Three-year outcome of phase-specific early intervention for first-episode psychosis: a cohort study in Hong Kong

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Key Messages

1. The 3-year outcome of 700 first-episode psychosis patients who received phase-specific early intervention were compared with that of 700 matched historical controls who received standard psychiatric care.
2. Patients in the early intervention group had longer full-time employment or study (P<0.001), fewer days of hospitalisation (P<0.001), less severe positive symptom (P=0.006), less severe negative symptom (P=0.001), fewer suicides (P=0.009) and fewer disengagements (P=0.002) than the historical control group. In addition, more patients in the early intervention group experienced a period of recovery (P=0.001), but the two groups had similar rates of relapse (P=0.08) and durations of untreated psychosis (P=0.72).
3. The 3-year outcome in phase-specific early intervention compared favourably with that of standard psychiatric care, particularly with respect to functional outcome and reduction in hospitalisations, suicides, and disengagements. However, intervention did not appear to reduce the rate of relapse.

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Introduction

Early intervention for psychotic disorders[1] aims to improve the long-term outcome for psychotic disorders by early detection to reduce delay in treatment[2,3] and phase-specific intervention during the early phase of the disorders. In one of the most comprehensive controlled studies of early intervention, the OPUS trial,[4] 547 first-episode psychosis patients were randomised to either intensive early intervention or standard treatment. At 2 years, the former group had a medium effect on improving negative symptoms, a small effect on improving positive symptoms, and 22% reduction in average hospital stay.[4] However, at 5 years, the effect on symptom levels had diminished, whereas the effect on hospitalisation was still significant.[5] Another randomised controlled study found that some of the improved outcome that resulted from an early specialised service at 18 months was not maintained at 5 years.[6,7]

Most early intervention studies are limited to 1 or 2 years.[8] In addition, early psychosis programmes often operate on a smaller scale and limit the generalisability of results.[3] The development of population-based clinical services and media education does not easily accommodate randomised controlled studies. Together with the overwhelming consensus that early intervention should not be withheld, ethical concerns have restricted the set up of randomised controlled studies.[9] Under these circumstances, the optimal approach to estimate the real-life impact of the programmes may be by a historical control design comparing patients who receive early intervention with those who are managed by standard care prior to the introduction of early intervention. A small number of historical control studies on early intervention programmes have reported reduction in negative symptoms and suicidal behaviour, and improved quality of life.[10,11] Nonetheless, one limitation of these studies is that the cases may not match the controls. Most of these studies are based on western populations with more mental health resources and their results might not be applicable to other populations.

In Hong Kong, until recently mental health services had been characterised by low resources, high caseloads, and relatively heavy reliance on inpatient care.[12] The Early Assessment Service for Young People with Psychosis (EASY) programme was launched in 2001.[13-15] We aimed to compare the 3-year outcome of a cohort of patients who received this service with a matched cohort treated prior to the introduction of the programme. The primary hypothesis was that the early intervention would improve functional outcome, as well as reduce suicides and hospitalisations.

Methods

Study design and setting

The study was approved by relevant local institutional review boards and ethics committees. A historical case-control design was adopted, as the territory-wide nature of the programme precluded a concurrent control group.

The EASY programme was introduced in Hong Kong in 2001. It was

directed at patients aged 15 to 25 years who presented with a first episode of psychotic symptoms. It consisted of five specialised teams, each composed of two clinicians and three case managers. Together, the five teams managed approximately 1400 cases at any one time. The phase-specific intervention included intensive medical follow-up and a protocol-based psychosocial intervention. A case management approach was adopted, in which a case manager provided psychosocial interventions according to the patient's stage of illness and needs. Psychosocial intervention aims to help patients develop a more positive attitude to the illness in order to facilitate recovery. Case managers aim to establish early therapeutic alliances with patients and their families, provide individual or family intervention in response to emotional maladaptation and coping difficulty, and provide psychoeducation. During the course of recovery, case managers also aim to guide patients to develop goals, maintain social networks, establish routines, and cope with stressful situations.[13-15] Standard care service was characterised by its high service volume, brief consultation time, and limited community support.[12]

Sample

From the Psychiatric Case Register, 700 consecutive cases who received the EASY programme between 2001 and 2003, and 700 controls who received standard care between 1998 and 2001 were identified. To minimise the potential cohort effect, cases and controls were individually matched for gender, diagnosis, and age (±3 years).

Cases were those who had any of the following diagnoses according to the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10): schizophrenia (ICD-10 code F20), acute and transient psychotic disorders (ICD-10 code F23), schizoaffective disorders (ICD-10 code F25), psychosis not otherwise specified (ICD-10 codes F28 or F29), and affective disorders with psychotic features (ICD-10 codes F30.2, F31.2, F31.5, F32.3 or F33.3). Patients with any severe organic condition, drug-induced psychosis, or mental retardation were excluded, as were those with >1 month of prior psychiatric treatment before presentation. Informed consent from each patient was waived by the institutional review boards and ethics committees of the hospitals.

Data acquisition procedure

Between 2006 and 2007, clinical records of the 1400 patients were retrieved systematically. Only data that could be reliably extracted from the records were retrieved and analysed. Outcomes were determined each month in the 3 years following first contact, unless otherwise specified.

Baseline data included age, gender, diagnosis, education (years of formal education completed), premorbid occupational functioning (impaired or not impaired), smoking status (smoker, non-smoker, or ex-smoker), and duration of untreated psychosis (DUP) [from appearance of first psychotic symptom to treatment].

Symptomatic outcome measures included positive and negative symptom levels according to the Clinical Global Impressions-Severity Scale (CGI-S).[16] Relapse was defined as an increase in the level of positive symptoms leading to a change in medication management or hospitalisation. Recovery was defined as having a CGI-S positive symptom score of ≤2 (borderline ill), having a CGI-S negative symptom score of ≤3 (mildly ill), and working or studying full-time for at least 12 consecutive months. Functional outcome was measured by engagement of full-time employment or study. Suicidal behaviours included suicide attempts and completed suicides. Participants were categorised by whether they had exhibited the target risk behaviour during the study period. Service utilisation measures included number of hospitalisations, duration of hospitalisations, compulsory hospital admissions, number of outpatient and paramedical contacts, length of engagement with service, and disengagement from service (defined as having no psychiatric contact at the end of the study).

Validity and reliability

Validity and inter-rater reliability for DUP, functioning, and duration of hospitalisation were measured based on 12 independent cases using an intra-class correlation coefficient (ICC). Validity compared ratings between clinicians and research staff (DUP: ICC=0.78; functioning: ICC=0.83; duration of hospitalisation: ICC=0.998). Inter-rater reliability compared ratings between two research staff (DUP: ICC=0.70; functioning: ICC=0.98; duration of hospitalisation: ICC=0.999). All the scores reflected satisfactory concordance in ratings. In addition, weekly consensus meetings among clinicians and research assistants were held during data collection to maintain data quality and resolve ambiguity in information.

Statistical analysis

The large sample size enabled detection of possible difference in suicides, which were rather uncommon events, between the phase-specific early intervention (EI) group and the historical control (HC) group. Demographic and treatment characteristics and outcome variables were compared between the two groups using t-tests and Chi squared tests. To assess the impact of second-generation antipsychotics (SGA) on clinical outcome, functional outcome, and hospitalisation, analysis of covariance and logistic regression were carried out for continuous variables and categorical variables, respectively. Two sets of Kaplan-Meier survival curves were constructed to estimate the proportion of suicide and the proportion of death from any cause, using tests of group difference by log-rank. The risk of suicide and death from any cause were analysed using the Cox-proportional hazards regression model. For patients who discontinued the service, the last observation was used to analyse the positive and negative symptom severities, as this was assumed to be the best approximation of the patient's mental state. Two sets of secondary analyses were performed based on the results of the primary analysis. First, considering that there was a group difference in the

proportion of patients hospitalised at initial treatment, a secondary analysis was performed by comparing outcomes of the two groups only in the patient subset hospitalised within the first month. Second, in view of the increased use of SGA in the EI group and as validation of the use of SGA as a covariate, another secondary analysis was performed, restricted only to those who had used SGA treatment. This analysis compared the 3-year outcome of the two groups using t-tests, Chi squared tests, and survival analyses.

Results

Demographic and treatment characteristics

Clinical records of 839 patients in the early intervention programme and 1318 patients in the standard care were screened. A total of 700 eligible cases from each sample were included in the study. The reasons of exclusion are listed in Table 1. Cases were matched with controls for gender, diagnosis, and age (Table 2). There was no significant difference in premorbid occupational functioning. The EI group had a slightly higher level of education. The absolute difference in education level was small (0.35 years). More EI patients had received at least one SGA (Table 2). The EI patients had significantly longer periods of SGA use during the preceding 3 years. The use of SGA was a covariate in the analysis of clinical outcome, functional outcome, and hospitalisation.

Functional outcome

The EI patients achieved longer durations of full-time employment than HC patients (Table 3). A higher proportion of EI patients engaged in a stable full-time position lasting for ≥6 consecutive months.

Clinical outcome

The EI group had lower overall levels of positive symptoms and negative symptoms than the HC group (Table 3). The cumulative relapse rate was analysed by year. In year 1, fewer EI patients than HC patients relapsed. However, the cumulative rate was equalised by year 2, and was sustained through year 3. Nevertheless, fewer EI patients had multiple relapses (defined as >2 relapses in 3 years) and more EI patients achieved at least a period of recovery.

Suicidal behaviour

There was no significant difference between the EI and

Table 1. Inclusion and exclusion of patients in the early intervention and standard care groups

Criteria	Early intervention	Standard care
Total No. of screened patients	839	1318
No. (%) of patients included	700 (83.4)	700 (53.1)
No. (%) of patients excluded	139 (16.6)	618 (46.9)
Reasons for exclusion (No. [%] of patients)		
Initial presentation outside of the specified period	16 (11.5)	386 (62.5)
Previous episodes or treatment	60 (43.2)	93 (15.0)
Delusional disorder	0 (0)	2 (0.3)
Drug-induced psychosis	6 (4.3)	33 (5.3)
Mental retardation	8 (5.8)	24 (3.9)
Age <15 years	0 (0)	3 (0.5)
Significant organic condition	0 (0)	7 (1.1)
No diagnosis of psychosis	10 (7.2)	28 (4.5)
Eligible cases but unable to be matched	18 (12.9)	8 (1.3)
Unable to retrieve clinical records	21 (15.1)	34 (5.5)

Table 2. Demographics and treatment characteristics of the early intervention (EI) and historical control (HC) groups*

Characteristics	EI (n=700)	HC (n=700)	χ^2/t	P value
Age (years)	21.1±3.4	21.3±3.4	-0.84	0.40
Education (years)	10.9±2.3	10.6±2.4	2.74	0.006
Duration of untreated psychosis (days)	239.8±373.4	232.0±428.3	0.36	0.72
Male	360 (51.4)	360 (51.4)	0.00	1.00
Smoking			4.29	0.12
Smoker	179 (26.3)	185 (27.2)		
Ex-smoker	20 (2.9)	9 (1.3)		
Non-smoker	481 (70.7)	485 (71.4)		
Premorbid occupational functioning†			0.00	0.99
Impaired	49 (7.00)	49 (7.00)		
Not impaired	651 (93.0)	650 (93.0)		
Diagnosis			0.05	1.00
Schizophrenia or schizoaffective disorder	484 (69.1)	486 (69.4)		
Acute and transient psychotic disorder	87 (12.4)	87 (12.4)		
Psychosis not otherwise specified	46 (6.6)	44 (6.3)		
Mania/bipolar affective disorder with psychotic symptoms	54 (7.7)	54 (7.7)		
Severe depressive episode with psychotic symptoms	29 (4.1)	29 (4.1)		
Treatment				
Prescribed at least one second-generation antipsychotic medication	424 (60.6)	179 (25.6)	174.86	<0.001
Use of second-generation antipsychotic medication (days)	403.5 (454.8)	125.2 (291.9)	13.63	<0.001

* Data are presented as mean±SD or No. (%) of patients

† Impaired premorbid occupational functioning refers to unemployment and prolonged educational stagnation

Table 3. Comparison of outcomes in the early intervention (EI) and historical control (HC) groups

Outcome variables	EI (n=700)*	HC (n=700)*	Test results†	P value
Functional outcome				
Full-time employment ≥6 months	450 (64.3)	339 (48.4)	Adjusted OR=1.69 (1.35–2.12)	<0.001
Duration engaged in full-time employment (months)	15.2±12.1	10.5±11.3	*F*=33.63	<0.001
Clinical outcome				
Clinical Global Impressions-Severity Scale (CGI-S) positive symptoms	1.6±0.6	1.7±0.9	*F*=7.62	0.006
CGI-S negative symptoms	1.5±0.5	1.6±0.7	*F*=12.03	0.001
Cumulative relapse rate by year 1	123 (17.6)	147 (21.0)	Adjusted OR=0.69 (0.52-0.92)	0.012
Cumulative relapse rate by year 2	273 (39.0)	264 (37.7)	Adjusted OR=0.82 (0.65-1.04)	0.10
Cumulative relapse rate by year 3	344 (49.1)	330 (47.1)	Adjusted OR=0.82 (0.65-1.03)	0.081
Multiple relapses (>2)	120 (17.1)	128 (18.3)	Adjusted OR=0.66 (0.49-0.90)	0.008
Having at least one period of recovery	255 (36.4)	189 (27.0)	Adjusted OR=1.48 (1.16-1.89)	0.001
Suicidal behaviour				
Suicide attempt	65 (9.3)	80 (11.4)	χ^2/t=1.73	0.19
Completed suicide‡	7	20	Hazard ratio=0.32 (0.13-0.75)	0.009
Death (all-cause)§	8	22	Hazard ratio=0.30 (0.13-0.71)	0.006
Service utilisation				
Duration of hospitalisation (days)	61.6±105.5	113.7±141.6	*F*=99.98	<0.001
No. of hospitalisations	1.0±1.1	1.8±1.3	*F*=178.47	<0.001
Hospitalisation in the first month	328 (46.9)	635 (90.7)	Adjusted OR=0.10 (0.07-0.13)	<0.001
Compulsory admission at first hospitalisation	91/435 (20.9)	264/680 (38.8)	Adjusted OR=0.49 (0.36-0.66)	<0.001
Compulsory admission at second hospitalisation	32/177 (18.1)	81/313 (25.9)	Adjusted OR=0.76 (0.47-1.23)	0.27
No. of medical outpatient visits	26.2±13.5	17.0±12.1	χ^2/t=13.57	<0.001
No. of contacts with clinical psychologist	1.4±3.8	0.7±2.4	χ^2/t=3.79	<0.001
No. of contacts with medical social worker	1.8±2.4	1.7±2.6	χ^2/t=0.48	0.63
Disengagement	161 (23.0)	211 (30.1)	χ^2/t=9.15	0.002
Length of engagement in service (months)	31.8±9.3	28.7±12.7	χ^2/t=5.30	<0.001

* Data are presented as mean±SD, No., No. (%) of patients, or No./total (%) of patients

† Data are presented as adjusted OR (95% CI) by logistic regression, *F* value by analysis of covariance, χ^2/t, or hazard ratio (95% CI) by Cox-proportional hazards regression

‡ The 3-year Kaplan-Meier estimate of the proportion of suicides was 1.1% (95% CI, 0.27-1.95%) in the EI group and 3.4% (95% CI, 1.90-4.90%) in the HC group (χ^2_1=7.64, P=0.006, log-rank test)

§ The time of death was missing in one patient in each group. The 3-year Kaplan-Meier estimate of the proportion of death from any cause was 1.1% (95% CI, 0.27-1.95%) in the EI group and 3.6% (95% CI, 2.02-5.10%) in the HC group (χ^2_1=8.48, P=0.004, log-rank test)

HC groups in terms of the number of patients attempting suicide over the 3-year period (65 vs 80, Table 3). Seven of 700 patients in the EI group and 20 of 700 patients in the HC group committed suicide. The EI group had lower Kaplan-Meier estimates of the proportions of suicide and death from any cause. Compared by Cox proportional hazards regression, the EI group had a significantly lower risk of suicide and death from any cause.

Service utilisation

Patients in the EI group had shorter and fewer hospitalisations in the 3-year period (Table 3). In the first month of treatment, fewer EI patients were hospitalised. The EI group had a lower percentage of compulsory admissions in the first hospitalisation, but not in the second. The EI patients had significantly better medical outpatient attendances and greater degree of contact with clinical psychologists, but a similar degree of contact with medical social workers. The EI patients stayed longer in the mental health system than HC patients. A smaller proportion of EI than HC patients disengaged from the service.

Secondary analysis

As the EI and SC groups differed in the proportion of patients treated as inpatients during the initial episode, 328 EI patients and 635 HC patients who were hospitalised for the first episode of illness (defined as hospitalisation in the first month of service contact) were compared. The results of the secondary analyses paralleled to the primary analyses (except that the two groups no longer differed significantly with respect to the number of patients having multiple relapses). Patients in the EI group also had shorter rehospitalisations and fewer rehospitalisations (Table 4).

The SGA secondary analysis differed from the primary analysis in several ways. The EI group (n=424) and the HC group (n=179) had comparable positive symptom severities (P=0.074), suicide rates (P=0.30), levels of contact with clinical psychologist (P=0.062), proportions of disengagement (P=0.17), and durations of contact with service (P=0.36). In contrast to the primary analysis, the EI group had a lower relapse rate than the HC group by year 3 (55.2% vs 65.9%, P=0.015).

Discussion

During the initial 3 years of psychiatric treatment, patients who received phase-specific intervention were more likely to hold full-time jobs, less likely to commit suicide, and spent less time in hospital than patients receiving standard care. Vocational functioning was significantly better in the EI group. The employment rates in the overall cohort were comparable with other studies.[5,17,18] There was a substantial reduction in hospitalisation (45.8%) in the EI group. This

Table 4. Secondary analysis of outcome in 328 early intervention (EI) patients and 635 historical controls (HC) treated as inpatients during their first episode of psychosis

Outcome variables	EI (n=328)*	HC (n=635)*	Test results†	P value
Functional outcome				
Full-time employment ≥6 months	209 (63.7)	302 (47.6)	Adjusted OR=1.78 (1.33-2.37)	<0.001
Duration engaged in full-time employment (months)	14.4±11.5	10.3±11.2	*F=17.84*	<0.001
Clinical outcome				
Clinical Global Impressions-Severity Scale (CGI-S) positive symptoms	1.5±0.6	1.7±0.9	*F=15.92*	<0.001
CGI-S negative symptoms	1.4±0.5	1.6±0.7	*F=9.36*	0.002
Cumulative relapse rate by year 1	55 (16.8)	133 (20.9)	Adjusted OR=0.66 (0.46-0.96)	0.027
Cumulative relapse rate by year 2	124 (37.8)	238 (37.5)	Adjusted OR=0.79 (0.59-1.07)	0.12
Cumulative relapse rate by year 3	171 (52.1)	297 (46.8)	Adjusted OR=0.94 (0.71-1.26)	0.70
Multiple relapses (>2)	55 (16.8)	109 (17.2)	Adjusted OR=0.70 (0.47-1.02)	0.064
Having at least one period of recovery	127 (38.7)	171 (26.9)	Adjusted OR=1.66 (1.23-2.24)	0.001
Suicidal behaviour				
Suicide attempt	42 (12.8)	71 (11.2)	χ^2/t=0.55	0.46
Completed suicide‡	4	20	Hazard ratio=0.34 (0.12-0.99)	0.049
Death (all-cause)§	5	22	Hazard ratio=0.32 (0.11-0.94)	0.038
Service utilisation				
Duration of rehospitalisation (days)	44.2±95.0	57.5±113.4	*F*=10.85	0.001
No. of rehospitalisations	0.7±1.0	0.8±1.2	*F*=10.81	0.001
Compulsory admission at second hospitalisation	27/147 (18.4)	78/294 (26.5)	Adjusted OR=0.75 (0.45-1.25)	0.28
No. of medical outpatient visits	25.7±12.7	16.5±11.7	χ^2/t=11.13	<0.001
No. of contacts with clinical psychologist	1.3±3.6	0.7±2.4	χ^2/t=2.78	0.006
No. of contacts with medical social worker	1.9±2.2	1.7±2.6	χ^2/t=1.22	0.22
Disengagement	59 (18.0)	193 (30.4)	χ^2/t=17.23	<0.001
Length of engagement in service (months)	33.1±7.7	28.6±12.8	χ^2/t=6.89	<0.001

* Data are presented as mean±SD, No., No. (%) of patients, or No./total (%) of patients

† Data are presented as adjusted OR (95% CI) by logistic regression, *F* value by analysis of covariance, χ^2/t, or hazard ratio (95% CI) by Cox-proportional hazards regression

‡ The 3-year Kaplan-Meier estimate of the proportion of suicides was 1.3% (95% CI, 0.01-2.61%) in the EI group and 3.8% (95% CI, 2.09-5.41%) in the HC group (χ^2_1=4.28, P=0.039, log-rank test)

§ The time of death was missing in one patient in each group. The 3-year Kaplan-Meier estimate of the proportion of death from any cause was 1.3% (95% CI, 0.01-2.61%) in the EI group and 3.9% (95% CI, 2.25-5.61%) in the HC group (χ^2_1=4.76, P=0.029, log-rank test)

suggests that with more intensive support, first-episode psychosis patients could be managed effectively in the community.[19] Significant reduction in rehospitalisation was also noted in the subset of patients who were hospitalised for their first episodes of illness. Nonetheless, the findings might not be generalisable because of the geographical variation in incidence, course, and outcome.[20] Our study has extended the findings on the efficacy of early intervention to a non-western population with limited resources for mental health service.

Our study adopted a historical control design. Although the two comparison cohorts were closely matched for age, gender, and diagnosis, they received different antipsychotic treatments (with greater usage of SGA in the EI cohort). Secondary analyses revealed the potential effect of SGA on outcome. By treating antipsychotics as a covariate in the analyses of the key variables, the effects remained significant, suggesting that the difference in outcome could not be accounted for by differences in the use of antipsychotics.

In our study, the DUP itself did not differ between the two cohorts. This is consistent with one historical control study,[21] but not with two others that reported a shortening of DUP with early intervention.[22,23] One potential reason for the lack of significant difference in DUP could be related to the EI cohort presenting soon after the historical control cohort. There might not be sufficient time for the public awareness programmes to have an impact on the DUP in the population. It was also conceivable that after the launch of the EASY programme, a number of patients who had hitherto had difficulty in accessing care (with long DUP) might have been engaged by the EASY programme because of its improved accessibility.

Whether the observed correlation between long DUP and poor outcome reflects a causal relationship has been contentious.[24] Although this issue has been explored using potential confounding variables such as premorbid adjustment, it has been difficult for intervention studies to separate the two major components of early intervention, namely early detection to reduce DUP and phase-specific intervention. This was because most intervention programmes included both components. The current data were obtained at an early stage of a programme when the impact on the DUP was still minimal. It provided an opportunity to inquire into the extent to which outcome could be improved without a shortened DUP. These improvements in functional outcome and hospitalisation were evident despite unchanged DUP, which suggests that the improvements were likely the result of phase-specific intervention rather than early detection.

In contrast to some studies,[25,26] our study did not detect a reduction in relapse rate in the intervention group, which

was similar to findings from other studies.[5,6,10] Whether the impact of intervention on relapse rate is a function of intervention intensity needs further studies. In addition, some early intervention programmes focused more on cognitive therapeutic approaches, whereas others adopted a more generic approach.[3,27] A number of studies using intensive cognitive therapy succeeded in reducing the number of relapses,[28-30] although some failed even with intensive cognitive therapy.[31,32]

Among early intervention programmes, there were variations in content and intensity. In our sample, the caseload (one case manager to 80 cases) was relatively heavy. The situation is characteristic of some affluent Asian communities, indicating that resources for mental health care may remain significantly smaller than for other health care fields.[33,34] Resource levels in both standard care and early intervention were not comparable with those in locations with more advanced developments in mental health services. This study was of pragmatic relevance to the many locations worldwide where mental health care is still relatively under-resourced.

There were several limitations in the study. As the study was based on clinical records, some potentially important outcome variables (such as quality of life) could not be addressed. A longer period of follow-up could be more informative. The current study design enabled the use of data from large cohorts to demonstrate that phase-specific early intervention, even with a high caseload, could result in improved outcome in the critical period of psychotic disorders, and that this improvement was not dependent on shortening of the DUP.

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