Stability of early-phase primary psychotic disorders with concurrent substance use and substance-induced psychosis. *British Journal of Psychiatry* **190**, 105–111.

Central Statistics Office (2003). Database Direct. Central Statistics Office: Cork, Ireland (www.cso.ie/census).

Chang WC, Pang SLK, Chung DWS, Chan SSM (2009). Five-year stability of ICD-10 diagnoses among Chinese patients presented with first-episode psychosis in Hong Kong. *Schizophrenia Research* **115**, 351–357.

Cheniaux E, Landeira-Fernandez J, Telles LL, Lessa JLM, Dias A, Duncan T, Versiani M (2008). Does schizoaffective disorder really exist? A systematic review of the studies that compared schizoaffective disorder with schizophrenia or mood disorders. *Journal of Affective Disorders* **106**, 209–217.

Conus P, Abdel-Baki A, Harrigan S, Lambert M, McGorry PD, Berk M (2010). Pre-morbid and outcome correlates of first episode mania with psychosis: is a distinction between schizoaffective and bipolar I disorder valid in the early phase of psychotic disorders? *Journal of Affective Disorders* **126**, 88–95.

Craddock N, Owen MJ (2010). The Kraepelinian dichotomy – going, going… but still not gone. *British Journal of Psychiatry* **196**, 92–95.

Daly I, Walsh D, Moran R, O'Doherty YK (2004). *Activities of Irish Psychiatric Services 2003*. Health Research Board: Dublin.

Daray FM, Thommi SB, Ghaemi SN (2010). The pharmacogenetics of antidepressant-induced mania: a systematic review and meta-analysis. *Bipolar Disorders* **12**, 702–706.

Demjaha A, Morgan K, Morgan C, Landau Dean K, Reichenberg A, Sham P, Fearon P, Hutchinson G, Jones PB, Murray RM, Dazzan P (2009). Combining dimensional and categorical representation of psychosis: the way forward for DSM-V and ICD-11? *Psychological Medicine* **39**, 1943–1955.

First MB, Spitzer RL, Gibbon M, Williams JB (2002). *Structured Clinical Interview for the DSM-IV Axis I Disorders*. Biometrics Research: New York.

Fischer BA, Carpenter WT (2009). Will the Kraepelinian dichotomy survive DSM-V? *Neuropsychopharmacology* **34**, 2081–2087.

Goldberg JF, Truman CJ (2003). Antidepressant-induced mania: an overview of current controversies. *Bipolar Disorders* **5**, 407–420.

Jablensky A (1999). The conflict of the nosologists: views on schizophrenia and manic-depressive illness in the early part of the 20th century. *Schizophrenia Research* **39**, 95–100.

Kelly BD, O'Callaghan E, Waddington JL, Feeney L, Browne S, Scully PJ, Clarke M, Quinn JF, McTigue O, Morgan MG, Kinsella A, Larkin C (2010). Schizophrenia and the city: a review of literature and prospective study of psychosis and urbanicity in Ireland. *Schizophrenia Research* **116**, 75–89.

Kenna HA, Poon AW, de los Angeles CP, Koran LM (2011). Psychiatric complications of treatment with corticosteroids: review with case report. *Psychiatry and Clinical Neurosciences* **65**, 549–560.

Ketter TA, Wang PW, Becker OV, Nowarkowska C, Yang Y (2004). Psychotic bipolar disorders: dimensionally similar to or categorically different from schizophrenia? *Journal of Psychiatric Research* **38**, 47–61.

Lake CR, Hurwitz N (2006). Schizoaffective disorders are psychotic mood disorders; there are no schizoaffective disorders. *Psychiatry Research* **143**, 255–287.

Linscott RJ, van Os J (2010). Systematic reviews of categorical versus continuum models in psychosis: evidence for discontinuous subpopulations underlying a psychometric continuum. Implications for DSM-V, DSM-VI, and DSM-VII. *Annual Review of Clinical Psychology* **6**, 391–419.

MacDonald AW, Schulz SC (2009). What we know: findings that every theory of schizophrenia should explain. *Schizophrenia Bulletin* **35**, 493–508.

Mahli GS, Green M, Fagiolini A, Peselow ED, Kumari V (2008). Schizoaffective disorder: diagnostic issues and future recommendations. *Bipolar Disorders* **10**, 215–230.

Maier W (2006). Do schizoaffective disorders exist at all? *Acta Psychiatrica Scandinavica* **113**, 369–371.

Malla AK, Payne J (2005). First episode psychosis: psychopathology, quality of life and functional outcome. *Schizophrenia Bulletin* **31**, 650–671.

Marchesi C, Paini M, Ruju L, Rosi L, Turrini G, Maggini C (2007). Predictors of the evolution towards schizophrenia or mood disorder in patients with schizophreniform disorder. *Schizophrenia Research* **97**, 1–5.

McCauley M, Rooney S, Clarke K, Carey T, Owens J (2003). Home-based treatment in Monaghan: the first two years. *Irish Journal of Psychological Medicine* **20**, 11–14.

Menezes NM, Arenovich T, Zipursky RB (2006). A systematic review of longitudinal outcome studies of first-episode psychosis. *Psychological Medicine* **36**, 1349–1362.

Müller-Oerlinghausen B, Berghöfer A, Bauer M (2002). Bipolar disorder. *Lancet* **359**, 241–247.

Nelson B, Yuen K, Yung AR (2011). Ultra high risk (UHR) for psychosis criteria: are there different levels of risk for transition to psychosis? *Schizophrenia Research* **125**, 62–68.

Owoeye O, Kingston T, Hennessy RJ, Baldwin PA, Browne D, Scully PJ, Kinsella A, Russell V, O'Callaghan E, Waddington JL (2010). The 'totality' of psychosis: epidemiology and developmental pathobiology. In *Advances in Schizophrenia Research* (ed. W. Gattaz and G. Busatto), pp. 377–385. Springer: New York.

Parnas J (2011). A disappearing heritage: the clinical core of schizophrenia. *Schizophrenia Bulletin* **37**, 1121–1130.

Ropacki SA, Jeste DV (2005). Epidemiology of and risk factors for psychosis of Alzheimer's disease: a review of 55 studies published from 1990 to 2003. *American Journal of Psychiatry* **162**, 2022–2030.

Ruggero CJ, Carlson GA, Kotov R, Bromet EJ (2010). Ten-year diagnostic consistency of bipolar disorder in a first-admission sample. *Bipolar Disorders* **12**, 21–31.

Ruggero CJ, Kotov R, Carlson GA, Tanenberg-Karant M, Gonzáles DA, Bromet EJ (2011). Diagnostic consistency of major depression with psychosis across 10 years. *Journal of Clinical Psychiatry* **72**, 1207–1213.

Schimmelmann BG, Conus P, Edwards J, McGorry PD, Lambert M (2005). Diagnostic stability 18 months after treatment initiation for first-episode psychosis. *Journal of Clinical Psychiatry* **66**, 1239–1246.

Scully PJ, Quinn JF, Morgan MG, Kinsella A, O'Callaghan E, Owens JM, Waddington JL (2002). First-episode schizophrenia, bipolar disorder and other psychoses in a rural Irish catchment area: incidence and gender in the Cavan-Monaghan study at 5 years. *British Journal of Psychiatry. Supplement* **181**, s3–s9.

Serra-Mestres J, Gregory CA, Tandon S, Stansfield AJ, Kemp PM, McKenna PJ (2000). Simple schizophrenia revisited: a clinical, neuropsychological, and neuroimaging analysis of nine cases. *Schizophrenia Bulletin* **26**, 479–493.

Strakowski SM (1994). Diagnostic validity of schizophreniform disorder. *American Journal of Psychiatry* **151**, 815–824.

Tandon R, Keshavan MS, Nasrallah HA (2008). Schizophrenia, 'Just the Facts': What we know in 2008. Part 1: Overview. *Schizophrenia Research* **100**, 4–19.

Tandon R, Nasrallah HA, Keshavan MS (2009). Schizophrenia, 'Just the Facts' 4. Clinical features and conceptualization. *Schizophrenia Research* **110**, 1–23.

Tohen M, Khalsa HM, Salvatore P, Vieta E, Ravichandran C, Baldessarini RJ (2012). Two-year outcomes in first-episode psychotic depression. The McLean-Harvard First-Episode Project. *Journal of Affective Disorders* **136**, 1–8.

van Os J, Linscott RJ, Myin-Germeys I, Delespaul P, Krabbendam L (2009). A systematic review and meta-analysis of the psychosis continuum: evidence for a psychosis proneness-persistence-impairment model of psychotic disorder. *Psychological Medicine* **39**, 179–195.

van Os J, Kapur S (2009). Schizophrenia. *Lancet* **374**, 635–645.

Waddington JL, Hennessy RJ, O'Tuathaigh CMP, Owoeye O, Russell V (2012). Schizophrenia and the lifetime trajectory of psychotic illness: developmental neuroscience and pathobiology, redux. In *The Origins of Schizophrenia* (ed. A. S. Brown and P. H. Patterson), pp. 3–21. Columbia University Press: New York.

Whitty P, Clarke M, McTigue O, Browne S, Kamali M, Larkin C, O'Callaghan E (2005). Diagnostic stability four years after a first episode of psychosis. *Psychiatric Services* **56**, 1084–1088.