Early psychosis intervention

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ABSTRACT

Early psychosis intervention programmes have been around for 20 years. The duration of psychosis has been hypothesised to be neurotoxic, and there is a critical period, postulated to be up to five years from the onset of psychosis, for intervention before the psychosis becomes established. Early intervention is expected to change the course of psychosis and hence, the outcome. However, despite the proliferation of early intervention services, research has shown that improvement in outcome is at best modest, lasting only for the duration of the intervention, and these benefits are not sustained after five years. Evidence for the cost-effectiveness of these services is accumulating and indicates that the reduction in costs is due to reduced inpatient stays.

Keywords: cost-effectiveness, duration of untreated psychosis, early psychosis intervention

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INTRODUCTION

Early psychosis intervention movement began in the 1990s and has become a mainstream approach to psychotic illnesses. Early intervention programmes for psychotic disorders have been established around the world.[1] In Singapore, the Early Psychosis Intervention Programme[2] was established in 2001. The aim was to provide a holistic, comprehensive and accessible service for those at risk of early psychosis, in addition to reducing the overall burden and costs of psychosis to the community.

The early psychosis intervention services have been considered a "waste of valuable resources"[3] by some, and the rapid implementation of these services have been charged with being a matter of "faith before facts"[4] by others. The debate[5,6] on whether early intervention in the major psychiatric disorders is justified continues. Some of these controversies may be related to how early intervention is defined. Early intervention can be divided into a prepsychotic phase, i.e. before the onset of psychosis, and a post-onset phase characterised by early initiation of treatment, symptomatic and functional recovery, and relapse prevention. So does early intervention in psychosis make a difference and is it cost-effective?

DURATION OF UNTREATED PSYCHOSIS AND OUTCOME

The duration of untreated psychosis (DUP)[7] is defined as the time from manifestation of psychotic symptoms to the initiation of adequate treatment. This is to be distinguished from the duration of untreated illness (DUI), which is the time from manifestation of the first symptom to the initiation of adequate treatment. The mean DUP is 1–2 years.[8]

The rationale underpinning the development of early intervention services is the "critical period" hypothesis.[9,10] The early phase of psychosis is hypothesised to be a "critical period" that influences its long-term outcome, and the early course of the disorder is particularly malleable to intervention. This provides an opportunity for secondary prevention. Furthermore, untreated psychosis has been hypothesised to be neurotoxic,[8,11] so that people with a longer DUP may have a poorer outcome due to the deterioration of brain function. Lappin et al found that temporal grey matter reductions were more marked in patients with a long DUP.[12] A recent study has shown the progressive reduction of grey matter of the superior temporal gyrus during the transition to psychosis, thus providing evidence for this hypothesis.[13]

Crumlish et al[14] recruited 118 participants in a prospective, naturalistic inception cohort study of first-episode non-affective psychosis. Both the DUP and DUI (defined in this study as the sum of the prodrome and DUP) were ascertained, and the sample was assessed at four years and eight years of follow-up. The authors found that negative and disorganised symptoms improved at between four and eight years, and that DUP predicted remission, positive symptoms and social functioning at eight years. The median DUP was 12 months.[14] Birchwood and Fiorillo,[10] however, suggested that the critical period was the first five years after onset, after which the illness stabilises. Crumlish et al's study did not support this hypothesis due to improvement in the functioning in a subgroup with DUI of two years or less. The DUP predicted an eight-year outcome after controlling for confounders. Their results provided qualified support for the critical period hypothesis and show that DUI seems to be more important than DUP in predicting outcome. The authors have suggested that the critical

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period could be extended to include the prodrome as well as early psychosis.[14]

A Cochrane review evaluating the effects of early detection, phase-specific treatments and specialised early intervention teams in the treatment of people with prodromal symptoms or first-episode psychosis (FEP) was unable to draw any definitive conclusions.[15] Since then, two meta-analyses[16,17] of follow-up studies on first-episode cohorts have shown the small to moderate effects of a longer DUP and poorer outcome. The clearest evidence for this was seen in Marshall et al's meta-analysis of correlated data at the six- and 12-month follow-up, where the association was consistent over a number of outcome measures, including total symptoms, depression/anxiety, negative symptoms, overall functioning, positive symptoms and social functioning. Patients with a long DUP were less likely to achieve remission.[16] Simonsen et al recruited 301 patients with first-episode, non-affective psychosis and followed them up for two years. They found that a long DUP predicted both three-month and two-year non-remission rates.[18] A meta-analysis conducted on the relationship of DUP and outcome in low- and middle-income (LAMI) countries found a similar association of longer DUP with poorer response to treatment and increased levels of disability.[19]

However, the association between longer DUP and poorer outcome does not establish causality, as the association could be due to a third factor. Poor premorbid adjustment[20-23] has been suggested to be the third factor moderating the relationship between DUP and outcome, although a meta-analysis[16] did not find this association. Jeppesen et al[24] studied a sample of 423 patients drawn from the OPUS trial (a randomised controlled trial, in which information about DUP was collected to allow for analysis of this variable as a prognostic factor), which examined the association between premorbid adjustment, DUP and outcome in FEP. This longitudinal, two-year follow-up study found that a longer DUP was associated with a poorer two-year outcome of psychosis in schizophrenia spectrum disorders that was independent of premorbid functioning and other prognostic factors. Impaired premorbid functioning was independently associated with more negative symptoms and poorer social outcome.[24]

Factors intrinsic to the illness have been suggested to be a possible factor contributing to the delay in treatment. Wyatt[11] argued that patients given antipsychotics earlier had better long-term outcomes. One of the sources from which he drew his evidence was the Northwick Park Study of First Episodes,[25] which was designed to study the value of maintenance antipsychotics following first-episode schizophrenia. A correlation was found between prolonged DUI and a shortened time to relapse. Two hypotheses were used to explain the results: certain features that were associated with a high relapse risk had led to a delay in admission, or the delay in starting treatment itself had led to poorer outcomes. Many studies have considered the association between DUP and outcome, but few have studied the DUI. A study that investigated the DUI and outcome in schizophrenia was carried out on 101 patients from the Northwick Park sample who completed 12 months of follow-up. The authors re-examined the data and found that a long DUI reflects the characteristics of psychosis rather than a delay in treatment.[26] Although DUP predicts short-term outcome, its role in the medium and long term is uncertain. White et al, in a ten-year follow-up of FEP, identified the following as independent predictors of poor long-term outcome: poor premorbid functioning, baseline symptoms, DUP and neurological soft signs at onset.[27]

REDUCING THE DURATION OF UNTREATED PSYCHOSIS

The Scandinavian Early Treatment and Intervention in Psychosis (TIPS)[28] project was the first[29] to reduce the DUP with a specialised early detection programme.[30] This was a four-site quasi-experimental prospective clinical trial conducted in Norway and Denmark, and was designed to investigate the timing of treatment in FEP. Two health sectors developed a system of early detection aimed at reducing the DUP, while two other sectors that were used as comparisons relied on existing referral systems for FEP. The system of early detection consisted of public education and prompt access to treatment via active outreach detection teams. One study found that in the early detection (ED) area, the mean DUP was significantly reduced compared to the no-ED area. The median DUP was five weeks in the ED area and 16 weeks in the no-ED area. The reduction in DUP is associated with better clinical status at baseline that is maintained after three months.[31] The differences become attenuated by one year, but not for the negative symptoms.[32] The early detection programme[33] also significantly lowered the rates of suicidal behaviour in areas with the ED programme compared to areas without it. Reducing the DUP[34] has effects on the course of the symptoms, including negative symptoms and functioning in first-episode schizophrenia during the first two years.

INTERVENTIONS IN THE EARLY PHASE OF PSYCHOSIS

Specialised intervention programmes for FEP have been around for some time now, but do they really make a difference to the outcome? A meta-analytic approach[35] that examined the benefits of enriched intervention (EI) and standard care (SC) for patients with recent onset psychosis found that EI was significantly more effective than SC for symptomatic improvement over a period of about one year. Most early intervention programmes last for about two years, and few studies have looked at longer-term outcomes.

The UK Lambeth Early Onset (LEO) study[36] is a randomised controlled clinical trial investigating the effectiveness of an 18-month specialised treatment programme for early psychosis. 144 patients presenting with first- or second-episode non-organic, non-affective psychosis were randomised into specialised care (assertive outreach with evidence-based biopsychosocial interventions) or standard care (control group) delivered by community mental health teams, and followed up for 18 months. The primary outcome measures were rates of relapse and readmission. The mean DUP was 10.5 months in the specialised care group and 7.6 months in the control group. Patients in the specialised care group were less likely to relapse and were admitted fewer times. The limitations of this study were the small sample size, which resulted in the study being underpowered, as well as the randomisation process, which did not produce well-matched groups, with the specialised care group at baseline having more features of better prognosis for gender, previous psychotic episodes and ethnicity than the standard care group. When the rates were adjusted for these factors, relapse was no longer significant, and only the total number of readmissions and the dropout rates remained significant.[36] The group that received specialised care showed improvements in social and vocational functioning, user satisfaction, quality of life and medication adherence.[37] The outcome at five years using case note review found no significant differences between the two groups in terms of the admission rate or the mean number of bed days.[38]

The OPUS study[39,40] is a randomised clinical trial involving 574 participants with first-episode schizophrenia spectrum disorder. The participants were randomised to integrated or standard treatment. The integrated treatment lasted two years and consisted of assertive community treatment with programmes for family involvement and social skills training. Standard treatment offered contact with a community mental health team. In the integrated treatment group, a primary team member was designated for each patient and was responsible for maintaining contact and coordinating the treatment. The median DUP was 46 weeks in the integrated treatment group and 53 weeks in the standard treatment group. At one year,[41] significant beneficial effects of integrated treatment over standard treatment on "any poor outcome" were observed. This was especially so for patients with schizophrenia. At two years,[39] the integrated treatment group demonstrated improvements in psychotic and negative symptoms,[42] greater patient satisfaction, reduced substance misuse, improved adherence to treatment and fewer days in hospital. However, integrated treatment did not have significant effects on depression, suicidal behaviour and suicidal ideation, unlike in other studies.[33,43] The improvements found in this study were not sustained at five years.[44] However, secondary outcome measures showed differences in the proportion of patients living in supported housing and the number of days in hospital, favouring the intensive early intervention group.

The long-term outcomes of individuals with FEP who were detected and treated in specialised early psychosis programmes are undetermined. The Early Psychosis Prevention and Intervention Centre (EPPIC)[45] follow-up study is the first to look at long-term outcomes. This is a naturalistic, prospective follow-up of an epidemiological sample of 723 consecutive FEP patients at a median of 7.4 years after initial presentation to EPPIC in Melbourne, Australia. The patients had been treated for up to two years in EPPIC, an early psychosis intervention programme. Relatively positive outcomes with symptomatic remission occurring in 37%–59% of the cohort and social/vocational recovery in 31% of the cohort were observed.

COST-EFFECTIVENESS OF EARLY INTERVENTION

There has been an ongoing debate regarding the cost-effectiveness of treating patients with FEP,[46] with some suggesting that specialist early intervention teams are a "waste of clinical resources". The cost-effectiveness of an early intervention service[47] for psychosis in London using a net-benefit approach showed that it did not increase costs and was highly likely to be cost-effective when compared to standard care. Hospitalisation was reduced, but the overall cost difference in favour of early intervention was not statistically significant. Three other economic evaluation studies[48-50] of early intervention services have also shown that early intervention teams are cost-effective because of the reduction in inpatient stay. A recent meta-analysis demonstrated that early

intervention services prevented relapse more effectively than treatment as usual.[51]

CONCLUSION

Early intervention services do improve outcomes in the first 1–2 years, although the effect ranges from small to moderate. Most studies supporting the effectiveness of these services are based on observational studies rather than on randomised controlled trials. The active components of an early intervention service that exerts this effect are still not understood. Whether these benefits are maintained in the longer term remains unclear, particularly after specialised service is withdrawn. At this point, more research is required in order to determine the long-term impact and optimal duration of early psychosis intervention programmes. Studies suggest that these services are cost effective because they reduce inpatient stay. The suggestion that the critical period could include the psychosis prodrome opens up a new area of early intervention and research – ultra high-risk services.

REFERENCES

1. McGorry PD, Killackey E, Yung AR. Early intervention in psychotic disorders: detection and treatment of the first episode and the critical early stages. Med J Aust 2007; 187(7suppl):s8-10.
2. Chong SA, Lee C, Bird L, Verma S. A risk reduction approach for schizophrenia: the Early Psychosis Intervention Programme. Ann Acad Med Singapore 2004; 33:630-5.
3. Pelosi AJ, Birchwood M. Is early intervention for psychosis a waste of valuable resources? Br J Psychiatry 2003; 182:196-8.
4. Bosanac P, Patton GC, Castle DJ. Early intervention in psychotic disorders: faith before facts? Psychol Med 2010; 40:353-8.
5. Pelosi A. Is early intervention in the major psychiatric disorders justified? No. BMJ 2008; 337:a710.
6. McGorry PD. Is early intervention in the major psychiatric disorders justified? Yes. BMJ 2008; 337:a695.
7. Compton MT, Carter T, Bergner E, et al. Defining, operationalizing and measuring the duration of untreated psychosis: advances, limitations and future directions. Early Interv Psychiatry 2007; 1:236-50.
8. McGlashan TH. Duration of Untreated psychosis in First-Episode Schizophrenia: Marker or Determinant of Course? Biol Psychiatry 1999; 46:899-907. Erratum in: Biol Psychiatry 2000; 47:473.
9. Birchwood M, McGorry P, Jackson H. Early Intervention in schizophrenia (Editorial). Br J Psychiatry 1997; 170:2-5.
10. Birchwood M, Fiorillo A. The Critical Period for Early Intervention. Am J Psychiatr Rehabil Skills 2000; 4:182-98.
11. Wyatt RJ. Neuroleptics and the natural course of schizophrenia. Schizophr Bull 17; 325-51.
12. Lappin JM, Morgan K, Morgan C, et al. Gray matter abnormalities associated with duration of untreated psychosis. Schizophr Res 2006; 83:145-53.
13. Takahashi T, Wood SJ, Yung AR, et al. Progressive gray matter reduction of the superior temporal gyrus during transition to psychosis. Arch Gen Psychiatry 2009; 66:366-76.
14. Crumlish N, Whitty P, Clarke M, et al. Beyond the critical period: longitudinal study of 8-year outcome in first-episode non-affective psychosis. Br J Psychiatry 2009; 194:18-24.
15. Marshall M, Rathbone J. Early intervention for psychosis. Cochrane Database of Syst Rev 2006; (4):CD004718.
16. Marshall M, Lewis S, Lockwood A, et al. Association between duration of untreated psychosis and outcome in cohorts of first-episode patients. Arch Gen Psychiatry 2005; 62:975-83.
17. Perkins Do, Gu H, Boteva K, Lieberman JA. Relationship between duration of untreated psychosis and outcome in first-episode schizophrenia: a critical review and meta-analysis. Am J Psychiatry 2005; 162:1785-804.
18. Simonsen E, Friis S, Opjordsmoen S, et al. Early identification of non-remission in first-episode psychosis in a two-year outcome study. Acta Psychiatr Scand 2010, Aug 18 [Epub ahead of print].
19. Farooq S, Large M, Nielssen O, Waheed W. The relationship between the duration of untreated psychosis and outcome in low-and-middle income countries: a systematic review and meta analysis. Schizophr Res 2009; 109:15-23.
20. Gupta S, Rajaprabhakaran R, Arndt A, Flaum M, Andreasen NC. Premorbid adjustment as a predictor of phenomenological and neurobiological indices in schizophrenia. Schizophr Res 1995; 16:189-97.
21. Norman RM, Malla AK, Manchanda R. Early premorbid adjustment as a moderator of the impact of duration of untreated psychosis. Schizophr Res 2007; 95:111-4.
22. Macbeth A, Gumley A. Premorbid adjustment, symptom development and quality of life in first episode psychosis: a systematic review and critical reappraisal. Acta Psychiatr Scand 2008; 117:85-99.
23. Petersen L, Thorup A, Øqhlenschlaeger J, et al. Predictors of remission and recovery in a first-episode schizophrenia spectrum disorder sample: 2-year follow-up of the OPUS trial. Can J Psychiatry 2008; 53:660-70.
24. Jeppesen P, Petersen L, Thorup A, et al. The association between pre-morbid adjustment, duration of untreated psychosis and outcome in first-episode psychosis. Psychol Med 2008; 38:1157-66.
25. Crow TJ, MacMillan JF, Johnson AL, Johnstone EC. A randomized controlled trial of prophylactic neuroleptic treatment. Br J Psychiatry 1986; 148:120-7.
26. Owens DC, Johnstone E, Miller P, Macmillan JF, Crow TJ. Duration of untreated illness and outcome in schizophrenia: test of predictors in relation to relapse risk. Br J Psychiatry 2010; 196:296-301.
27. White C, Stirling J, Hopkins R, et al. Predictors of 10-year outcome of first-episode psychosis. Psychol Med 2009; 39:1447-56.
28. Johannessen JO, Larsen TK, Joa I, et al. Pathways to care for first-episode psychosis in an early detection healthcare sector: part of the Scandinavian TIPS study. Br J Psychiatry Suppl 2005; 48:s24-8.
29. Larsen TK, McGlashan TH, Johannessen JO, et al. Shortened duration of untreated first episode of psychosis: changes in patient characteristics at treatment. Am J Psychiatry 2001; 158:1917-9.
30. Johannessen JO, McGlashan TH, Larsen TK, et al. Early detection strategies for untreated first-episode psychosis. Schizophr Res 2001; 51:39-46.

31. Melle I, Larsen TK, Haahr U, et al. Reducing the duration of untreated first-episode psychosis: effects on clinical presentation. Arch Gen Psychiatry 2004; 61:143-50.
32. Larsen TK, Melle I, Auestad B, et al. Early detection of First-Episode psychosis: the effect on 1-year outcome. Schizophr Bull 2006; 32:758-64.
33. Melle I, Johannesen JO, Friis S, et al. Early detection of the first episode of schizophrenia and suicidal behaviour. Am J Psychiatry 2006; 163:800-4.
34. Melle I, Larsen TK, Haar U, et al. Prevention of negative symptom psychopathologies in first-episode schizophrenia: two-year effects of reducing the duration of untreated psychosis. Arch Gen Psychiatry 2008; 65:634-40.
35. Harvey P, Lepage M, Malla A. Benefits of enriched intervention compared with standard care for patients with recent-onset psychosis: a metaanalytic approach. Can J Psychiatry 2007; 52:464-72.
36. Craig TK, Garety P, Power P, et al. The Lambeth Early Onset (LEO) Team: randomised controlled trial of the effectiveness of specialised care for early psychosis. BMJ 2004; 329:1067-71.
37. Garety PA, Craig TK, Dunn G, et al. Specialised care for early psychosis: symptoms, social functioning and patient satisfaction: randomised control trial. Br J Psychiatry 2006; 188:37-45. Erratum in: Br J Psychiatry 2006; 9:36.
38. Gafoor R, Nitsch D, McCrone P, et al. Effect of early intervention on 5-year outcome in non-affective psychosis. Br J Psychiatry 2010; 196:372-6.
39. Petersen L, Jeppesen P, Thorup A, et al. A randomized multicentre trial of integrated versus standard treatment for patients with first episode of psychotic illness. BMJ 2005; 331:602. Erratum in: BMJ 2005; 331:1065.
40. Jørgensen P, Nordentoft M, Abel MB, et al. Early detection and assertive community treatment of young psychotics: the Opus Study Rationale and design of trial. Soc Psychiatry Psychiatr Epidemiol 2000; 35:283-7.
41. Petersen L, Nordentoft M, Jeppesen P, et al. Improving 1-year outcome in first-episode psychosis: OPUS trial. Brit J Psychiatry Suppl 2005; 48:s98-103.
42. Thorup A, Petersen L, Jeppesen P, et al. Integrated treatment ameliorates negative symptoms in first episode psychosis – results from the Danish OPUS trial. Schizophr Res 2005; 79:95-105.
43. Harris MG, Burgess PM, Chant DC, et al. Can specialized early psychosis programs reduce suicide rates in first episode psychosis? Schizophr Bull 2007; 33:483-84.
44. Bertelsen M, Jeppesen P, Petersen L, et al. Five-year follow-up of a randomized multicentre trial of intensive early intervention vs standard treatment for patients with first episode of psychotic illness: the OPUS trial. Arch Gen Psychiatry 2008; 65:762-71.
45. Henry LP, Amminger PG, Harris MG, et al. The EPPIC follow-up study of first-episode psychosis: longer-term clinical and functional outcome 7 years after index admission. J Clin Psychiatry 2010; 71:716-28.
46. Malla A, Pelosi AJ. Is treating patients with first-episode psychosis cost-effective? Can J Psychiatry 2010; 55:3-8.
47. McCrone P, Craig TKJ, Power P, et al. Cost-effectiveness of an early intervention service for people with psychosis. Br J Psychiatry 2010; 196:377-82.
48. Mihalopoulos C, Harris M, Henry L, Harrigan S, McGorry P. Is early intervention in psychosis cost-effective over the long term? Schizophr Bull 2009; 35:909-18.
49. Cullberg J, Mattsson M, Levander S, et al. Treatment costs and clinical outcome for first episode schizophrenia patients: a 3-year follow-up of the Swedish "Parachute Project" and two comparison groups. Acta Psychiatr Scand 2006; 114:274-81.
50. Serretti A, Mandelli L, Bajo E, et al. The socio-economical burden of schizophrenia: a simulation of cost-offset of early intervention program in Italy. Eur Psychiatry 2009; 24:11-6.
51. Alvarez-Jimenez M, Parker A, Hetrick SE, et al. Preventing the Second Episode: a Systematic Review and Meta-analysis of Psychosocial and Pharmacological Trials in First-Episode psychosis. Schizophr Bull 2009.