Early intervention in psychosis: another triumph of hope over experience?

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Evidence that longer duration of untreated psychosis (DUP) was associated with poor premorbid functioning in the year before onset, insidious onset and more negative symptoms at onset, led to the assumption that reducing DUP could improve long-term outcome – hence the development of early intervention in psychosis (EIP) services. The authors investigate the evidence for and against EIP services and discuss how societal / family issues can also strongly influence mental health.

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Table 1. Summary of evidence supporting EIP

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<td>Mihalopoulos et al, 2009\cite{25}</td>
<td>Economic evaluation showing EIP can be cost-effective by delivering a higher recovery rate at one-third of the cost of conventional treatment.</td>
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<td>McCrone et al, 2009\cite{26}</td>
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<td>van der Gaag et al, 2013\cite{21}</td>
<td>Meta-analysis showed reduced transition to psychosis in EIP patients and demonstrated efficacy of pharmacological and behavioural interventions.</td>
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Evidence in favour of early treatment

The seminal publication of Scully et al.\cite{7} reported that in 48 chronic schizophrenia inpatients, most of whom became ill before the advent of antipsychotic treatment, current severity both of negative symptoms and cognitive impairment was predicted strongly by increasing duration of untreated psychosis. By contrast the duration of the subsequent period of active treatment was not associated with any variable, even though it was much longer. This suggested that in the most severely afflicted patients, those who failed to be discharged after many years...
in hospital, there might have been some benefit had antipsychotic treatment been possible earlier than it was.

Other work challenged the Kraepelinian idea of gradual and inevitable decline. Long-term outcome studies confirmed the heterogeneity of outcome in schizophrenia particularly when economic and political issues were taken into account. Furthermore, it was pointed out that many indices of severity may reach a maximum after 2–5 years, then remain static or even decrease: the ‘plateau effect’. The untreated period may cause social, psychological and biological processes which would prove ‘toxic’ to the brain, potentially irreversibly so. This argument led to the ‘critical period’ hypothesis, there may be a window of opportunity for early intervention, and avoidance of the worst outcomes.

Did these lines of argument put two and two together and make five? This review examines the effectiveness of early interventions, and the unanticipated ‘bystander’ of non-cases and its implications. We searched the literature (Excerpta Medica Database, EMBASE) over the last ten years, using key words and phrases including ‘first episode psychosis’ ‘early interventions services’ ‘early psychosis services’ ‘prolonged duration of untreated psychosis’, etc. We viewed abstracts where the title was of relevance, and scrutinised full articles as necessary.

**For and against the effectiveness of early intervention services**

One single-blinded RCT against treatment as usual demonstrated that although the EIP group utilised fewer services after five years, there was no difference in positive or negative symptoms. A review not long afterwards argued that early interventions had produced ‘an embryonic evidence-base, notably in terms of any long-term benefits’. However, another study showed some advantages for ‘bed days’ and readmissions over six years, compared with treatment as usual. A later observational study suggested that benefits were maintained after 12 months, two years and five years in symptomatic and functional terms. Improvement accrued even after two years, at which point the intensity of the interventions was stepped down.

Some studies, by contrast, have demonstrated that the advantages of early intervention are lost after it ends, with benefits being irreproducible in five and ten-year follow-up studies. Good, holistic clinical care therefore ought to continue, but notions of ‘recovery’ and ‘stepped down care’ may prove unrealistic. Furthermore, reducing DUP from 16 to four weeks (the TIPS study) is of dubious clinical significance. At 10 years it was noted that early intervention was no guarantee against poor outcome: about half the patients in both early detection and routine detection groups failed to achieve symptomatic and functional recovery – 48% and 52% respectively.

Moreover, the early detection group contained more non-recovered patients with no capacity for independent living – 21% versus 11% of the routine detection group. That the early detection group presented better outcomes was based on an assumption that the greater numbers of routinely detected patients lost to follow-up, 48% versus 28% in the early detection group, had particularly poor outcomes. Evidence for this assumption was that at their last available assessment, the early detection non-completers had fewer negative symptoms than the completers, while the routinely detected non-completers had more negative symptoms than the completers. Dropping out of the early detection group was interpreted as compatible with a good outcome, but dropping out of the routine detection group was considered to indicate poor outcome, per se.

A later publication clearly reiterated that chances of recovery in early-detected patients were greater than those routinely detected. Recovered patients in the early detection group had milder deficits and lower unemployment rates. Nonetheless, a further publication concluded that ‘more assertive intervention may be needed in patients who do not respond robustly in the first year of treatment, whether or not they have been detected “early”.’

A subsequent systematic review compared the effects of different EIP regimens with ‘treatment as usual’ in mainstream mental health services. There was some evidence that CBT slowed transition to psychosis at 12 months. The evidence for pharmacological, nutritional and other psychotherapeutic interventions was inconclusive at best. By contrast, a subsequent meta-analysis of ultra-high-risk group studies demonstrated an overall risk reduction of 54% and a number needed to treat of 9. Both antipsychotic and cognitive behavioural interventions were considered effective.

**Service and other issues**

A recent paper succeeded in demonstrating that the largest contributor to DUP, even greater than failing to seek help, was caused by generic community mental health teams, which, despite patients’ psychotic symptoms, omitted to refer them to early intervention services. Closer scrutiny reveals that the DUP across the group studied was bimodal, patients with DUP greater than six months averaged a DUP far
Evidence | Effect
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Bertelsen et al, 2008<sup>12</sup> | Improvements in outcomes at 2 years were not replicated in this 5-year RCT follow-up.
Larsen et al, 2010 (TIPS study)<sup>16</sup> | Improved clinical outcome at 2 years not sustained at 5 years. Reducing DUP from 16 to 4 weeks was of dubious clinical significance.
Friis et al, 2011<sup>17</sup> | 10-year follow-up of TIPS study showed that about half the patients in both study arms failed to achieve symptomatic and functional recovery. Moreover, the EIP group had significantly more patients who had no capacity for independent living.
Castle, 2011<sup>24</sup> | EIP not cost-effective.

Table 2. Summary of evidence opposing EIP

longer than this, nearly two years. Despite one third of patients falling into this category, they were described as ‘outliers’. The mean DUP of patients whose DUP was less than six months was just over five weeks. Even so, delays in referral to and within services exceeded delay in help seeking, for the greater than six months DUP group, as well as the less than six months DUP group. This perhaps demonstrates that not only do a significant minority of patients fail to seek help; they continue to fail to ensure that they get help, even after their difficulties are brought to medical attention. This lack of proactive engagement may, again, reflect a more severe form of schizophrenia: these patients suffered more positive symptoms and general psychopathology. Another meta-analysis of DUP and long-term outcome<sup>23</sup> concluded that although longer DUP predicted severe symptoms and decreased functionality, this did not increase the need for treatment, or decrease quality of life, or employment prospects. Nevertheless, the analogy with physical medicine and its emphasis on primary and secondary prevention suggests that early interventions may obviate later ineffective, essentially palliative care. Whether early intervention services save money to contribute towards the care of the serious enduring mentally ill, is, however, controversial.<sup>24</sup> Even so, there is some work demonstrating cost advantages over usual care, for example,<sup>25,26</sup> albeit with some caveats relating to methodology and robustness to sensitivity analysis.

An inescapable issue, however, is that ‘accepted wisdom’ schizophrenia inception rates of 7-14 per 100 000 population per year stand in stark contrast to referral rates to EIP services of 100 per 100 000 per year. Just what is going on here?

**The issue of ‘bycatch’**
An issue elicited by several authors is ‘bycatch’ – those referred to EIP services who are neither prodromal, nor cases. In Norway,<sup>27</sup> a six-year audit observed a referral to case ratio of 3:1. O’Donoghue<sup>28</sup> audited referrals to their Dublin service for four years. Forty-one per cent were non-cases, the referrals to cases ratio being 2:1. Referrals were increasing, whilst case incidence was stable, only 5% of the referrals were found to be in an ‘at-risk’ state. The remaining patients, however, attracted a variety of diagnoses. This was echoed by an audit [Mortimer, in preparation]<sup>29</sup> of 85 EIP referrals who subscribed to 155 clinical diagnoses. Of just over half (44) with psychosis, in three-quarters (33) this was, clinically, persistent substance-induced psychotic disorder. In other words, ‘but for’ extensive substance abuse, usually cannabis, stimulants or both, it seemed unlikely that psychosis would have supervened. Even in the 11 patients thought to have idiopathic schizophrenia, six also abused substances. It was particularly striking that over a quarter of the total (21) were known to have suffered an adverse, abusive or neglectful childhood. Nineteen patients manifested substantial antisocial personality disorder traits, and there was a particular association with childhood adversity and substance-induced psychotic disorder in these patients. A small minority, 13 patients, were diagnosable with DSM-IV-TR brief psychotic, schizophreniform or not otherwise specified psychotic disorder, the only categories which could reflect any prodromal state.

Despite such varied and genuine psychopathology in EIP patients, it has been argued that EIP risks ‘medicalising’ normal behaviour in ‘troubled teens’, which is stigmatising and unnecessary. By contrast, O’Donoghue<sup>28</sup> recommended recognised pathways to alternative care for non-cases of psychosis. Furthermore, patients with substance use issues, personality dysfunction and childhood adversity, whether psychotic transiently, persistently or not at all, are also worthy of effective intervention in our opinion.

**The future of EIP**
The ‘bycatch’ issue has been, tacitly, recognised in the context of the perceived inadequacy of transitional services between child and adolescent, and adult mental health provision.<sup>30,31</sup> This is ‘weakest where it should be strongest’.<sup>32,33</sup> Seventy five per cent of
mental health problems begin before the age of 25 years. The lifelong nature of chronic mental illness has led to predictions that it will match cardiovascular disease as the joint most encumbering health problem of the next 20 years. Moreover, lack of provision may contribute to high rates of suicide in young people. Only 13% of young Australian males with mental health problems sought help: overwhelming evidence that adult mental health problems have their roots in adolescence should be the ‘clarion call’ for early primary and secondary intervention. Redesigned services need to be ‘youth friendly’ and closely allied to other health and educational provision.

Discussion
There is quite strong evidence for the possibility that lengthy DUP is associated with severity factors, and will remain relatively resistant to resolution. This is consistent with the somewhat disappointing results of EIP evaluation studies. Another major issue is ‘bycatch’, although effective mental health services for young people, whatever their issues, are sorely needed. The reality of life for many young people these days is inimical to good mental health and a successful transition to adulthood. Pertinent issues include experiences of being poorly parented, with family poverty, neglect and abuse (family breakdown, parental unemployment, parental mental disorder, personality disorder and substance abuse) and the young person’s own poverty, substance abuse and unemployment. Indeed, the TIPS study demonstrated that two thirds of patients suffered close personal trauma before the age of 18 years, including physical, psychological and sexual abuse: trauma was associated with longer duration of untreated psychosis, and hence may have impeded help-seeking.

Nevertheless, childhood adversity and its causes are social problems, which rationally require social solutions, not young people’s mental health services post hoc. Ensuring that every child is adequately parented, securely integrated within their family, and benefits from caring educational provision and supportive workplaces, is an ideal that perhaps should not be compromised by the enormous task of its realisation. Early intervention can only be expected to work if it addresses treatable disease, as in the rest of medicine. Such approaches may not be capable of extrapolation to deeply ingrained social exclusion and family dysfunction, because the damage has already been done.

Should evidence for poor effectiveness and high cost of EIP services accrue, they will risk being dismantled. There is a UK precedent from the disinvestment in assertive outreach treatment (AOT). Despite good evidence of effectiveness from a variety of research methodologies, one negative RCT was followed by the closure or similar of a third of services by 2010.

It seems inescapable that EIP and its heirs must demonstrate that they really do prevent the accumulation of the large cohorts of mentally ill people who comprise such a focus of western government expenditure in later adulthood. That EIP can reverse the effects of childhood adversity, unemployment and substance abuse in these vulnerable and troubled young people may be too much to ask.

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Declaration of interests
No conflicts of interest were declared.

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