Early intervention in schizophrenia

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Therapeutic intervention in psychotic disorders has been evolving steadily in recent years with notable changes in the content of treatment (e.g. atypical neuroleptics and the cognitive/psychosocial interventions) and the locus of care. While the therapeutic focus continues to emphasise acute and treatment-resistant symptoms and longer-term interventions, for example assertive community treatment, the primary and secondary prevention of psychosis has received little attention since Cameron's (1938) pioneering work. We believe that our understanding of variables influencing the outcome of the early phase of psychosis is sufficiently well developed to begin exploring their therapeutic implications. More speculatively, we believe this early phase of psychosis is formative in biological, psychological and social terms, thus affording major opportunities for secondary prevention. We propose three key elements of an early intervention strategy: early detection of 'at-risk' mental states; early treatment of the first psychotic episode; and interventions targeted during the early phase of psychosis (the 'critical period').

DETECTION OF 'AT RISK' OR PRODROMAL MENTAL STATES

The approach in DSM–III–R (American Psychiatric Association, 1987) suggested that it is possible to characterise an illness-specific prodrome and that once a prodrome is clearly present, it would be appropriate at least to raise the question of the diagnosis, even prior to the emergency of frank psychosis. Although the utility of early or prodromal symptoms of relapse among those with a clear diagnosis of schizophrenia has received some empirical support, the specificity of these symptoms for psychosis and for diagnostic subgroups within the psychotic spectrum is relatively low at the first episode (Yung & McGorry, 1996). Such doubts have led to specific prodromal criteria being dropped in DSM–IV (American Psychiatric Association, 1994). Nevertheless, it is known that premorbid social dysfunction (a DSM–III–R early symptom) can be documented in over one-third of people who later develop schizophrenia and has been reported to start, on average, between 98.5 (Loebel *et al*, 1992) and 115.2 (Beiser *et al*, 1993) weeks before the onset of psychotic symptoms, which has been hypothesised to be a manifestation of an abnormal neurodevelopmental process. The first-episode prodrome concept remains an essentially retrospective one, which is difficult to translate into a prospective framework in which the false positives are potentially numerous. An alternative approach is to view such putative prodromes, when assessed prospectively, as an 'at-risk mental state'; that is, as a risk factor which may affect the probability of a subsequent psychotic episode (Yung & McGorry, 1996). This implies that only a percentage of cases that are assessed prospectively in such an at-risk mental state go on to develop a psychotic episode. In this concept it is also possible that individuals may experience multiple periods of 'at-risk mental states' prior to the onset of psychosis, and variables known to raise the probability of a psychotic relapse (e.g. life events, family stress) may also be drawn into the equation when attempting to predict when and in whom the first episode of psychosis will appear.

Early intervention strategies

We believe a research case can be made for cautious monitoring of individuals who may be considered 'at risk'. Specific criteria will be required to define risk, which might include: a clear change in social functioning from a baseline level, the presence of an at-risk mental state (perceptual change, ideas of reference, delusional mood) or schizotypal personality disorder. At-risk individuals and their families may be offered problem-focused support and, should a frank psychosis emerge, delay in receiving effective treatment will be kept to a minimum. This will require a low-stigma setting and would be an ideal setting in which to conduct prospective research into the transition between risk status and a first morbidity. It is important, however, to take stock of some of the logical and ethical issues involved in implementing preventive strategies at the present time. Since there are no data on the relative risk of transition to a first episode of psychosis of such mental states or other factors, it would be clearly inappropriate to intervene as if they represented early psychosis. A great deal more information about risk and the process of transition to psychosis is required before intervention trials can begin.

THE FIRST PSYCHOTIC EPISODE

Treatment lag

In spite of the profound and distressing changes that accompany a first episode of psychosis, time to first presentation and treatment after the onset of frank psychotic symptoms averages approximately one year (see Table 1). Where reported, the standard deviation is greater than the mean and in McGorry & Singh (1995) the median was much less than the mean (74 *v.* 20 weeks) suggesting a significant effect of outliers with long durations. Treatment lag could be confounded with mode of onset (acute/insidious) but the studies of Loebel *et al* (1992), McGorry & Singh (1995) and Beiser *et al* (1993) attempted to measure the duration of prodrome (onset of first noticeable change to onset of psychotic symp-

Table 1 Treatment lag in five studies of first-episode schizophrenia

Study	Setting	*n*	Definition	Treatment lag (weeks)
Beiser *et al* (1993)	Vancouver	72	DSM–III	56
Birchwood *et al* (1992)	Birmingham	128	ICD–9	30
Johnstone *et al* (1986)	London	253	ICD–9	28% < 8 weeks, 26% > 52 weeks
Loebel *et al* (1992)	New York	70	RDC	52
McGorry & Singh (1995)	Melbourne	60	DSM–III–R	74

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toms), which was used to define mode of onset. In the Northwick Park Study (Johnstone *et al*, 1986) time to first presentation was associated with increasing complications of frank psychotic illness including severe behavioural disturbance and family difficulty (often involving multiple failed attempts to access care) and life-threatening behaviour, underlying that individuals were in need of urgent treatment.

Two studies have demonstrated a close link between the duration of untreated psychosis and the early course of schizophrenia. Johnstone *et al* (1986) found that those taking longer than one year to access and exit services revealed a threefold increase in relapse rate over the following two years, compared with those with a briefer duration of untreated illness. Untreated illness emerged as the strongest predictor of relapse, irrespective of the use of maintenance medication which was manipulated in this study. Loebel *et al* (1992) followed up their first-episode sample for three years using a standardised treatment and assessment protocol, and found that the time to remission as well as the degree of remission was closely related to duration of untreated psychosis when other prognostic variables were controlled. These findings may be the result of type of illness (those with an inherently high risk of relapse may include symptoms that delay treatment) or the result of psychosocial disruption arising from a long period of untreated psychosis. Wyatt (1995) has suggested that untreated psychosis is biologically toxic and responsible for long-term morbidity. Vulnerability models have been invoked to explain the problem of heterogeneity in schizophrenia: we would propose that some of the variance in vulnerability may have its origins in events surrounding the first episode, in particular untreated psychosis.

Early treatment and recovery

The link between treatment lag and early outcome remains circumstantial; understanding the reasons for delay are crucial to determine the direction of causality and the potential for reducing delay. *Recognition* of psychosis may be delayed when it is preceded by a long prodrome, in which transition from poor premorbid state to at-risk mental state and frank psychosis may be difficult for relatives and professionals to discern. First-episode psychosis does not always present in neat parcels and there may be changes in presentation from the first to the second episode (Fennig *et al*, 1995), creating problems for early diagnosis.

Help-seeking by patients and relatives will be impeded by negative social attitudes to mental illness and the *visibility* of behavioural change may be obscured, for example where individuals live alone in the inner city (Birchwood *et al*, 1992). Problems of *access* were highlighted by Johnstone *et al* (1986) who noted that relatives reported the multiple failed attempts to access care through general practitioners (GPs); in a recent study three-quarters of cases consulted their GPs at some point on matters connected with their developing psychosis (Cole *et al*, 1995).

We propose the following strategies to reduce treatment delay. First, a community education programme emphasising the treatability of psychosis and focusing on the professional and voluntary agencies likely to encounter psychosis (e.g. college counsellors, Gurdwara, homeless agencies, police). An example of good practice here is the IRIS project run by the National Schizophrenia Fellowship and the National Union of Students, which aims to promote awareness of the earliest manifestations of psychosis at a crucial transition point of further education. Second, we suggest training GPs in the recognition of psychosis and offering secondary referral where a psychosis is suspected; however, it may be necessary to monitor and support ambiguous cases for a period without treatment until a clear psychosis is declared. The early assignment of a keyworker to promote service engagement may reduce the need for later coercive methods. Third, patients and their families are more likely to accept early treatment if it is provided at home or in a low-stigma setting, for example through a home treatment team.

Reducing the duration of *treated* psychosis will require a drug strategy: Lieberman *et al* (1993) found that 85% of their first-episode cohort achieved a full remission within six months. There is no consensus, however, about the optimum drug dose in first-episode psychosis (Wyatt, 1995); we believe this is important in the light of the findings of McEvoy *et al* (1991) that low, 'neuroleptic threshold' doses (an average of 3.4 mg haloperidol) led to symptomatic recovery in a sample of acutely ill, recent-onset patients for whom higher doses did not accelerate treatment response. We believe that a protocol of treatment for first-episode psychosis needs to be agreed and evaluated and should include drugs, cognitive therapy for hallucinations and delusions and therapy to promote psychological adjustment to what can be a traumatising diagnosis (Drury *et al*, 1996).

THE CRITICAL PERIOD

This concept is borrowed from the child development literature and here we argue in analogous fashion that the early phase of psychosis, and the variables that influence it, are formative, and that long-term outcome is strongly predictable early in the course, and that crucial biological and psychosocial changes are laid down in this period. What is the evidence for this? Long-term follow-up studies have conclusively shown that the diagnosis of schizophrenia, broadly or narrowly defined, is associated with significant deterioration in clinical and social functioning but is neither homogenous nor exclusive to schizophrenia (as Kraepelin suggested a century ago) and that clinical and social deterioration is overemphasised (e.g. Mason *et al*, 1995). Long-term prospective studies of first-episode samples are rare; a landmark study from Madras (Thara *et al*, 1994) followed up 90 patients monthly for 10 years with very little attrition and found that positive and negative symptoms stabilised by the second year, affecting 25% of the sample, with no significant further deterioration or evidence of substitution of positive for negative symptoms. This may be taken to suggest that long-term treatment resistance is apparent within two years. The notion of deterioration plateauing in the early phase of psychosis was first described by Bleuler (1978) and reinforced by reports from centres involved in the International Pilot Study of Schizophrenia (e.g. Carpenter & Strauss, 1991).

Early psychosocial adjustment to psychosis is not a well-researched topic, yet there is evidence that problems in this area can have major consequences, notably suicide. Westermeyer *et al* (1991) reported a 14-year follow-up of 586 first-episode and early-phase schizophrenic patients and found that the first six years was the maximum period of risk by which time nearly two-thirds of the suicides had taken place. The sense of entrapment in relapsing psychotic illness, the absence of a means of achieving valued goals and roles and the loss of social status are, we believe, critical appraisals that underlie the meaning of known risk factors for suicide (youth, male gender, unemployment, higher educational

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aspirations) which have been linked to problems of self-regard and hopelessness (Birchwood *et al*, 1993). The psychosocial adjustment of the family is also in a state of flux during this period. Stirling *et al* (1991) report on ontogeny of high expressed emotion involving an apparent metamorphosis of familial over-involvement into criticism within two years of first presentation.

Intervention strategies

The notion of early psychosis as a critical period remains a hypothesis that requires to be tested by intervention trials. We propose the following three elements.

Relapse prevention

Relapse can be expected in 40–60% of patients within two years of first treatment (Ram *et al*, 1992), which carries with it a raised possibility of treatment resistance and lasting impact on social functioning and negative symptoms (Davis *et al*, 1993). Maintenance medication confers protection but trials in first-episode psychosis are rare: Johnstone *et al* (1986) found advantage for active drug over placebo (58 *v.* 70%) but the effect size was not large; relapse occurred in nearly two out of three 'active' patients and occupational outcome was better for many of those receiving placebo. There is, of course, the perennial problem of determining who will fare well without drugs and who will fare poorly in spite of them. The use of a targeted medication strategy in the context of a low-dose regime has shown that the rate of relapse over two years can be halved without apparently any detrimental effect associated with low doses (approximately 5 mg fluphenazine decanoate every two weeks; see Davis *et al*, 1993). Such a strategy would seem ideally suited to first-episode patients and deserves evaluation, particularly as such a strategy could enhance medication compliance, if it reduced side-effects (Hoge, 1990). Social isolation is a robust predictor of early relapse (Ram *et al*, 1992): the provision of a keyworker may help to mitigate this and facilitate social engagement. Family intervention has only minimal impact on early relapse (Linszen *et al*, 1996), probably because of the fluid nature of family attitudes during this period. The co-morbidity of drug misuse and psychosis is well known and in one study the use of cannabis was linked to a two-fold increase in early relapse (Linszen *et al*, 1994), suggesting the potential for an evaluation of drug counselling.

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Psychosocial recovery

Concepts of insight, denial and non-compliance have tended to govern thinking about the individual's response to psychosis. Placing the individual at the centre of our thinking locates psychosis as a 'life event' which can threaten self and identity, valued goals and roles and social status. This may be understood as a set of appraisals or beliefs involving *loss* of social roles, *entrapment* in psychotic illness and symptoms, *causal attribution* (self *v.* disease) and *self-evaluative beliefs* (failure, worthlessness), which can be challenged and tested using cognitive therapy. Psychoeducation should encourage blame-free acceptance of illness, inculcation of strategies to promote control of illness (e.g. by recognising and responding to early warning signs of relapse or learning to control voices); and highlighting and challenging the social stereotypes of mental illness, using a group format to rebut the challenge to social status (Drury *et al*, 1996). First-episode psychotics are young people who value autonomy, employment and youth culture, from which psychosis can tend to exclude them. We believe it is important to take these values seriously and take a positive approach to meeting these aspirations; for example, a vocational outcome should be a central aim of the recovery process.

Treatment resistance

The long-term stability of symptoms after three years reinforces Wyatt's (1995) notion that treatment resistance is apparent within the early phase and should therefore be an explicit target of early intervention. Targeting treatment-resistant symptoms at this point with modern techniques (atypical neuroleptics or cognitive therapy) would be predicted to substantially reduce long-term symptoms; our recent trial of cognitive therapy in acute psychosis (Drury *et al*, 1996) offers one strategy to reduce early treatment resistance.

CONCLUSIONS

The main approaches to the treatment of psychosis have yet to address the special importance of age and/or stage of illness. We have argued for a complementary approach, which focuses on the early phase of psychosis, and propose intervention strategies dedicated to what we have argued could be a critical period both biologically and psychosocially. The possibility of preventing the development of some of the secondary disability and handicap, together with a recognition that young people at this phase of life may have special needs in the context of a serious mental illness, justifies a separation from patients with more established illnesses; such 'streaming' would facilitate better understanding of their needs, the development of specialised therapeutic interventions and the development and evaluation of preventive approaches. Research will need to demonstrate that such intervention not only improves outcome, but, if it is indeed a 'critical period', then, when the grip is relaxed, any changes will be maintained and not followed by a return to baseline.

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