5-year Stability of ICD-10 Psychiatric Diagnoses in Patients presented with First Episode Psychosis to the EASY Program of HKSAR

Dissertation submitted for the Part III Fellowship Examination of the Hong Kong College of Psychiatrists

Candidate:

Dr. Chang, Wing Chung, MRCPsych

Medical Officer, Department of Psychiatry, Tai Po Hospital

9, Chuen On Road, Tai Po, New Territories,

Hong Kong

Supervisor:

Dr. Chung, Wai Sau Dicky, MRCPsych; FHKCPsych; FHKAM (Psychiatry)

Chief of Service, Department of Psychiatry, Tai Po Hospital

9, Chuen On Road, Tai Po, New Territories,

Hong Kong

Date of Submission: 29th September 2008

Abstract

Background: Stability of diagnosis is one measure of predictive validity for psychiatric syndromes. It is an under-studied area in functional psychosis despite its clinical and research implications. The objective of this study was to determine the diagnostic stability in a sample of young people with first episode psychosis and to evaluate the patterns and factors associated with diagnostic shift.

Method: One hundred and sixty-six individuals consecutively enrolled in a specialized treatment program for first episode psychosis in New Territories East, Hong Kong from July 2001 to December 2002 were studied. Subjects were followed back retrospectively over 5 years and their baseline and final longitudinal consensus diagnoses were formulated according to ICD-10 DCR via systematic medical records review incorporating all available information. The analysis focused on (1) temporal stability of diagnoses; and (2) the effects of socio-demographic characteristics, family history of psychosis, hospitalization and clinical variables on diagnostic transition to schizophrenia spectrum disorder.

Results: The overall consistency between baseline and final longitudinal diagnoses was 80.7%. The most stable diagnostic categories over 5 years were bipolar affective disorder and schizophrenia with prospective consistency of 100% and 95.8% respectively. The least stable baseline diagnoses were unspecified non-organic psychosis, acute and transient psychotic disorders and delusional disorder. One in five subjects in our first episode psychosis cohort had diagnostic revision in 5 years. The predominant pattern of diagnostic shift was towards schizophrenia spectrum disorder. Family history of psychosis and longer duration of untreated psychosis were identified as predictors of change to schizophrenia spectrum diagnosis.

Conclusions: In a first episode psychosis sample in Hong Kong Chinese, we demonstrated that well-defined diagnostic entities i.e., schizophrenia and bipolar affective disorder were diagnostically stable and could be reliably classified at intake according to ICD-10 criteria. The greatest instability occurred in the least prevalent diagnostic categories of functional psychosis. In the absence of biological marker, diagnostic process taking into account longitudinal observation across consecutive episodes will be a major requirement for definitive diagnosis.

Keywords: Diagnostic stability, diagnostic shift, functional psychosis, first episode psychosis

Declaration of the work of author in this study

I, hereby, declare that the research in this dissertation represents my own original work and has not been submitted to other University or professional association for admission to a degree or fellowship.

In carrying out this study, I was responsible for collecting data, performing data analysis and writing up the dissertation.

_____

Wing Chung, Chang

Medical Officer

Department of Psychiatry

Tai Po Hospital

Word counts: 9,985 words (excluding tables, figures, footnote and references)

Acknowledgements

I would like to express my gratitude to my seniors Dr. Dicky W. S. Chung and Prof. Sandra S. M. Chan for their endless support and invaluable comments on my research project.

Last but not least, I would also like to thank Miss Shirley Pang for her kind assistance and advice on data input and analysis.

Table of Contents

"*Diagnosis, including its conceptual foundation, is a sine qua non of scientific medicine and of scientific psychiatry.*"

Guze S.B.

"*The follow-up is the great exposer of truth……It is to the psychiatrist what the post-mortem is to the physician.*"

Scott P.D.

Chapter 1 Introduction

Classifying entities into different categories on the basis of their shared attributes is an essential step in science (Millon, 1991). In medicine, and hence in psychiatry, classification is diagnosis (Robins & Guze, 1970). Diagnosis is essential in clinical practice and research. It provides information about patients' symptom profiles, prognosis and treatment outcome, and sets the boundaries for research through delineating homogeneous patient groups (Parnas & Zahavi, 2002). Unlike other branches in medicine with better understanding of underlying biological underpinnings, most of the diagnoses in psychiatry are still based on identification of clinical syndromes. In fact, the continuous use of the terminology of "functional" psychosis indicates that despite advance in neurosciences, the aetiology and pathophysiology of this group of "functional" psychotic disorders still remains unknown.

Functional psychosis is a heterogeneous condition encompassing various diagnostic entities defined by current psychiatric nomenclature including schizophrenia, schizoaffective disorder, affective psychosis, acute and brief psychoses, delusional disorder and unspecified psychosis. In the past, progress in research for psychosis has been hampered by its low diagnostic reliability among clinicians and across different countries (Kendell *et al.* 1971). Introduction of explicit operational criteria and rule-based classifications significantly improved diagnostic

agreement (Kendell & Jablensky, 2003). However, adequate diagnostic reliability does not necessarily provide information about the construct of disorders (Allardyce *et al.* 2007). Currently, other than criterion-based definitions, there is no objective measure for definitive diagnosis. In this context, operationalized diagnoses should be regarded as a set of clearly stated working hypotheses and the validity of diagnoses of functional psychotic disorders incorporated by the contemporary classifications cannot be taken for granted (McGuffin *et al.* 1991; Kendell & Jablensky, 2003).

It is stated that the most valid diagnoses are assumed to be aetiologically based. Kendell and Jablensky (2003) proposed that a valid diagnostic category should be defined by more fundamental characteristics such as physiological, pathological or genetic abnormality. Although diagnosis based on phenomenological-syndromal approach has been criticized for low epistemological ranking (McGorry, 1991), accurate delineation of clinical syndromes is suggested as a means to facilitate the process of uncovering biological dysfunctions via enhancing homogeneity (Kendell, 1989; Peralta & Cuesta, 2000).

In order to establish diagnostic validity of psychiatric disorders, a systematic biomedical approach has been put forward (Robins & Guze, 1970; Kendler, 1980; Krishnan, 2005). Outcome has been regarded as the most important and the most widely applicable criterion of

validity in the context of clinical psychiatry (Kendell, 1989). Diagnostic stability over time, being an outcome measure, has been proposed as one of the five validating criteria for verifying psychiatric syndromes (Robins & Guze, 1970). It is the measure of the degree to which a diagnosis remains the same at subsequent evaluations (Stanton & Joyce, 1993). It is assumed that the more stable the diagnosis, the more likely it is to reflect a basic and consistent psychopathological or pathophysiological process and hence, the more valid it is (Beiser *et al.* 1989).

Diagnostic revision can be attributable to change of clinical picture and methodological artifacts such as information variance, unreliable assessment, inconsistent application of diagnostic criteria and low inter-rater reliability (Fennig *et al.* 1994). Stability of diagnosis is crucial for research and clinical management (Bromet & Naz, 2006). Psychiatric disorders like schizophrenia and affective disorder are considered a chronic disorder. It is most common in epidemiological studies that subject's lifetime diagnosis used for longitudinal outcome analysis is based on cross-sectional diagnosis deriving from baseline assessment (Schwartz *et al*. 2000). Yet, it is known that diagnosis of a given patient is not static and can change over time (Marneros *et al*. 1991; Chen *et al*. 1996). Diagnostic instability longitudinally thus raises concerns regarding the validity of research results on aetiology, genetics, prognosis and treatment efficacy (Baca-Garcia *et al.* 2007). Clinically, diagnostic misclassification can lead

to iatrogenic effects to patients through inappropriate treatment recommendations (Schimmelmann *et al*. 2005).

Despite the implications in both clinical and research aspects, the question of diagnostic change in psychotic disorders has not been widely explored in the literature. Even fewer studies have investigated the patterns and correlates of diagnostic shifts across the spectrum of psychotic disorders. Examining patients with first episode psychosis longitudinally allows the course and evolution of psychotic illness from its onset to be better elucidated (Clarke & O'Callaghan, 2003). Up until recently, however, only a limited number of studies have addressed this issue in first-episode sample and almost all of them were conducted in western countries.

The Tenth Revision of International Classification of Disease (ICD-10) (WHO, 1992) was reported to be the most frequently and widely used diagnostic system in psychiatric clinical practice and training worldwide (Mezzich, 2002). It has been implemented as the official classification by public health care system in Hong Kong since 1 January 1997. To the best of my knowledge, there was no published data on diagnostic stability in patients presenting with first episode psychosis in Hong Kong. As well, no first-episode study has been conducted in examining factors associated with diagnostic shift on the basis of ICD-10 criteria.

This study examined a representative first episode psychosis cohort retrospectively over 5 years to determine the intake (baseline) and final longitudinal diagnoses of individual patients via systematic medical records review with all available information integrated across multiple episodes. Diagnoses were assigned by consensus procedure and ICD-10 Diagnostic Criteria for Research (DCR) (WHO, 1993) was strictly applied. The current report aimed at addressing the following questions:

(1) How stable were the diagnoses of functional psychotic disorders in first-episode sample over 5 years?

(2) What were the patterns of diagnostic shifts among various categories of functional psychosis?

(3) What were the factors associated with diagnostic instability?

Chapter 2 Literature Review

A search of literature via MEDLINE computerized database was conducted to identify relevant English-language articles published since 1950. Keywords used as search terms included: diagnostic stability, temporal stability, diagnostic consistency, psychotic disorders, functional psychosis and first-episode psychosis. Citations within identified papers and relevant chapters in some textbooks were also included as an additional source of references.

2.1 Methodological Considerations

Methodological heterogeneity was observed with respect to subject collection, diagnostic scope, sample size, diagnostic assignment and time intervals studied (Bromet *et al*. 2002). These differences would certainly affect the comparability of findings across studies. Therefore, it would be appropriate to examine some key methodological issues in the first place. (Table 2.1)

Sample recruitment and diagnostic assignment are the two fundamental issues in evaluating results of diagnostic stability. Methodologies varied widely in these two aspects and were discussed below.

Table 2.1 Methodological variations in studies examining Diagnostic Stability

Sample
Readmission versus first-episode sample
First contact to treatment versus first-admission sample
Diagnostic scope (broad spectrum of functional psychosis or single diagnostic category)
Inclusion of comorbid substance abuse
Age distribution criteria
Single hospital or academic centre or multiple treatment settings
Diagnostic Ascertainment
Diagnostic criteria (e.g. ICD-10, DSM-IV)
Longitudinal versus cross-sectional
Case registers or medical records review or structured interview
Consensus diagnosis versus individual psychiatrist's diagnosis
Follow-up issues
Length of follow-up
Number of interim follow-up assessments
Inclusion of face-to-face interview during assessment
Assessment scales and tools
Attrition rate

2.1.1 Sample Selection

2.1.1a Readmission versus First-Episode Sample

Many studies recruited subjects from readmission sample. However, such studies were limited by bias that was inherent in sampling rehospitalized patients. These patients were much more likely to have established chronic illness, causing an overestimation of diagnostic stability (McGlashan 1984).

Relatively few studies have investigated diagnostic stability in first-episode samples. It is postulated that the first few years following the onset of psychosis would be the critical period of illness evolution (Birchwood *et al.* 1998). Study of first-episode sample allows researchers to capture the true diversity in the course of functional psychosis since onset. It also ensures the relative homogeneity within the sample with respect to illness chronicity and treatment exposure (Clarke & O'Callaghan, 2003).

It should be noted that "first-admission" sample is not synonymous with "first-episode" sample. The former comprises inpatients only and excludes those with less severe first psychotic episode without requiring hospitalization. Cohort of first presentation for treatment i.e., "first contact to treatment" sample is less biased and thus more representative for patients with first-onset psychosis (Bromet *et al.* 2005).

2.1.1b Diagnostic Scope

Some studies only focused on non-affective psychosis (Addington *et al*. 2006). As there is significant overlap and unclear relationship between affective and psychotic symptoms in the early phase of illness (Fennig *et al.* 1994), exclusion of affective psychosis would introduce bias by automatically removing those who might have their baseline diagnosis of affective disorder reclassified at follow-up from study analysis.

Another sampling bias arises from exclusion of patients with comorbid substance abuse. Concomitant substance use is frequently observed among patients presenting for treatment with psychosis (Canton *et al.* 2007). It is reported that approximately one-third of those with first episode psychosis had co-existing substance use disorder (Cantwell *et al*. 1999). Because of the pervasiveness of substance abuse problems in patients with psychosis, generalizability of findings from studies with this exclusion criterion would be severely compromised.

2.1.2 Diagnostic Ascertainment

Two important issues related to diagnostic ascertainment need to be addressed. The first one is the diagnostic criteria applied. The second one is the diagnostic evaluation procedure with particular emphasis on how the clinical information is gathered for diagnostic judgment (Bromet *et al*. 2002).

2.1.2a Diagnostic Criteria

Various diagnostic schemes have been used in studies investigating diagnostic stability. However, there is little consensus on established superior validity of one particular diagnostic system over the others under the background of lack of objective indicator for definitive diagnosis (McGorry *et al.* 1995). Different diagnostic criteria denoting the same disorder will certainly identify patient groups with overlapping but non-identical characteristics. These discrepancies in diagnostic definitions need to be considered while interpreting the findings.

2.1.2b Methods of Diagnostic Assignment

Misclassification of diagnosis could also be attributed to diagnostic evaluation procedure per se i.e., procedural validity (McGorry *et al*. 1995). Case registers, structured interviews and medical records review were methods applied either alone or in combination for diagnostic assignment. Studies deriving diagnoses from case registers i.e., facility clinical diagnoses were limited by variance in information and variability in application of diagnostic criteria (Fennig *et al*. 1994). Structured interview provided a systematic way to formulate differential diagnosis. However, as denial of symptoms and recall bias are common in patients with psychosis and affective disorders, making diagnosis or verifying previous episodes mainly relying on structured interviews without incorporating other sources of information impaired its reliability and validity in generating a longitudinal diagnosis (Tsuang *et al.* 1981; Bromet & Naz, 2006).

Medical record is a valuable source of information for assessing clinical changes of patient over time. It is particularly important in documenting the presence of psychotic symptoms that had been denied in structured interviews and when there is absence of active symptoms during follow-up assessment (Fennig *et al.* 1994; Pillmann & Marneros, 2004). Retrospective application of diagnostic criteria to case notes was adopted in numerous studies and was shown to be reliable in diagnostic ascertainment (McGlashan, 1984; McGuffin *et al.* 1991).

Studies using such diagnostic approach showed comparable findings of stability and change of diagnosis to those adopting prospective design with structured interview-derived diagnosis (Forrester *et al*. 2001; Schimmelmann *et al.* 2005). It is noted that validity of the results is limited by documentation quality of case notes

Although there is no gold-standard method in formulating diagnosis of psychotic disorders, employing consensus diagnostic procedure by using all available information from multiple sources has been considered a reliable and currently accepted standard method for diagnostic assignment (Leckman *et al.* 1982).

2.2 Review of Study Findings and Methodology

2.2.1 Studies before the Introduction of Operational Diagnostic Criteria

Several investigators studied stability of psychiatric diagnoses using retrospective register-based data (Odegaard, 1966; Kendell, 1974; Amara, 1979) and hospital chart review on readmission sample (Cooper, 1967). These studies consistently showed that around 50% of subjects had diagnostic change. Kendell (1974) found that around 70% of subjects with affective disorder and schizophrenia at baseline retained the same diagnosis over 5 years. Cooper (1967) demonstrated change in doctors accounted for more diagnostic transition than changes in patient's condition. In these early studies it is difficult to discriminate between the effects of low reliability and other factors possibly contributing to diagnostic instability.

2.2.2 Studies in the Era of Operational Criteria: Non-First Episode Psychosis Study

2.2.2a Methodology

Most of these studies selected patients from readmission samples (Tsuang *et al.* 1981; Munk-Jorgensen, 1985; Jorgensen & Mortensen, 1988; Marneros *et al*. 1991; Hollister, 1992, Vetter & Koller, 1993; Stanton & Joyce, 1993, Rabinowitz *et al.* 1994; Chen *et al.* 1996; Daradkeh *et al.* 1997; Huguelet *et al*. 2001; Forrester *et al.* 2001). One study assessed stability of diagnoses derived from outpatient and emergency settings (Baca-Garcia *et al*. 2007). A study initiated by WHO recruited a mixture of both consecutive-admission and first-episode samples from four different cohorts for analysis (Craig *et al*. 2007). There was a wide variation of follow-up period ranging from 40 years to 2 years with majority less than 5 years.

Diagnostic criteria adopted were diverse, including ICD-8, ICD-9, ICD-10, DSM-III, DSM-IIIR, Research Diagnostic Criteria (RDC) and Feighner criteria. Most studies were retrospective in design, using case registers as the only source of information for diagnostic ascertainment (Munk-Jorgensen, 1985; Jorgensen & Mortensen, 1988; Hollister, 1992; Stanton & Joyce, 1993, Rabinowitz *et al*. 1994; Chen *et al*. 1996; Daradkeh *et al.* 1997; Huguelet *et al*. 2001; Baca-Garcia *et al.* 2007). Forrester *et al*. (2001) applied operational criteria checklist (OPCRIT) on case notes of readmission subjects to generate diagnoses. Other researchers utilized combination of either case registers (Vetter & Koller *et al.* 1993) or

case notes review (Tsuang *et al*. 1981; Marneros *et al.* 1991) and follow-up interview for diagnostic assignment. Baseline diagnosis was determined retrospectively while final diagnosis was formulated via information obtained from both interviews and medical records. However, only single follow-up interview was conducted and the time interval between the initial episode and follow-up assessment ranged from 12.5 years to 40 years.

2.2.2b Findings of Diagnostic Stability

Schizophrenia was found to have the highest diagnostic stability across studies with a range of around 70% to 90%, followed by affective disorder (mostly below 70%) (Tsuang *et al.* 1981; Munk-Jorgensen, 1985; Jorgensen & Mortensen, 1988; Marneros *et al*. 1991; Hollister, 1992, Vetter & Koller, 1993; Chen *et al*. 1996; Daradkeh *et al.* 1997; Huguelet *et al*. 2001). Many studies did not differentiate affective disorder into bipolar affective disorder and depressive disorder. No discrimination between psychotic and non-psychotic affective disorders was also observed in most of these studies. Relatively few studies examined diagnostic stability of other psychotic disorders such as delusional disorder, schizoaffective disorder and acute psychoses which were reported to be diagnostically unstable over time.

2.2.2c Findings of Diagnostic Shift

Few studies assessed the pattern and associated factors of diagnostic change. Conflicting results regarding diagnostic shift between schizophrenia and bipolar affective disorder were noted. Some studies demonstrated an absence of significant diagnostic switch (Stanton & Joyce, 1993; Tsuang *et al.* 1981) while others found considerable conversions among schizophrenia, bipolar affective disorder and schizoaffective disorder (Marneros *et al.* 1991; Chen *et al.* 1996). Findings regarding factors associated with diagnostic change were also inconsistent. Some researchers revealed no variables associated with diagnostic shift, apart from the diagnostic group memberships themselves (Huguelet *et al*. 2001). On the other hand, other reports showed that sex (Chen *et al*. 1996), age and hospital changes (Stanton & Joyce, 1993) were associated with change of schizophrenia diagnosis. Diagnostic consistency was also found to be correlated with treatment settings and inpatient diagnosis was more stable than that derived in outpatient and emergency settings (Baca-Garcia *et al.* 2007).

2.2.3 Studies in the Era of Operational Criteria: First Episode Psychosis Study

2.2.3a Methodology

Majority of these studies examined wider spectrum of psychotic disorders (Beiser *et al.* 1989; Lenz *et al.* 1991; Fennig *et al*. 1994; Mason *et al*. 1997; Goater *et al.* 1999; Amin *et al.* 1999; Schwartz *et al.* 2000; Veen *et al.* 2004; Baldwin *et al.* 2005; Whitty *et al*. 2005; Schimmelmann *et al.* 2005; Amini *et al.* 2005; Addington *et al*. 2006; Subramaniam *et al*. 2007; Rahm *et al*. 2007) though some reports only focused on single diagnostic category such as schizophrenia (Mason *et al.* 1997), schizophreniform disorder (Zarate Jr. *et al.* 2000) and acute and transient psychotic disorders (ATPD) (Jorgensen *et al*. 1997; Sajith *et al*. 2002; Castagnini *et al*. 2008). Affective psychosis (Addington *et al.* 2006) and comorbid substance abuse (Beiser *et al*. 1989; Subramaniam *et al*. 2007) were excluded by some studies.

With regard to length of follow-up, most studies had short follow-up interval with majority less than 2 years (6 months to 13 years). Only three studies had follow-up duration of 5 years or above (Lenz *et al*. 1991; Mason *et al.* 1997; Goater *et al.* 1999). However, one such study assessed schizophrenia only (Mason et al. 1997) and another one was limited by small sample size (Goater *et al.* 1999).

DSM-IV was the most common diagnostic criteria adopted in these studies and only three reports used ICD-10 for diagnostic assignment (Mason *et al*. 1997; Amin *et al*. 1999; Amini *et al*. 2005). Many studies conducted only one follow-up assessment with long time interval after the onset diagnostic evaluation. Some studies ascertained diagnosis via structured interviews without detailed case notes review over the interval between two remote assessment time points (Lenz *et al.* 1991; Mason *et al*. 1997; Whitty *et al*. 2005; Addington *et al.* 2006; Subramaniam *et al*. 2007, Rahm *et al* 2007). Information on subject's diagnostic status and clinical changes within these intervals might be missed and thereby misjudged diagnostic stability (Fennig *et al*. 1994).

Concerning diagnostic evaluation, some studies relied on single rater for making either initial or final diagnosis or even the same researcher for determining both diagnoses of individual subjects (Lenz *et al*. 1991; Whitty *et al.* 2005; Addington *et al.* 2006). Even though a more reliable consensus procedure was adopted, large variation still remained. Only very few studies conducted independent diagnostic assignment by at least two psychiatrists who were blind to facility diagnosis (Fennig *et al*. 1994; Schwartz *et al*. 2000; Amini *et al*. 2005). Some studies involved two diagnosticians for consensus procedure but one of them was responsible for compiling all the necessary information and presented the data to the other to generate consensus diagnosis (Beiser *et al.* 1989; Amin *et al* 1999; Goater *et al.* 1999; Veen *et al* 2004;

Baldwin *et al*. 2005). In this context, bias might possibly be introduced in formulating consensus diagnosis which would be more likely dependent on the judgment by one diagnostician who prepared the clinical information for this diagnostic process.

2.2.3b First-Episode Studies conducted in Asia

Thus far, most first-episode studies examining diagnostic stability were done in western countries. Only three such studies were conducted in Asia. The study in India only focused on ICD-10 diagnosis of acute polymorphic psychotic disorder without schizophrenia symptoms (Sajith *et al*. 2002). The study in Iran recruited first-admission sample rather than first contact to treatment sample, and was limited by small sample size (N=60) and short follow-up duration (1 year) (Amini *et al*. 2005). Concomitant substance abuse was an exclusion criterion of the study conducted in Singapore and subjects with affective psychosis were not further differentiated into bipolar affective disorder and depressive disorder for analysis. The first-episode cohort of this study was followed up for 2 years only and the consensus procedure was not adopted for diagnostic assignment (Subramaniam *et al*. 2007).

2.2.3c Findings of Diagnostic Stability

Overall diagnostic consistency was around 70%. Schizophrenia was the most stable initial diagnosis (above 90%) followed by bipolar affective disorder (above 80%) and depressive disorder (about 70%). Diagnostic categories like schizophreniform disorder, schizoaffective disorder and unspecified psychosis were the least stable. Inconsistent results were observed in delusional disorder (32% to 100%) and acute and brief psychosis (34% to 100%).

2.2.3d Findings of Diagnostic Shift

It was shown that the most frequent diagnostic flux was towards schizophrenia. There were more shifts from affective disorder to schizophrenia spectrum than vice versa. Substantial diagnostic movement to affective disorder and schizophrenia from acute psychosis was also demonstrated by certain studies (Jorgensen *et al*. 1997; Amin *et al.* 1999; Sjith *et al*. 2002).

Few studies examined predictors of diagnostic instability. Results thus far were inconclusive. Longer duration of untreated psychosis (DUP) and poorer premorbid adjustment were found to be predictive of diagnostic shift to schizophrenia spectrum or schizophrenia (Schwartz *et al.* 2000; Schimmelmann *et al.* 2005; Addington *et al.* 2006). Conflicting results regarding comorbid substance abuse and baseline symptom severity as predictors of diagnostic change towards schizophrenia spectrum were observed (Schwartz *et al*. 2000; Whitty *et al*. 2005).

Chapter 3 Materials and Methods

3.1 Sample

The sampling population constituted clients who were consecutively enrolled in the Early Assessment Service for Young People with Psychosis (EASY) in New Territories East (NTE), Hong Kong from July 2001 to December 2002. EASY is a government-funded territory-wide program in Hong Kong and the NTE team serves a catchment area with an urban population of approximately 1.2 million.

EASY is an enriched specialized program established since 2001, aiming at shortening DUP and increasing case-detection and treatment rate among young people with first-onset psychosis. It adopts case-management approach and provides comprehensive assessment and intervention programs over a 2-year period. All clients are assigned to a designated case manager who works closely with the family and the multidisciplinary EASY team. Case review in inter-disciplinary team-round has been held regularly for close monitoring of each client's course of illness, treatment plan and clinical progress. The scope of service includes intensive outpatient care, inpatient treatment, psychoeducational programs, carers and patients support groups, pharmacological intervention, cognitive-behavioural therapy and psychosocial rehabilitation training (Chen, 2004). Clients would be discharged to generic

psychiatric team for continuous follow-up at the end of the EASY program (2 years).

3.2 Inclusion and Exclusion Criteria

The inclusion and exclusion criteria for enrolment in EASY were as follows:

Inclusion Criteria

-age 15 to 25 years

-first lifetime presentation of psychotic episode

-onset of psychosis less than 2 years prior to enrolment in EASY

-residents of NTE catchment area

Exclusion Criteria

-moderate or severe mental retardation

-psychotic episode due to general medical condition or organic brain disease

-psychotic episode due to direct effect of substance use (intoxication, withdrawal state or substance-induced psychosis)

3.3 Diagnostic Review and Assignment

3.3.1 Intake Diagnosis

We adopted an all-source approach to record review. Information on subject's first psychotic episode was obtained from outpatient and inpatient medical records, and formatted outpatient intake summary and/or inpatient discharge summary via local computerized medical database, namely Psychiatric Clinical Information System (Psy-CIS). The raw information in medical records detailed longitudinal entries by multidisciplinary professionals, namely the consultant psychiatrist, treating psychiatrist, case manager and nursing staff. Supplementary information from clinical psychologist, occupational therapist and social worker was secured when available. Formatted summary and case notes were evaluated systematically and clinical data were recorded in standardized entry forms by principal investigator (PI) to compile an extracted summary. Two senior psychiatrists, who were blind to the facility diagnoses, raw data from medical records and subjects' identities, reviewed the extracted summaries and assigned intake (baseline) diagnosis independently according to ICD-10 DCR using diagnostic protocol and algorithm. Any diagnostic discordance between the two psychiatrists was resolved at the consensus meetings chaired by PI and the clinical information (kept anonymous) was systematically re-evaluated to yield the ultimate consensus diagnoses.

3.3.2 Interim Diagnosis

Interim diagnostic review was conducted when one of the following conditions was fulfilled:

-any psychiatric hospitalization

-any identified change of principal facility diagnosis responsible for psychotic disorder

-any episode of acute exacerbation treated in outpatient setting

An extracted summary for each interim review was prepared by PI from medical records and Psy-CIS summaries. The same diagnostic review procedure as described in 3.3.1 (Intake Diagnosis) was adopted.

3.3.3 Final Longitudinal Diagnosis

A compiled file of serial extracted summaries over the entire follow-up interval (including all inpatient admissions and interim episodes) was prepared by PI using all available information. Diagnostic procedure identical to that used to formulate intake and interim consensus diagnoses was applied to assign a final longitudinal consensus diagnosis.

3.4 Factors associated with Diagnostic Shift

Five domains of variables were used to examine potential factors associated with diagnostic shift. Data was obtained from Psy-CIS, formatted summaries and case notes, and were recorded in a standardized form.

1. Baseline Demographic Data

Age, gender and marital status

2. Baseline Socioeconomic Status

Occupational status, living condition and the highest level of education attained at intake

3. Family History of Psychotic Illness (in first degree relatives)

4. Clinical Characteristics

Nine clinical variables were retrieved and categorized into two groups:

(1) First-episode: age of onset of first episode psychosis, duration from onset of psychosis to enrolment in EASY (DUP*), mode of onset (less or more than 4 weeks), duration of first psychotic episode and the presence of substance abuse before onset of psychosis.

* **DUP** was defined in this study as the time from onset of first psychotic symptom to enrolment in EASY

(2) Clinical history: history of suicidal attempt, history of substance use, history of aggressive behaviour to others and Priority Follow-Up (PFU) status *

5. Hospitalization and Follow-up variables

Number of psychiatric hospitalizations, compulsory admission status, conditional discharge status**, total length of psychiatric hospitalization and mean length of psychiatric inpatient stay per admission.

This study was approved by the local research and ethics committee (CREC Reference No.: CRE-2007.296).

* **PFU system** is a classification system formally adopted by the Hospital Authority of Hong Kong to denote the need for more intensive follow-up in patients with history of violence.

** Under the Mental Health Ordinance, patient will be **conditionally discharged** if he or she has history of serious aggression and is evaluated as having high propensity to violence upon discharge

3.5 Data Analysis

3.5.1 Diagnostic Stability

Diagnostic stability was considered to be present if information within the 5-year period subsequent to intake diagnosis confirmed the original baseline diagnosis, irrespective of whether the symptoms of the original diagnosis were actively present at follow-up assessments (Fennig *et al*. 1994). It was assumed that the original baseline diagnosis would be maintained when there was no emergence of new information during follow-up after intake assessment (Amin *et al*. 1999).

The analysis of diagnostic stability between intake and final longitudinal consensus diagnoses was based on a cross-tabulation of seven diagnostic categories. (Table 4.4, p.37) Two measures of stability were presented for each diagnostic category. First, prospective consistency equalled the proportion of subjects in a category at baseline assessment who retained the same diagnosis at the end of follow-up. This would correspond to positive predictive value if the final longitudinal diagnosis was assumed to be the gold standard. The second measure was retrospective consistency which was the proportion of subjects with a given diagnosis at the end of follow-up who had received the same diagnosis at baseline assessment. This was conceptually similar to sensitivity. Specificity and negative predictive value of schizophrenia were also measured.

3.5.2 Diagnostic Concordance

Cohen's kappa values were used to calculate the concordance between intake and final longitudinal consensus diagnoses correcting the effect of chance. The kappa statistics were also used to analyze the congruence between consensus and facility diagnoses and the mutual agreement between two independent psychiatrist-assigned diagnoses.

3.5.3 Pattern and Factors associated with Diagnostic Shift

Diagnoses across spectrum of psychotic disorders were grouped into three broad categories:

(1) Schizophrenia spectrum (schizophrenia and schizoaffective disorder)

(2) Affective disorder (bipolar affective disorder and depressive disorder)

(3) Other psychosis (ATPD, delusional disorder and unspecified non-organic psychosis)

Diagnostic shift patterns were summarized into three groups:

(1) Stable schizophrenia spectrum disorder

(2) Stable non-schizophrenia spectrum disorder

(3) Non-schizophrenia spectrum diagnosis at baseline shifting to schizophrenia spectrum at follow-up.

Two comparative analyses were carried out. Firstly, subjects shifting from non-schizophrenia spectrum disorder to schizophrenia spectrum were compared to those with stable schizophrenia spectrum diagnosis over the follow-up interval. Group differences were analyzed using t test for continuous measures and the chi-square test of independence for categorical variables. Fisher's exact test was performed when the assumption of chi-square test was not met.

A second analysis compared subjects shifting from non-schizophrenia spectrum disorder to schizophrenia spectrum with those who remained outside the schizophrenia spectrum. Those variables that were significantly associated with diagnostic shift in the bivariate analyses were then entered into stepwise logistic regression analysis to determine which factors independently predict diagnostic transition to schizophrenia spectrum. The level of statistical significance for all analyses were set at $p<0.05$.

Chapter 4 Results

4.1 Descriptive Characteristics of the Sample

The sampling population comprised of 203 subjects who were enrolled in the NTE-EASY program from July 2001 to December 2002. Thirty-seven patients were excluded upon verification owing to: (1) non-psychotic diagnosis (N=12); (2) substance-induced psychosis at intake (N=15); (3) short duration of follow-up (less than 1 year) despite having baseline diagnosis of functional psychosis (N=10). A total of 166 subjects were included in the final sample with 56.6% as outpatients and 43.3% as inpatients at intake. The mean age at entry was 19.8 years. Compared with the final sample, those excluded cases with functional psychosis were over-represented by male sex (70%, χ^2=2.0), had an older mean age at entry (21.2 years, t=1.4) and greater proportion of “other psychosis” (70%, χ^2=13.4).

4.1.1 Socio-Demographic Data and Family History

The subjects of the study sample were predominantly single (88.6%), 53.6% were male, 94% were living with family and 53.6% attained Form 5 educational level or above at intake. Concerning occupational status, 64 subjects (38.6%) were unemployed, 37.3% were students and 22.3% were gainfully employed at entry. Twenty-one subjects (12.7%) had family history of psychotic illness in their first degree relatives. (Table 4.1)

Table 4.1 Socio-Demographic characteristics & Family history of the sample (*N*=166)

Characteristics	**mean ± SD**	
Age at entry	19.8 ± 3.11	
	N	**%**
Gender		
Male	89	53.6
Female	77	46.4
Marital status		
Single	147	88.6
Married	3	1.8
Stable relationship	15	9
Divorced or separated	1	0.6
Educational level		
Below Form 5	74	44.6
Below Form 7 but completed Form 5	69	41.6
Completed Form 7	10	6
University graduate or above	10	6
Special education for mentally retarded	3	1.8
Occupational status		
Unemployed	64	38.6
Full-time paid	35	21.1
Part-time / supported employment / sheltered workshop	3	1.8
Household duties	2	1.2
Student	62	37.3
Living condition		
With family members	128	77.1
With others	7	4.2
Living alone	3	1.8
Family history of psychotic illness (first degree relatives)	21	12.7

4.1.2 Hospitalization and Follow-up Variables

One hundred and twenty-five patients (75.3%) were hospitalized at least once during the study period. Among these patients, 27.2% had been compulsorily detained in psychiatric hospital before and only four subjects (3.2%) were conditionally discharged due to high propensity to violence. The mean total length of psychiatric hospitalization was 98.4 days (S.D. 125.1, range 1 to 870) and the mean length of inpatient stay per admission was 47.3 days (S.D. 59.6, range 1 to 435). (Table 4.2)

Concerning follow-up status, 75.9% of 166 subjects completed 5-year follow-up in NTE catchment area. The mean duration of follow-up of the whole sample was 53.4 months (S.D. 13.3). For those who had less than 5 years follow-up (N=40), eight subjects were transferred to other catchment areas for continuous treatment, 18 subjects were defaulters and 10 patients required no further follow-up. Three subjects committed suicide and one died of medical illness. Of these 40 subjects, 57.5% had final schizophrenia spectrum diagnosis (with one schizoaffective disorder), 25% had affective disorder and 17.5% had “other psychosis”. These individuals had higher prevalence of substance abuse before onset of illness (χ^2=6.4, p=0.20), single episode with full remission (χ^2=10.2, p<0.01), and were less likely to have been hospitalized (t=3.4, *df*=164, p<0.01). Their mean follow-up duration was 32.5 months (S.D. 12.1).

Table 4.2 Hospitalization & Follow-up variables of the sample (*N*=166)

Hospitalization variables		
Psychiatric hospitalizations	**N**	**%**
One admission	49	29.5
Two admissions	38	22.9
Three admissions	17	10.2
Four admissions	10	6
Five admissions or above	11	6.6
Compulsory admission status	34	27.2
Conditionally discharged	4	3.2
Length of inpatient stay, in days	**mean ± S.D.**	
Total duration	98.4 ± 125.1	
Mean duration per admission	47.3 ± 59.6	
Follow-up variables		
Treatment setting of intake assessment	**N**	**%**
Outpatient	94	56.6
Inpatient	72	43.4
Follow-up status at the end of study period	**N**	**%**
Continuous follow-up in NTE	126	75.9
	mean ± S.D.	
Length of follow-up, in months	53.4 ± 13.3	

4.1.3 Clinical Characteristics

With respect to clinical variables at entry, 93 subjects (56%) were enrolled in EASY within 3 months from onset of psychosis and 11.5% presented for treatment 1 year after onset of illness. The mean DUP was 25.1 weeks (S.D. 30.6, range 1 to 104). Fifty-three patients (31.9%) had their first-episode duration lasting less than 3 months. The mean duration of first-episode was 19.1 weeks (S.D. 19.5, range 1 to 130). Ninety-four subjects (56.6%) had gradual onset of first psychotic episode (more than 4 weeks). The mean age of onset of psychosis was 19.3 years (S.D. 19, range 13 to 25).

As regards clinical history variables, 18.7% had history of suicidal attempt and 12.7% had history of substance use in which 90.5% abused psychoactive substances before the onset of psychotic illness. During the follow-up period, thirty-seven subjects (32.3%) had history of violence and among them 16.2% had serious aggression (attacking others with objects). Ten patients (6%) were labelled “Priority Follow-Up” (PFU) status during the follow-up interval. (Table 4.3)

Table 4.3 Clinical characteristics of the sample (*N*=166)

Clinical history variables		
	N	**%**
History of suicidal attempt	31	18.7
History of substance abuse	21	12.7
History of aggression	37	32.3
Priority Follow-Up (PFU) status	10	6
First-episode variables		
	mean ± S.D.	
Age of onset of psychosis	19.3 ± 3.1	
Duration from onset of psychosis to EASY (DUP), in weeks	25.1 ± 30.1	
First-episode duration, in weeks	19.1 ± 19.5	
	N	**%**
Duration from onset of psychosis to EASY (DUP), less than 3 months	93	56
Onset of psychosis, less than 4 weeks	72	43.4
First-episode duration, less than 6 months	91	54.8
Substance abuse before onset of psychosis	19	11.4

4.2 Diagnostic Stability

Table 4.4 showed a cross-tabulation of baseline and final longitudinal consensus diagnoses for the total sample. The overall rate of consistency was 80.7%; 134 of the 166 subjects received the same diagnosis at both intake and at the end of follow-up. Bipolar affective disorder and schizophrenia had the highest prospective consistency* of 100% and 95.8% respectively, followed by depressive disorder (62.5%). “Other psychosis” was observed to be diagnostically unstable over time. The prospective consistency was 50% for delusional disorder, 35.3% for ATPD and 22.2% for unspecified non-organic psychosis.

Depressive disorder and ATPD had among the highest retrospective consistency** (100%). The retrospective consistency was 82.9% for schizophrenia, 73.1% for bipolar affective disorder and 14.3% for schizoaffective disorder.

* The proportion of subjects in a category at baseline assessment who retained the same diagnosis at the end of follow-up, i.e., positive predictive value.

** The proportion of subjects with a given diagnosis at the end of follow-up who had received the same diagnosis at baseline assessment, i.e., sensitivity.

Table 4.4 Cross-Tabulation of Baseline & Final Longitudinal ICD-10 Consensus Diagnosis in First-episode Psychosis Subjects (*N*=166)

		Final Longitudinal Diagnosis, N									
Baseline Diagnosis	**N**	**SCZ Spectrum**	Schizophrenia	SAD	**Affective Disorder**	BPD	Depressive Disorder	**Other Psychosis**	ATPD	Delusional Disorder	Unspecified NOP
SCZ Spectrum	**97**	94			3			0			
Schizophrenia	**96**		92	1		3	0		0	0	0
SAD	**1**		0	1		0	0		0	0	0
Affective Disorder	**35**	5			30			0			
BPD	**19**		0	0		19	0		0	0	0
Depressive Disorder	**16**		2	3		1	10		0	0	0
Other Psychosis	**34**	19			3			12			
ATPD	**17**		6	2		3	0		6	0	0
Delusional Disorder	**8**		4	0		0	0		0	4	0
Unspecified NOP	**9**		7	0		0	0		0	0	2
Total	**166**	**118**	**111**	**7**	**36**	**26**	**10**	**12**	**6**	**4**	**2**
Prospective consistency, %*		96.9	95.8	-	85.7	100	62.5	35.3	35.3	50	22.2
Retrospective consistency, %†		79.7	82.9	14.3	83.3	73.1	100	100	100	-	-

*Percentage of patients at baseline with the same diagnosis at the end of follow-up

† Percentage of patients at the end of follow-up with the same diagnosis at baseline

Prospective or retrospective consistency were not calculated for those diagnoses with less than five patients at baseline or at the end of follow-up

Abbreviation: SCZ spectrum = Schizophrenia spectrum, SAD = Schizoaffective disorder, BPD = Bipolar affective disorder, ATPD = Acute and Transient Psychotic Disorders, Unspecified NOP = Unspecified Non-Organic Psychosis

Table 4.5 Comparison of Baseline & Final Consensus Diagnosis of Schizophrenia

	Final longitudinal diagnosis		
Baseline diagnosis	Schizophrenia	Other diagnoses	Total
Schizophrenia	**92**	**4**	96
	"True-positive"	"False-positive"	
Other diagnoses	**19**	**51**	70
	"False-negative"	"True-negative"	
Total	111	55	166
Sensitivity‡	82.9%		
Specificity	92.7%		
Positive predictive value§	95.8%		
Negative predictive value	72.9%		
Kappa coefficient	0.71		

‡Sensitivity = retrospective consistency
§Positive predictive value = prospective consistency

Alternative measures for diagnostic stability of schizophrenia were presented in Table 4.5. The specificity was 92.7% while the negative predictive value was lower (72.9%). The kappa coefficient of $\kappa=0.71$ ($p<0.01$) indicated substantial agreement between baseline and final schizophrenia diagnoses.

The kappa value of consensus baseline and final diagnoses for all diagnostic categories was 0.67 ($p<0.01$).

4.3 Reanalysis of Diagnostic Stability

Subjects who achieved full remission with no further psychotic episodes after their first-onset psychosis retained their intake diagnosis as final longitudinal diagnosis due to absence of clinical change in subsequent follow-up. Inclusion of patients with single episode might overestimate the overall diagnostic stability. Thirty subjects (22.1%) who experienced single episode were thus excluded and the remaining 136 subjects were reexamined. The baseline diagnostic distribution of the remaining group was comparable to that of the whole sample. The overall consistency and diagnostic stability of schizophrenia and affective disorders of the remaining group were similar to that of the whole sample except that the prospective consistency of “other psychosis” in the former group was lower than that of latter (24.1% v. 35.3%). (Table 4.6) Compared to those who had single episode, patients in the remaining group were more likely to be hospitalized (χ^2=12.6, p<0.01), unemployed (χ^2=7.4, p<0.01), having longer duration of follow-up (t=3.7, *df*=164, p<0.01), gradual onset of illness (more than 4 weeks) (χ^2=6.3, p<0.01) and aggressive behaviour to others (χ^2=5.2, p<0.01).

Next, a subgroup of patients with less than 5-year follow-up duration (24.1%) was excluded to examine whether the length of follow-up might influence the degree of diagnostic consistency. When we restricted the analysis to those having 5-year follow-up, we observed similar results to that of the whole cohort in terms of overall consistency and diagnostic stability of schizophrenia and bipolar affective disorder. Lower prospective consistency of depressive disorder (37.5% v. 62.5%) and “other psychosis” (20.8% v. 35.3%) were noted in this subgroup otherwise. (Table 4.7) Compared with the whole sample, the remaining group had slightly lower prevalence of baseline diagnosis of depressive disorder (9.6% v. 6.3%).

4.4 Diagnostic Concordance

The concordance between final consensus and facility diagnoses was moderate ($\kappa=0.60$, $p<0.01$). The kappa values indicated a good agreement for both intake baseline ($\kappa=0.77$, $p<0.01$) and final longitudinal diagnoses ($\kappa=0.79$, $p<0.01$) between independently assigned diagnoses by the two psychiatrists.

Table 4.6 Reanalysis of Diagnostic Stability: Single episode excluded (*N*=136)

Diagnosis	**Prospective consistency %**	**Retrospective consistency %**
Schizophrenia	95	80
Schizoaffective Disorder*	-	14.3
Bipolar Affective Disorder	100	63.2
Depressive Disorder	57.1	100
Other Psychosis¶	24.1	100

* Prospective consistency was not calculated as less than five patients with this diagnosis at baseline

¶Other Psychosis included ATPD, Delusional disorder and Unspecified non-organic psychosis

Table 4.7 Reanalysis of Diagnostic Stability: FU less than 5 years excluded (*N*=126)

Diagnosis	**Prospective consistency %**	**Retrospective consistency %**
Schizophrenia	94.8	82
Schizoaffective Disorder*	-	14.3
Bipolar Affective Disorder	100	73.9
Depressive Disorder	37.5	100
Other Psychosis¶	20.8	100

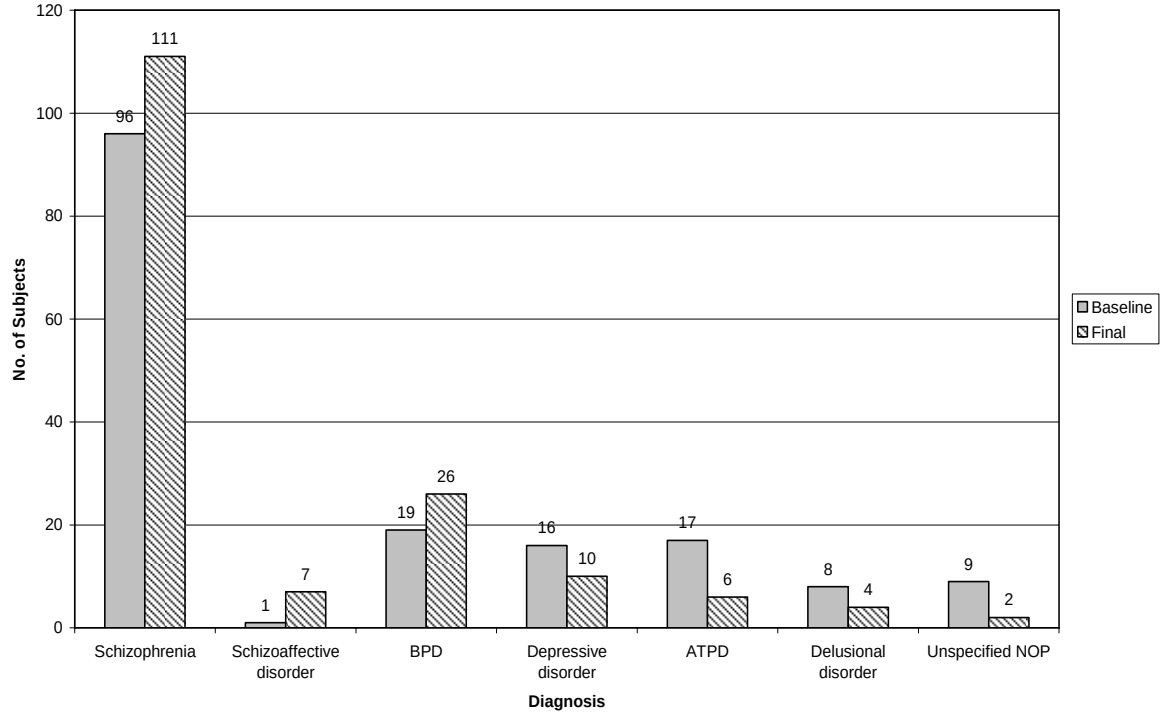
* Prospective consistency was not calculated as less than five patients with this diagnosis at baseline

¶Other Psychosis included ATPD, Delusional disorder and Unspecified non-organic psychosis

4.5 Pattern of Diagnostic Shift

Thirty-two of 166 subjects (19.3%) had diagnostic revision. Three-fourth occurred within the first three years since entry to EASY and almost 90% changed their diagnoses by the end of fourth year. Diagnostic shift towards schizophrenia spectrum occurred most frequently, accounting for 77.4% of those having diagnostic switch. Within this group, the majority shifted into schizophrenia diagnosis (59.4%). Figure 4.1 illustrated the change of diagnostic distribution across 5-year interval.

Figure 4.1 Diagnostic Distribution of Consensus Diagnoses at Baseline & at the End of Follow-up

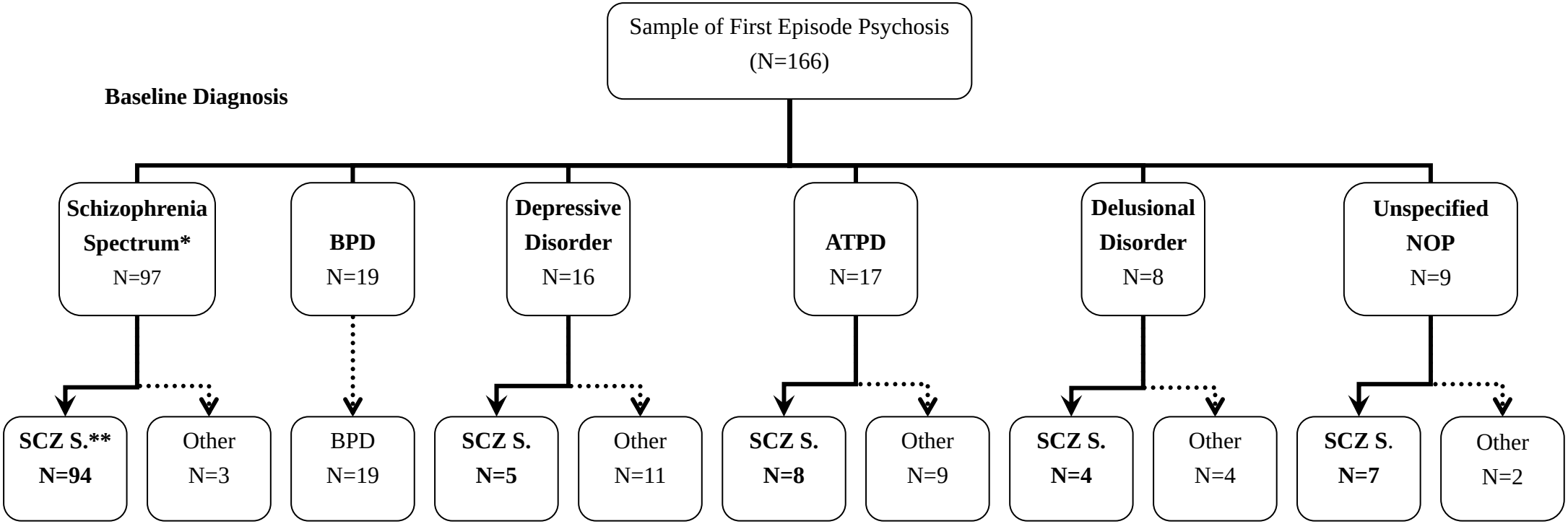


Abbreviations: BPD = Bipolar affective disorder, ATPD = Acute and transient psychotic disorders
Unspecified NOP = Unspecified non-organic psychosis

Diagnostic change towards schizophrenia spectrum was illustrated in Figure 4.2. Diagnostic shift to schizophrenia was mainly from the group “other psychosis” including seven with unspecified non-organic psychosis, six with ATPD and four with delusional disorder. The remaining were initially diagnosed as depressive disorder (N=2). No subjects with bipolar affective disorder at baseline shifted to schizophrenia spectrum. Conversely, three of seven subjects (42.9%) who received their final diagnosis as bipolar affective disorder were originally classified as schizophrenia. Schizoaffective disorder had among the lowest retrospective consistency of 14.3%, indicating that the majority having this final diagnosis received different diagnostic labels at baseline including depressive disorder, ATPD and schizophrenia.

With regard to subjects having baseline ATPD, it was shown that those reclassified as having schizophrenia spectrum disorder were all diagnosed as “non-polymorphic” subtype at intake assessment (75% from acute schizophrenia-like psychotic disorder, N=6). For patients with baseline diagnosis of ATPD “polymorphic” subtype who had diagnostic revision later on, all were re-diagnosed as bipolar affective disorder (N=2). Despite the small cell numbers in each subcategory of ATPD, the change in number (i.e., pattern of diagnostic shift) under different diagnostic subcategories across follow-up interval was statistically significant ($\chi^2=6.6$, $p<0.05$, by *Fisher’s exact test*). (Table 4.8)

Figure 4.2 Diagnostic Flow towards Schizophrenia Spectrum across 5-year interval



Abbreviations: SCZ S. = Schizophrenia spectrum, BPD = Bipolar affective disorder, ATPD = Acute and transient psychotic disorder, Unspecified NOP = Unspecified Non-organic psychosis

* Baseline schizophrenia spectrum included 1 diagnosis of schizoaffective disorder

** Final longitudinal schizophrenia spectrum included 7 diagnoses of schizoaffective disorder

Table 4.8 Cross-Tabulation of Diagnostic Change in Acute and Transient Psychotic Disorders (*N*=17)

		Final Longitudinal Diagnosis, N						
					ATPD Polymorphic type		**ATPD Non-Polymorphic type**	
Baseline Diagnosis		SCZ.Spectrum			With SCZ	Without SCZ	Acute	Other acute predominantly
ATPD subtype	**N**	SCZ	SAD	BPD	symptoms	symptoms	SCZ-like	Delusional
Polymorphic	**5**	0	0	**2**	**3**		**0**	
With SCZ symptoms	3	0	0	1	2	0	0	0
Without SCZ symptoms	2	0	0	1	0	1	0	0
Non-Polymorphic	**12**	**6**	**2**	**1**	**0**		**3**	
Acute SCZ-like	9	5	1	1	0	0	2	0
Other acute predominantly Delusional	3	1	1	0	0	0	0	1
Total	**17**	6	2	3	2	1	2	1

Abbreviations: ATPD = Acute and transient psychotic disorders, SCZ = Schizophrenia, SAD = Schizoaffective disorder, BPD = Bipolar affective disorder, Acute SCZ-like = Acute schizophrenia-like psychotic disorder
Other acute predominantly Delusional = Other acute predominantly delusional psychotic disorder

4.6 Factors associated with Diagnostic Shift

Table 4.9 displayed the baseline socio-demographic, hospitalization and clinical variables of the three groups characterized by different patterns of diagnostic shift.

4.6.1 Differences between patients with Stable Schizophrenia Spectrum Disorder and those shifting to Schizophrenia Spectrum Disorder

The comparison of subjects who shifted into schizophrenia spectrum with those stably diagnosed schizophrenia spectrum patients revealed no significant differences in socio-demographic and hospitalization characteristics. Individuals with diagnostic change were more likely to have family history of psychotic illness (χ^2=13.6, p<0.01), had significantly shorter DUP (less than 3 months) (χ^2=8.0, p<0.01) and shorter first-episode duration (t=3.9, *df*=78.8, p<0.01) than subjects with stable schizophrenia spectrum diagnosis.

4.6.2 Factors associated with Shift to Schizophrenia Spectrum Disorder

Subjects shifting to schizophrenia spectrum diagnosis were then compared with those who remained outside the spectrum. There were no significant differences in demographic data, hospitalization characteristics and clinical history variables between these two patient groups. Patients who were re-diagnosed as schizophrenia spectrum disorder were significantly more likely to be unemployed at intake (χ^2=4.5, p<0.05), to have family history of psychotic illness (χ^2=6.2, p<0.05) and longer DUP (t=2.4, *df*=25.2, p<0.05) than those with stable non-schizophrenic spectrum diagnosis. Gradual onset of illness was also more common in cases switching to schizophrenia spectrum and achieved a near statistical significance (χ^2=3.4, p=0.065).

Stepwise logistic regression analysis was performed to assess the prediction of diagnostic shift to schizophrenia spectrum disorder. DUP and family history of psychotic illness entered the final model and fulfilled the criteria for inclusion as independent predictors. A test of the full model against a constant-only model was statistically reliable (χ^2= p< 0.01), indicating that the predictors, as a set, reliably distinguished between the group with stable non-schizophrenia spectrum diagnosis and those who shifted towards schizophrenia spectrum (Nagelkerke: R^2=0.32). (Figure 4.3)

Table 4.9 Baseline & Clinical Characteristics of Subjects Groups with Different Patterns of Diagnostic Change

Characteristics	**Stable SCZ Spectrum** (*N*=94)	**Stable Non-SCZ Spectrum** (*N*=45)	**Shift to SCZ Spectrum** (*N*=25)
Socio-demographic variables			
Age at entry, mean ± SD	20.1 ± 3.2	19.1 ± 2.7	19.9 ± 3.4
Male, N (%)	58 (61.7)	18 (40.0)	11 (44.4)
Single, N (%)	84 (89.4)	36 (80.0)	24 (96.0)
Unemployed, N (%)	43 (45.7)	9 (20.0)*****	11 (44.0)
Below Form 5 level, N (%)	48 (51.1)	17 (37.8)	10 (40.0)
Living with family or others, N (%)	92 (97.9)	43 (95.6)	25 (100)
Family history of Psychotic illness, N (%)	7 (7.4)******	5 (11.1)*****	9 (36.0)
Hospitalization variables			
Compulsory admission status, N (%)	21 (22.3)	7 (15.6)	6 (24.0)
Conditionally discharged status, N (%)	3 (3.2)	0 (0.0)	1 (4.0)
Total length of admissions, in days, mean±SD	104.9 ± 137.8	68.2 ± 73.2	114.0 ± 142.6
Mean length per admission, in days, mean± SD	55.3 ± 71.1	34.1 ± 33.3	38.0 ± 42.5
Clinical history variables			
Lifetime suicidal attempt, N (%)	15 (16.0)	8 (17.8)	7 (28.0)
Lifetime substance abuse, N (%)	15 (16.0)	4 (8.9)	2 (8.0)
Aggression history, N (%)	21 (22.3)	7 (15.6)	7 (28.0)
Priority Follow-Up (PFU) status, N (%)	5 (5.3)	1 (2.2)	4 (16.0)
First-episode clinical variables			
Age at onset of psychosis, mean ± SD	19.5 ± 3.3	19.0 ± 2.7	19.6 ± 3.1
DUP in weeks, mean ± SD	33.8 ± 32.6	6.8 ± 7.1†	23.3 ± 33.9
DUP of more than 3 months, N (%)	77 (81.9)******	18 (40.0)	14 (56.0)
Onset of more than 4 weeks, N (%)	66 (70.2)	15 (33.3)¶	14 (56.0)
First-episode duration in weeks, mean±SD	24.4 ± 23.3‡	12.4 ± 8.4	11.1 ± 11.8
Substance abuse before onset, N (%)	14 (14.9)	3 (6.7)	2 (8.0)

***** $p < .05$ for stable non-SCZ spectrum vs. shift to SCZ spectrum (χ^2 test, df = 1, N = 70)
† $p < .05$ for stable non-SCZ spectrum vs. shift to SCZ spectrum (t test, df = 25.2)
¶ $p = .065$ for stable non-SCZ spectrum vs. shift to SCZ spectrum (χ^2 test, df = 1, N = 70)
****** $p < .01$ for stable SCZ spectrum vs. shift to SCZ spectrum (χ^2 test, df = 1, N = 119)
‡ $p < .01$ for stable SCZ spectrum vs. shift to SCZ spectrum (t test, df = 78.8)
Abbreviations: SCZ = schizophrenia, DUP = duration of untreated psychosis

Figure 4.3 Logistic Regression Analysis for Predictors of Shift to Schizophrenia Spectrum Diagnosis

Variables entering stepwise logistic regression model for determining independent predictors of diagnostic shift to schizophrenia spectrum:

1. Unemployed occupational status
2. Family history of psychotic illness (first degree relatives)
3. Duration from onset of psychosis to EASY (DUP)
4. Onset of first episode psychosis (less than 4 weeks) *

**near statistical significance with p = 0.065 (χ^2 test, df = 1)*

Variables in the Equation	B	S.E.	Wald	df	Sig.	Exp(B)
Family history of psychotic illness	1.943	0.689	7.959	1	0.005	6.978
DUP	-0.064	0.026	5.951	1	0.015	0.938
Constant	-0.202	0.584	0.120	1	0.729	

Nagelkerke R^2 = 0.316
$\chi^2 = 18.3$, $p < 0.001$

Variables not in the Equation	Score	df	Sig.
Unemployed occupational status	2.010	1	0.156
Onset of first episode psychosis	0.203	1	0.652

No more variables can be deleted or added.

Chapter 5 Discussion

5.1 Interpretation of Results

5.1.1 Diagnostic Stability

The overall diagnostic consistency was 80.7%. Schizophrenia and bipolar affective disorder were demonstrated to be highly stable diagnostic categories, followed by depressive disorder. In accordance with earlier first-episode studies (Mason *et al*. 1997; Schwartz *et al*. 2000; Veen *et al.* 2004; Baldwin *et al.* 2005; Whitty *et al*. 2005; Schimmelmann *et al*. 2005; Addington *et al*. 2006), our findings showed that the prospective consistency of schizophrenia was above 90% (95.8%). The relatively lower retrospective consistency of schizophrenia and a higher proportion of false-negatives (N=19) in comparison with false-positives (N=4) indicated that more subjects changed their diagnoses towards rather than away from schizophrenia across 5-year interval. Schizophrenia diagnosis was also shown to have high level of specificity (92.7%). Therefore patients without schizophrenia at follow-up rarely received this diagnosis at baseline. Consistent with other studies, schizoaffective disorder accounted for a small proportion of schizophrenia spectrum diagnosis (5.9%). Majority of subjects classified as schizoaffective disorder at the end of follow-up were initially assigned a different diagnosis at intake as reflected by its low retrospective consistency (14.3%).

In general, bipolar affective disorder was demonstrated to be remarkably stable with prospective consistency of above 80% in most first-episode studies. Comparatively higher stability of bipolar affective disorder was observed in the present report. However, it should be noted that 36.8% of subjects in this study who presented with manic episode as their first-onset psychosis did not experience further episodes after achieving remission. In this context, diagnostic stability of bipolar affective disorder might be overestimated. Overall, both schizophrenia and bipolar affective disorder displayed high level of diagnostic stability, which supported the distinct nature of these disorders (Winokur *et al*. 1996).

Confirming results of earlier studies, “other psychosis” had low diagnostic stability (Amin *et al.* 1999; Schwartz *et al.* 2000; Veen *et al.* 2004; Baldwin *et al.* 2005; Whitty *et al*. 2005; Schimmelmann *et al.* 2005; Addington *et al*. 2006; Subramaniam *et al*. 2007). Unspecified non-organic psychosis was the most unstable diagnosis, followed by ATPD and delusional disorder.

5.1.2 Reanalysis of Diagnostic Stability

There are many reasons why diagnoses change, including emergence of new information and changing psychopathology. This study did not investigate all potential causes for diagnostic change due to constraints of its retrospective design. However, we examined two subgroups in order to evaluate whether the length of follow-up and the number of episodes affected diagnostic stability. Neither did, in terms of overall consistency and diagnostic stability of schizophrenia and bipolar affective disorder. Hence it was unlikely that these factors had confounded the observation of diagnostic consistency in both schizophrenia and bipolar affective disorder. On the other hand, prospective consistency of “other psychosis” was reduced when single-episode subjects were excluded (24.1% v. 35.3%). Lower prospective consistency of depressive disorder (37.5% v. 62.5%) and “other psychosis” (20.8% v. 35.3%) were also noted after excluding those with less than 5 years follow-up. These findings suggested that patients with depressive disorder or “other psychosis” were more likely to sustain remission from their first psychotic episode without further recurrence and thus less likely to stay in psychiatric service due to stable condition. It also indicated that for subjects with baseline diagnosis of either depressive disorder or “other psychosis” who remained in treatment at the end of follow-up, they were more likely to have their diagnoses revised when compared with those with less than 5 years follow-up as reflected by the lower prospective consistency of these two diagnostic categories in the remaining sample.

5.1.3 Pattern of Diagnostic Shift

Around one-fifth of subjects in this study who presented with first-onset psychosis were reassigned a different diagnosis at the end of follow-up. Among these patients, 75% changed their diagnoses in the first three years since enrolment in EASY. These findings were in line with the clinical observation that temporal instability and diagnostic uncertainty were common in early stage of functional psychosis (McGorry, 1994).

5.1.3a Schizophrenia Spectrum Disorder

Consistent with earlier reports, the category receiving the largest influx of cases at follow-up was schizophrenia spectrum diagnosis (Amin *et al*. 1999; Schwartz *et al.* 2000; Veen *et al.* 2004; Whitty *et al*. 2005; Schimmelmann *et al.* 2005; Addington *et al.* 2006; Subramaniam *et al*. 2007; Craig *et al.* 2007). The majority changed to schizophrenia (79.1%) while 20.8% moved into schizoaffective disorder. “Other psychosis” was the major source of diagnostic transition towards schizophrenia spectrum. Within this category, ATPD, unspecified non-organic psychosis and delusional disorder accounted for 33.3%, 29.1% and 16.7% respectively of those who moved into schizophrenia spectrum.

Similar to previous first-episode studies which reported a diagnostic flux towards schizophrenia from unspecified psychosis at follow-up (Schwartz *et al*. 2000; Whitty *et al.*

2005; Schimmelmann *et al*. 2005; Addington *et al*. 2006), our results showed that around 80% of those with baseline diagnosis of unspecified non-organic psychosis shifted to schizophrenia at later time. Our findings therefore echoed the concept of differentiation, which hypothesized that initial atypical and non-specific clinical picture of functional psychosis might become clearer over time and evolve into prototypical categories such as schizophrenia (McGorry, 1994). It also highlighted the difficulty to accurately diagnose those who presented with first-onset psychosis despite intensive initial assessments because a significant proportion of them might fail to fit in with specific diagnostic categories under current classification systems in early stage of illness (McGorry, 1994; Fennig *et al.* 1995).

Depressive symptoms are common in schizophrenia (Zisook *et al*. 1999) and are more frequently associated with early phase of illness (Baynes *et al*. 2000). Depressive symptoms are even noted to be precursor of psychosis in a proportion of subjects who develop schizophrenia at later time (Hafner *et al*. 2005). In this study, baseline depressive disorder accounted for 20.8% of those who switched to schizophrenia spectrum disorder at follow-up. Our findings indicated that the prominence of depressive symptomatology in patients suffering from first episode psychosis might be an important factor contributing to the misclassification of schizophrenia spectrum diagnosis to “psychotic depression” at intake.

5.1.3b Bipolar Affective Disorder

In contrast with studies using readmission samples which demonstrated that patients presenting with manic episode at younger age of onset were frequently misdiagnosed as schizophrenia (Joyce, 1984; Stanton & Joyce, 1993), our findings revealed that only 3.1% of 96 subjects who were initially assigned schizophrenia diagnosis changed to bipolar affective disorder at follow-up. The results of this report and that of other first-episode studies therefore suggested that this misclassification bias was no longer a major reason for diagnostic inaccuracy in bipolar affective disorder (Carlson *et al.* 1994; Swartz *et al* 2000). Nonetheless, a high frequency of mood-incongruent or Schneiderian first-rank psychotic symptoms in bipolar affective disorder, particularly in first-episode mania might be attributable to diagnostic ambiguity in early phase of psychotic illness (Gonazlez-Pinto *et al.* 1998; Strakowski *et al*. 2000).

5.1.3c Acute and Transient Psychotic Disorders (ATPD)

Previous studies showed that ATPD was diagnostically unstable and frequently shifted to schizophrenia and affective disorder at follow-up (Jorgensen *et al*. 1997; Marneros *et al*. 2003; Singh *et al*. 2004; Castagnini *et al*. 2008). Consistent with these studies, our results revealed that only 35.5% of subjects with ATPD at intake retained their diagnoses over 5 years. Similar to the study initiated by WHO (Craig *et al.* 2007), our findings showed that 55.6% (v. 51.2%

in WHO study) of those with baseline acute schizophrenia-like psychotic disorder were reclassified as schizophrenia at follow-up. On the other hand, no patients initially assigned as ATPD “polymorphic” subtype (both with and without schizophrenic symptoms) moved into schizophrenia spectrum. Marneros and Pillmann (2004) suggested that subdividing acute polymorphic psychotic disorder into the groups with and without schizophrenic symptoms might be unwarranted since such differentiation has no bearing on outcome and diagnostic shift. The distinctive patterns of diagnostic shift of ATPD subcategories, i.e., (1) from “non-polymorphic” subtype (mostly from acute schizophrenia-like psychotic disorder) towards schizophrenia spectrum; and (2) from “polymorphic” subtype to bipolar affective disorder, demonstrated by this study reached statistical significance despite its small sample size. These findings therefore lent support to the suggestion of removing acute schizophrenia-like psychotic disorder from ATPD and subsuming this diagnostic category under the rubric of schizophrenia spectrum (Malhotra & Malhotra, 2003; Marneros & Pillmann, 2004). Our results also supported that polymorphic symptomatology should be maintained as the key differentiating feature in ATPD to facilitate delineation of a more homogeneous patient groups for clinical and research purposes (Marneros & Pillmann, 2004).

5.1.4 Factors associated with Diagnostic Shift

Compared with those stably diagnosed schizophrenia spectrum patients, subjects who shifted into schizophrenia spectrum were more likely to have family history of psychotic illness, shorter DUP and duration of first psychotic episode. Our findings noted that there were no differences between these two groups in terms of socio-demographic characteristics, hospitalization and clinical history variables. It seemed that subjects with their diagnoses revised might have been treated earlier and took longer time for “definitive” diagnosis to consolidate.

With regard to comparison between subjects switching to schizophrenia spectrum and those who remained outside the spectrum, the multivariate analysis revealed that longer DUP and family history of psychotic illness were predictive of diagnostic change to schizophrenia spectrum. Our findings thus echoed an earlier first-admission study (Schwartz *et al*. 2000) that demonstrated longer interval from onset of psychosis to first hospitalization as an independent predictor of subsequent diagnostic shift to schizophrenia spectrum at 2 years follow-up.

Several hypotheses might explain the association between DUP and subsequent diagnostic transition towards schizophrenia spectrum. Firstly, DUP might be a marker rather than a

determining factor for such diagnostic shift. Patients who changed their diagnoses to schizophrenia spectrum had more insidious illness onset. Gradual deterioration and less dramatic clinical manifestations likely caused a delay in help-seeking and presentation to treatment and therefore prolonged untreated psychosis. The conceptually more intriguing alternative explanation is that DUP might be a determinant of illness outcome (Loebel *et al*. 1992; Perkins *et al*. 2005). It is hypothesized that untreated psychosis may result in neurotoxicity which induces irreversible brain damage that is clinically detectable as deterioration (Wyatt, 1991; Lieberman, 1999). Shortening the length of untreated psychosis might reduce the duration and intensity of exposure to such toxic effect via earlier initiation of antipsychotic treatment, thereby decreasing the risk of evolution towards schizophrenia from less well-defined psychosis at the early phase. In this sense, DUP is considered a potential modifiable factor and serves as a target for early intervention in minimizing progression towards a more severe form of psychotic disorder. Longitudinal follow-up on those experiencing “other psychosis” with particular emphasis on diagnostic conversion towards schizophrenia spectrum and its relationship with DUP might reveal a more definitive answer.

It should be noted that most previous first-episode studies examined the prediction of diagnostic shift on the basis of DSM-IV criteria (Schwartz *et al*. 2000; Whitty *et al.* 2005; Schimmelmann *et al.* 2005; Addington *et al*. 2006). Some of these studies investigated factors

associated with conversion from schizophreniform disorder to schizophrenia (Schimmelmann *et al*. 2005; Addington *et al*. 2006) rather than diagnostic change from non-schizophrenia spectrum disorders into schizophrenia spectrum as in the present report. However, schizophreniform disorder was shown to be diagnostically unstable and 50% to 100% of patients with this initial diagnosis switched to schizophrenia or rarely schizoaffective disorder at follow-up (Amin *et al.* 1999; Zarate Jr. *et al.* 2000; Veen *et al*. 2004; Whitty *et al*. 2005; Schimmelmann *et al.* 2005; Addington *et al*. 2006). It was therefore suggested that such high temporal instability was in part due to an arbitrary separation between these two diagnoses and the subsequent conversion merely reflected the natural illness evolution rather than diagnostic change per se (Amin *et al.* 1999; Whitty *et al.* 2005). In this context, it might be conceptually and clinically more meaningful to investigate potential predictors of diagnostic transition from other functional psychotic disorders towards schizophrenia spectrum instead of examining diagnostic flow to schizophrenia from schizophreniform disorder which has been criticized for lacking diagnostic validity and clinical utility (Strakoski, 1994).

In summary, our results suggested that “longer DUP” and “family history of psychotic disorder” were independent predictors of diagnostic shift towards schizophrenia spectrum. Owing to the paucity of relevant data on this issue, our findings should be viewed as preliminary and required replication to confirm its predictive value.

5.2 Implications

5.2.1 Clinical Implications

The clinical implications of this study were that with intensive and comprehensive assessments provided by specialized team, schizophrenia and bipolar affective disorder could be reliably diagnosed in patients presenting with first episode psychosis. However, our findings revealed that more than half of those having initial diagnosis of “other psychosis” and one in three patients with “psychotic depression” at baseline switched to schizophrenia spectrum disorder over 5 years. Our results thus highlighted the fact of greater phenomenological fluidity in the early phase of psychotic illness and the difficulty in correctly differentiating certain diagnostic categories at initial assessment particularly those less frequent diagnostic entities such as” other psychosis” and “psychotic depression”.

Since provision of particular treatment modalities is partly dependent on specific diagnostic categories, misdiagnosis would therefore expose patients and their families to inappropriate treatment and adverse psychological impact. As well, information and education about diagnosis was shown to improve patients’ treatment adherence, illness outcome and their sense of well-being (Edward *et al*. 1998). Apart from “family history of psychosis” and “longer DUP”, we identified no other predictors of diagnostic shift towards the more severe

form of functional psychosis i.e., schizophrenia spectrum disorder. It is therefore recommended that patients suffering from early psychosis should be under close scrutiny with thorough assessment and regular diagnostic review to minimize misclassification. Clinicians should also be aware of the possibility of diagnostic conversion to schizophrenia spectrum at later time when treating patients with first-onset psychosis, especially those who present with nonspecific psychotic features or prominent depressive symptoms which may be an early manifestation of schizophrenia.

5.2.2 Research Implications

Diagnostic instability has implications on research. Schizophrenia is considered a lifetime diagnosis (Chen *et al.* 1996). However, our findings replicated those of earlier reports and suggested that there was a diagnostic flux towards schizophrenia. A proportion of patients with final longitudinal schizophrenia diagnosis were misclassified as other functional psychotic disorders at intake assessment. Therefore, our results underscored the need to recruit a broad spectrum of functional psychosis instead of restricting sample to those subjects who fulfill diagnostic criteria for schizophrenia at baseline. Otherwise, a significant proportion of patients with lifetime schizophrenia diagnosis i.e., false-negative cases would be missed from study entry and the validity of research findings would be undermined by this misclassification bias (Clarke & O'Callaghan, 2003; Bromet *et al.* 2005).

With respect to the choice of diagnostic criteria for research, our findings confirmed the results of previous studies which demonstrated that ICD-10 schizophrenia had comparable diagnostic stability, specificity and predictive validity to DSM-IIIR / DSM-IV (APA, 1987, 1994) schizophrenia diagnosis (Mason *et al.* 1997; Amin *et al*. 1999). This study, however, revealed a relatively high sensitivity of ICD-10 schizophrenia (82.9%) which was higher than that of other studies utilizing DSM-IV criteria. Some researchers stated that DSM-IV definition with 6-month duration criterion was overly restrictive and underdiagnosed

schizophrenia at first-episode sample (Schwartz *et al*. 2000; Veen *et al*. 2004). DSM-IV criteria for schizophrenia has also been criticized for only identifying a subgroup of patients with a more chronic illness and poorer prognosis (Maj, 1998). Our results thus supported that the broader concept of schizophrenia as defined by ICD-10 criteria might represent a clinically more useful definition for first episode psychosis studies without compromises in predictive validity and diagnostic stability (Mason *et al*. 1997; Amin *et al.* 1999).

5.2.3 Nosological Implications

It is widely believed that further significant improvement in future editions of ICD and DSM hinges very much on enhancement of validity of the diagnostic concepts they embraced (Kendell & Jablensky, 2003). Diagnostic uncertainty and frequent shifts of “other psychosis” as shown by this study reflected limitations of the current taxonomy in classifying this group of less prevalent diagnostic entities. In particular, subdivision of ATPD into six categories has been criticized by some researchers (Susser *et al*. 1998; Mojtabai *et al*. 2003) and recognized by ICD-10 (WHO, 1992, p99) for lack of empirical evidence. Simplifying ICD-10 subclassification of ATPD on the basis of presence of polymorphic symptoms and reassigning acute schizophrenia-like psychotic disorder into schizophrenia spectrum might improve its applicability and validity (Malhotra & Malhotra, 2003; Marneros & Pillmann, 2004; Craig *et al.* 2007).

5.3 Methodology

5.3.1 Strengths of the Study

The strength of the study was that this was a “first contact to treatment” sample. This well-defined first-episode cohort was representative of the subjects enrolled in the EASY program in the whole of Hong Kong and ensured that all patients included were relatively homogeneous in terms of their stage of psychotic illness. Furthermore, a wide spectrum of functional psychosis as would be expected in first-episode sample was examined including affective psychosis and those having comorbid substance abuse, thus rendering our results generalizable to real-life clinical practice. The other strength of this study was the adoption of consensus diagnostic procedure utilizing information from multiple sources, systematic records review and independent diagnostic ascertainment by two experienced psychiatrists who were blind to facility diagnosis. Diagnostic protocol and algorithm were also employed to ensure strict adherence to ICD-10 criteria to enhance diagnostic reliability. Moreover, this study evaluated diagnostic change of individual patient across multiple episodes through interim review of consecutive cross-sectional diagnoses. This longitudinal validation approach enabled diagnosticians to capture temporal changes of clinical picture along the course of illness and generated a more definitive final 5-year diagnosis.

5.3.2 Limitations of the Study

There were a number of limitations in this study. The sample size was modest and the number of subjects in diagnostic categories other than schizophrenia was small, which compromised the statistical power when analyzing the correlates of diagnostic shift of other functional psychotic disorders. Another limitation came from retrospective diagnostic assignment via medical records review, which may be biased by varying degrees of documentation quality. Prospective design with regular follow-up assessments incorporating structured interviews would likely improve the procedural validity further. In the present report, as the final diagnosis of individual subject was based, in part, on the same information used in formulating the initial and interim diagnoses, and the two diagnosticians could not be blind to their independently assigned intake diagnoses, thus diagnostic stability might be artificially magnified. However, it conferred an advantage by allowing diagnosticians to focus on the interval course of symptoms evolution and to clarify contradictory information obtained over time for making a more accurate longitudinal diagnosis. Another limitation was that potential factors affecting diagnostic stability such as modalities of intervention and treatment response were not assessed in this study. As well, although being one of the few first-episode studies which investigated diagnostic stability with follow-up duration of up to 5 years, conclusions of the present report were only applicable to the early phase of illness. Reassessment at a later time may reveal different patterns of diagnostic shift and degree of instability.

5.4 Future Research Directions

Contemporary diagnostic systems have been shown to be relatively consistent in reconfirming the prototypical diagnostic entities i.e., schizophrenia and bipolar affective disorder (Chen *et al.* 1996; Schwartz *et al.* 2000). However, diagnostic stability and the pattern of diagnostic shift of those less common diagnostic categories such as ATPD and delusional disorder were far from conclusive. Future studies focusing on these specific diagnostic subgroups with larger sample size will certainly better elucidate their illness trajectories, and the boundaries among these psychotic disorders, schizophrenia and affective disorder.

As evidence suggested that great majority of patients with bipolar affective disorder experienced psychotic symptoms at some time over their illness (Benabarre *et al.* 2001), the distinction between psychotic and non-psychotic mania may be arbitrary. In this context, future first-episode studies should also include those presenting with mania without psychotic symptoms to ensure a more complete sample and thus less biased estimation of diagnostic stability and illness outcome (Baldwin *et al*. 2005).

Little is known about the differences and relationship between functional psychosis and psychosis induced by substance abuse despite the fact of the high rate of co-existence and the apparently similar clinical manifestations (Mathias *et al.* 2008). More research is needed to

evaluate the longitudinal course of substance-induced psychosis and its diagnostic change to functional psychosis as the distinction between these two conditions has important implications in treatment strategies (Carol *et al*. 2007). Results of these studies may also shed light on the potential aetiological links and pathophysiological mechanisms of functional psychosis (Rounsaville, 2007).

Chapter 6 Conclusions

Despite wide variation of methodologies, convergent findings have emerged. This study confirmed reports in the literature that well-defined diagnostic entities i.e., schizophrenia and bipolar affective disorder were diagnostically stable and could be reliably classified at intake assessment according to ICD-10 criteria. One in five subjects presenting with first episode psychosis had diagnostic revision over 5-years and the greatest instability occurred in the least prevalent diagnostic categories of functional psychosis. The major diagnostic flux was towards schizophrenia spectrum. Family history of psychosis and longer DUP were found to be predictive of such diagnostic shift. In the absence of biological marker, diagnostic process taking into account longitudinal observation across consecutive episodes will be a major requirement for definitive diagnosis.

References

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

Allardyce, J., Gaebel, W., Zielasek, J., Van Os, J. (2007). Deconstructing psychosis conference February 2006: the validity of schizophrenia and alternative approaches to the classification of psychosis. *Schizophrenia Bulletin,* **33**, 863-867.

American Psychiatric Association (1987). Diagnostic and statistical manual of mental disorders, 3rd edition revised. Washington DC: APA.

American Psychiatric Association (1994). Diagnostic and statistical manual of mental disorders, 4th edition. Washington DC: APA.

Amin, S., Singh, S.P., Brewin, J., Jones, P.B., Medley, I., Harrison, G. (1997). Diagnostic stability of first-episode psychosis: comparison of ICD-10 and DSM-IIIR systems. *British Journal of Psychiatry,* **175**, 537-543.

Amini, H., Alahgband-rad, J., Omid, A., Sharifi, V., Davari-Ashtiani, R., Momeni, F. et al. (2005). Diagnostic stability in patients with first-episode psychosis. *Australasian Psychiatry,* **13**, 388-392.

Amara, I.B. (1978). Consistency in the diagnosis of the functional psychoses. *Canadian Psychiatric Association Journal*, **23**, 329-336.

Baca-Garcia, E., Perez-Rodriguez, M.M., Basurte-Villamor, I., Fernandez Del Moral, A.L., Jimenez-Arriero, M.A., Gonzalez De Rivera, J.L. et al. (2007). Diagnostic stability of psychiatric disorders in clinical practice. *British Journal of Psychiatry,* **190**, 210-216.

Baldwin, P., Browne, D., Scully, P.J., Quinn, J.F., Morgan, M.G., Kinsella, A. et al. (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.

Baynes, D., Mulholland, C., Cooper, S.J. Montgomery, R.C., MacFlynn, G., Lynch, G. et al. (2000). Depressive symptoms in stable chronic schizophrenia: prevalence and relationship to psychopathology and treatment. *Schizophrenia Research,* **45**, 47-56.

Beiser, M., Iacono, W.G., Erickson, D. (1989). Temporal stability in the major mental disorders. In *The validity of psychiatric diagnosis*, Robins, L.N. and Barrett, J.E. ed. New York: Raven Press, pp. 77-97.

Benabarre, A., Vieta, E., Colom, F., Martinez-Aran, A., Gasto, C. (2001). Bipolar disorder, scizoaffective disorder and schizophrenia: epidemiologic, clinical and prognostic differences. *European Psychiatry*, **16**, 167-172.

Brichwood, M., Todd, P., Jackson, C. (1998). Early intervention in psychosis: the critical period hypothesis. *British Journal of Psychiatry,* **172** (supp. 33) 53-59.

Bromet, E.J., Mojtabai, R., Fennig, S. (2002). Epidemiology of first-episode schizophrenia: the Suffort County Mental Health Project. In *The early stages of schizophrenia.* Zipursky, R.B. and Schulz, S.C. ed. Washington DC: American Psychiatric Publishing, pp. 33-54.

Bromet, E.J., Naz, B., Fochtmann, L.J., Carlson, G.A., Tanenbert-Karant, M. (2005). Long-term diagnostic stability and outcome in recent first-episode cohort studies of schizophrenia. *Schizophrenia Bulletin,* **31**, 639-649.

Bromet, E.J., Naz, B. (2006). Diagnostic variability in the early course of schizophrenia. In *The early course of schizophrenia*. Sharma, T. and Harvey, P.D. ed. New York: Oxford University Press, pp. 131-145.

Canton, C.L.M., Hasin, D.S., Shrout, P.E., Drake, R.E., Dominguez, B., First, M.B. et al. (2007). Stability of early-phase primary psychotic disorders with concurrent substance use and substance-induced psychosis. *British Journal of Psychiatry*, **190**, 105-111

Cantwell, R., Brewin, J., Glazebrook, C. Darkin, T., Fox, R., Medley, I. et al. (1999). Prevalence of substance misuse in first episode psychosis. *British Journal of Psychiatry*, **174**, 150-153.

Carlson, G. A., Fennig, S., Bromet, E.J. (1994). The confusion between bipolar disorder and schizophrenia in youth: where does it stand in the 1990s? *Journal of American Academy of Child and Adolescence Psychiatry*, **33**, 453-459.

Castagnini, A., Bertelsen, A., Berrios, G.E. (2008). Incidence and diagnostic stability of ICD-10 acute and transient psychotic disorders. *Comprehensive Psychiatry*, **49**, 255-261.

Chen, E. (2004). Developing an early intervention service in Hong Kong. In *Best care in early psychosis intervention: global perspectives.* Ehmann, T., MacEwan, G. W., Honer, W.G. ed. London: Tayor & Francis, pp.125-130.

Chen, R.Y., Swann, AC., Burt, D.B. (1996). Stability of diagnosis in schizophrenia. *American Journal of Psychiatry,* **153**, 682-686.

Clarke, M., O'Callaghan, E. (2003). In *The epidemiology of schizophrenia.* Murray RM., Jones, P.B., Susser, E., Van Os, J., Cannon, M. ed. Cambridge: Cambridge University Press, pp. 148-166.

Cooper, J.E. (1967). Diagnostic change in a longitudinal study of psychiatric patients. *British Journal of Psychiatry,* **113**, 129-142.

Craig, T.J., Wanderling, J.A., Janca, A. (2007). Long-term diagnostic stability in International cohorts of persons with schizophrenia and related psychoses. In *Recovery from schizophrenia: an international perspective: a report from the WHO collaborative project, the international study of schizophrenia.* Hopper K., Harrison G., Janca A., Sartorius N. ed. New York: Oxford University Press, pp. 50-60.

Daradkeh, T.K., El-Rufaie, O., Younis, Y.O., Ghubash, R. (1997). The diagnostic stability of ICD-10 psychiatric diagnoses in clinical practice. *European Psychiatry,* **12**, 136-139.

Edwards, J., Maude, D., McGorry, P.D. Harrigan, S.M., Cocks, J.T. (1998). Prolonged recovery in first-episode psychosis. *British Journal of Psychiatry*, **172,** (Suppl.), 107-116.

Fennig, S., Kovasznay, R., Rich, C., Ram, R., Pato, C., Miller, A. et a. (1994). Six-month stability of psychiatric diagnoses in first-admission patients with psychosis. *American Journal of Psychiatry,* **151**, 1200-1208.

Fennig, S., Bromet, E.J., Craig, T., Jandorf, L., Schwartz, J.E. (1995). Psychotic patients with unclear diagnoses: a descriptive analysis. *Journal of Nervous and Mental Disease*, **183**, 207-213.

Forrester, A., Owens, D.G.C., Johnstone, E.C. (2001). Diagnostic stability in subjects with multiple admissions for psychotic illness. *Psychological Medicine*, **31**, 151-158.

Goater, N., King, M. Cole, E., Leavey, G., Johnson-Sabine, E., Blizard, R. et al. (1999). Ethnicity and outcome of psychosis. *British Journal of Psychiatry*, **175**, 34-42.

Gonzalez-Pinto, A., Gutierrez, M., Mosquera, F., Ballesteros, J., Lopez, P., Ezcurra, J. et al. (1998). First episode in bipolar disorder: misdiagnosis and psychotic symptoms. *Journal of Affective Disorders*, **50**, 41-44.

Hafner, H., Maurer, K., Trendler, G., An der Heiden, W., Schmidt, M., Konnecke, T. (2005). Schizophrenia and depression: challenging the paradigm of two separate diseases – a controlled study of schizophrenia, depression and healthy controls. *Schizophrenia Research*, **77**, 11-24.

Hollister, L.E. (1992). Stability of psychiatric diagnoses among acutely ill patients. *Psychopathology,* **25**, 204-208.

Huguelet, P., Schneider, N., Gueddari, E., Glauser, D. (2001). Stability of DSM-IIIR diagnoses: study of a case register. *Psychopathology,* **34**, 118-122.

Jorgensen, P.B. Bennedsen, B., Christensen, J., Hyllested, A. (1997). Acute and transient psychotic disorder: a 1-year follow-up study. *Acta Psychiatrica Scandinavica,* **96**, 150-154.

Jorgensen, P., Mortensen, P.B. (1988). Admission pattern and diagnostic stability of patients with functional psychoses in Denmark during a two-year observation period. *Acta Psychiatrica Scandinavica,* **78**, 361-365.

Joyce, P.R. (1984). Age of onset in bipolar affective disorder and misdiagnosis as schizophrenia. *Psychological Medicine,* **14**, 145-149.

Kendell, R.E., Cooper, J.E., Gourley, A.J., Copeland, J.R.M., Sharpe, L., Gurland, B.J. (1971). Diagnostic criteria of American and British psychiatrists. *Archives of General Psychatry,* **25**, 123-130.

Kendell, R.E., (1974). The stability of psychiatric diagnoses. *British Journal of Psychiatry,* **124**, 352-356.

Kendell, R.E. (1989). Clinical validity. *Psychological Medicine,* **19**, 45-55.

Kendell, R., Jablensky, A. (2003). Distinguishing between the validity and utility of psychiatric diagnoses. *American Journal of Psychiatry,* **160**, 4-12.

Kendler, K.S. (1980). The nosologic validity of paranoia (simple delusional disorder): a review. *Archives of General Psychiatry,* **37**, 699-706.

Krishnan, K.R. (2005). Psychiatric disease in the genomic era: rational approach. *Molecular Psychiatry,* **10**, 978-984.

Leckman, J.F., Sholomskas, D., Thompson, D., Belanger, A., Weissman, M.M. (1982). Best estimate of lifetime psychiatric diagnosis: a methodological study. *Archives of General Psychiatry* **39**, 879-883.

Lenz, G., Simhandl, C., Thau, K., Berner, P., Gabriel, E. (1991). Temporal stability of diagnostic criteria for functional psychoses: results from the Vienna follow-up study. *Psychopathology,* **24**, 328-335.

Lieberman, J.A. (1999). Is schizophrenia a neurodegenerative disorder? a clinical and neurobiological perspective. *Biological Psychiatry,* **46**, 729-739.

Loebel, A.D., Liebermann, J.A., Alvir, J.M.J., Mayerhoff, D.I., Geisler, S.H., Szymanski, S.R. (1992). Duration of psychosis and outcome in first-episode schizophrenia. *American Journal of Psychiatry*, **149**, 1183-1188.

Maj, M. (1998). Critique of the DSM-IV operational diagnostic criteria for schizophrenia. *British Journal of Psychiatry*, **172**, 458-460.

Malhotra, S., Malhotra S. (2003). Acute and transient psychotic disorders: comparison with schizophrenia. *Current Psychiatry Reports*, **5**, 178-186.

Marneros, A., Deister, A., Rohde, A. (1991). Stability of diagnoses in affective, schizoaffective and schizophrenic disorders: cross-sectional versus longitudinal diagnosis. *European Archives of Psychiatry and Clinical Neuroscience*, **241**, 187-192.

Marneros, A., Pillmann, F., Haring, A., Balzuweit, S., Bloink, R. (2003). Features of acute and transient psychotic disorders. *European Archives of Psychiatry and Clinical Neurosciences*, **253**, 167-174.

Marneros, A., Pillmann, F. (2004). Acute and transient psychoses. Cambridge: Cambridge University Press.

Mason, P., Harrison, G., Croudace, T., Glazebrook, C., Medley, I. (1997). The predictive validity of a diagnosis of schizophrenia: a report from International Study of Schizophrenia (ISoS) coordinated by the World Health Organization and the Department of Psychiatry, University of Nottingham. *British Journal of Psychiatry*, **170**, 321-327.

Mathias, S., Lubman, D.I., Hides, L. (2008). Substance-induced psychosis: a diagnostic conundrum. *Journal of Clinical Psychiatry*, **69**, 358-367.

McGlashan, T.H. (1984). Testing four diagnostic systems for schizophrenia. *Archives of General Psychiatry,* **41**, 141-144.

McGorry, P.D. (1991). Paradigm failure in functional psychosis: review and implications. *Australian and New Zealand Journal of Psychiatry*, **25**, 43-55.

McGorry, P.D. (1994). The influence of illness duration on syndrome clarity and stability in functional psychosis: does the diagnosis emerge and stabilize with time? *Australia and New Zealand Journal of Psychiatry,* **28**, 607-619.

McGorry, P.D., Milhalopoulos, C., Henry, L., Dakis, J., Jackson, H.J., Flaum, M. et al. (1995). Spurious precision: procedural validity of diagnostic assessment in psychotic disorders. *American Journal of Psychiatry,* **152**, 220-223.

McGuffin, P., Farmer, A., Harvey, I. (1991). A polydiagnostic application of operational criteria in studies of psychotic illness: development and reliability of the OPCRIT system. *Archives of General Psychiatry,* **48**, 764-770.

Mezzich, J.E. (2002). International surveys on the use of ICD-10 and related diagnostic systems. *Psychopathology*, **35**, 72-75.

Millon, T. (1991) Classification in psychopathology: rationale, alternatives and standards. *Journal of Abnormal Psychology,* **100**, 245-261.

Mojtabai, R., Susser, E.S., Bromet, E.J. (2003). Clinical characteristics, 4-year course, and DSM-IV classification of patients with nonaffective acute remitting psychosis. *American Journal of Psychiatry*, **160**, 2108-2115.

Munk-Jorgensen, P. (1985). The schizophrenia diagnosis in Denmark: a register-based investigation. *Acta Psychiatrica Scandinavica,* **72***,* 266-273.

Odegaard, O. (1966). An official classification in actual hospital practice. *Acta Psychiatrica Scandinavica*, **42**, 329-337.

Parnas, J., Zahavi, D. (2002). The role of phenomenology in psychiatric diagnosis and classification. In *Psychiatric diagnosis and classification.* Maj, M., Gaebel, W., Lopez-Ibor, J., Sartorius, N ed. New York: John Wiley & Sons, pp. 137-161.

Peralta, V., Cuseta, M.J. (2000). Clinical models of schizophrenia: a critical approach to competing conceptions. *Psychopathology,* **33**, 252-258.

Perkins, D.O., Hongbin, Gu., Kalina, B., Liebermann, J.A. (2005). Relationship between duration of untreated psychosis and outcome in first-episode schizophrenia: a critical review and meta-analysis. *American Journal of Psychiatry*, **162**, 1785-1804.

Rabinowitz, J., Slyuzberg, M., Ritsner, M., Mark, M., Popper, M., Ginath, Y. (1994). Changes in diagnosis in a 9-year national longitudinal sample. *Comprehensive Psychiatry,* **35**, 361-365.

Rahm, C., Cullberg, J. (2007). Diagnostic stability over 3 years in a total group of first-episode psychosis patients. *Nordic Journal of Psychiatry*, **61**, 189-193.

Robins, E., Guze, S.B. (1970). Establishment of diagnostic validity in psychiatric illness: its application to schizophrenia. *American Journal of Psychiatry,* **126**, 983-987.

Rounsaville, B.J. (2007). DSM-V research agenda: Substance abuse / psychosis comorbidity. *Schizophrenia Bulletin,* **33**, 947-952.

Sajith, S.G., Chandrasekaran, R., Sadanandan, U.K.E., Sahai, A. (2002). Acute polymorphic psychotic disorder: diagnostic stability over 3 years. *Acta Psychiatrica Scandinavica,* **105**, 104-109.

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

Schwartz, J.E., Fennig, S., Tanengerg-Karant, M., Carlson, G., Craig, T., Galambos, N. et al. (2000). Congruence of diagnoses 2 years after a first-admission diagnosis of psychosis. *Archives of General Psychiatry,* **57**, 593-600.

Singh, S.P., Burns, T., Amin, S., Jones, P.B., Harrison, G. (2004). Acute and transient psychotic disorders: precursors, epidemiology, course and outcome. *British Journal of Psychiatry*, **185**, 452-459.

Stanton, M.W., Joyce, P.R. (1993). Stability of psychiatric diagnoses in New Zealand psychiatric hospitals. *Australian and New Zealand Journal of Psychiatry,* **27**, 2-8.

Strakowski, S.M. (1994). Diagnostic validity of schizophreniform disorder. *American Journal of Psychiatry*, **151**, 815-824.

Strakowski, S.M., Williams, J.R., Fleck, D.E., Delbello, M.P. (2000). Eight-month functional outcome from mania following a first psychiatric hospitalization. *Journal of Psychiatric Research,* **34***,* 193-200.

Subramaniam, M., Pek, E., Verma, S., Chan, Y.H., Chong, S.A. (2007). Diagnostic stability 2 years after treatment initiation in the Early Psychosis Intervention Programme in Singapore. *Australian and New Zealand Journal of Psychiatry,* **41**, 495-500.

Susser, E., Varma, V.K., Mattoo, S.K., Finnerty, M., Mojtabai, R., Tripathi, B.M. et al. (1998). Long-term course of acute brief psychosis in a developing country setting. *British Journal of Psychiatry,* **173**, 226-230.

Tsuang, M.T., Woolson, R.F., Winokur, G., Crowe, R.R. (1981). Stability of psychiatric diagnosis: schizophrenia and affective disorders followed up over 30- to 40-year period. *Archives of General Psychiatry,* **38***,* 535-539.

Veen, N.D., Selten, J.P., Schols, D., Lann, W., Hoek, H.W., Van der Tweel, I. et al. (2004). Diagnostic stability in a Dutch psychosis incidence cohort. *British Journal of Psychiatry,* **185***,* 460-464.

Vetter, P., Koller, O. (1992). Stability of diagnoses in various psychiatric disorders: a study of long-term course. *Psychopathology*, **26**, 173-180.

Whitty, P., Clarke, M., McTigue, O., Browne, S., Kamali, M., Larkin, C. et al. (2005). Diagnostic stability four years after a first episode of psychosis. *Psychiatric services,* **56**, 1084-1088.

Winokur, G., Monahan, P., Coryell, W. Zimmerman, M. (1996). Schizophrenia and affective disorder: distinct entities or continuum ? an analysis based on a prospective 6-year follow-up. *Comprehensive Psychiatry*, **37**, 77-87.

World Health Organization (1992). The ICD-10 classification of mental and behavioural disorders: clinical descriptions and diagnostic guidelines. Geneva: WHO.

World Health Organization (1993). The ICD-10 classification of mental and behavioural disorders: diagnostic criteria for research. Geneva: WHO.

Wyatt, R.J. (1991). Neuroleptics and the natural course of schizophrenia. *Schizophrenia Bulletin*, **17**, 325-351.

Zarate, Jr. C.A., Tohen, M., Land, M.L. (2000). First-episode schizophreniform disorder: comparisons with first-episode schizophrenia. *Schizophrenia Research*, **46**, 31-34.

Zisook, S., McAdams, L.A., Kuck, J., Harris, M.J., Bailey, A., Patterson, T.L. et al. (1999). Depressive symptoms in schizophrenia. *American Journal of Psychiatry*, **156**, 1736-1742.

Appendix: Ethics Committee Approval Letter

香港中文大學醫學院
Faculty Of Medicine
The Chinese University Of Hong Kong

Hospital Authority
New Territories East Cluster

Joint The Chinese University of Hong Kong – New Territories East Cluster Clinical Research Ethics Committee
香港中文大學–新界東醫院聯網 臨床研究倫理 聯席委員會

Flat 3C, Block B, Staff Quarters, Prince of Wales Hospital, Shatin, HK
Tel : (852) 2632 3935 Fax : (852) 2646 6653 Website : http://www.crec.cuhk.edu.hk

To: Dr. Wing Chung CHANG (Principal Investigator)
Dept. of Psychiatry
Tai Po Hospital

7 August 2007

Ethics Approval of Research Protocol

CREC Ref. No.:	**CRE-2007.296**
Date of Approval:	**07 August 2007***
Protocol Title:	**5-Years Stability of ICD-10 Psychiatric Diagnoses in Patients Presented with First Episode Psychosis to the EASY (Early Assessment Service for Young People with Psychosis) Program in HKSAR**
Investigator(s):	**Wing Chung CHANG, Dicky W.S. CHUNG and Sandra S.M. CHAN**

I write to inform you that ethics approval has been given to you to conduct the captioned study in accordance with the following document(s) submitted:

- Research Protocol

This ethics approval* will be valid for 12 months. Application for further renewal can be made by submitting the Ethics Renewal and Research Progress Report Form to the CREC (Download the electronic form template from the http://www.crec.cuhk.edu.hk or http://ntec.home/Research%20Ethics/main.asp). It will be much appreciated if the completion of the project will be reported to the Committee in due course.

The Joint CUHK-NTEC Clinical Research Ethics Committee serves to confirm that research complies with the Declaration of Helsinki, ICH GCP Guidelines, local regulations, HA and University policies.

(Ms. Eva Kong)
Hospital Administrator
Joint CUHK-NTEC
Clinical Research Ethics Committee

Encl. CREC/CT0001 – w.e.f. 4/2003 for HA(NTEC) employee concerned ONLY
EK/ci