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# "A stitch in time"... the scope for preventive strategies in early psychosis

**Abstract** Preventive endeavours in psychotic disorders have been hampered by many obstacles over the past century. One important barrier has been the corrosive pessimism which has attached to the treatment prospects for schizophrenia in particular since the time of Kraepelin, and the isolation of this disorder from progressive models of preventive intervention which operate in general health care. This paper outlines a rationale, logic and model for realistic preventive efforts in early psychosis, focusing on indicated prevention in the pre-psychotic phase and early intervention from the onset of frank psychotic symptoms through the early years of illness. The latter is discussed through a series of clinical challenges which will be familiar to clinicians during this phase of illness. The existing evidence is introduced and the gaps indicated. It is argued that the case for a preventive approach possesses more than face validity alone, and that momentum is building for a significant paradigm shift. If this to be securely based and durable, it will need to become increasingly evidence based and demonstrate cost-effectiveness. The nature of the evidence and the strategy for its assembly are also considered.

**Key words** Prevention · Psychosis · Schizophrenia · Prodrome

"It is of the greatest practical importance to diagnose cases of dementia praecox with certainty and at an early stage" (Kraepelin 1896/1987, pp 13–24).

"The sooner the patients can be restored to an earlier life and the less they are allowed to withdraw into the world of their own ideas, the sooner do they become socially functional" (Bleuler 1980/1987, pp 59–74).

## Introduction

The notion of prevention in psychotic disorder has a long yet tenuous pedigree. In one sense, drawing on the ideas of the early pioneers of the schizophrenia field is like quoting from the Bible. One can usually find something to support one's perspective, even if it is essentially out of sympathy with the original author's main thesis. Kraepelin and Bleuler, observing the scene during the preneuroleptic era, were heavily and understandably influenced by the devastation wrought by the unchecked erosive force of the disorders they witnessed. Kraepelin in particular, at least initially, through his concepts and classification, became the architect of an entrenched pessimism which continues to exert its influence. Yet even he hints at some preventive implications of early diagnosis.

Sullivan also observed many years ago: "The psychiatrist seems too many end states and deals professionally with too few of the pre-psychotic" (Sullivan 1927). This is undoubtedly true of a range of mental disorders not merely the psychoses; nevertheless, the surprisingly prolonged delays in treatment for first-episode-psychosis patients (Loebel et al. 1992) and the concentration of those patients with the most persistent and disabling forms of illness in services mean that the sensitivity of the average clinician to the issues and preventive possibilities surrounding the onset phase of illness is severely blunted. Such a distortion of clinical experience is closely related to the clinician's illusion (Cohen and Cohen 1984), a phenomenon of which Bleuler (1908/1987) in particular was well aware: "Only a very small proportion of all schizophrenics come under observation in our institutions, and which it comes to individual groups of the illness we see only a selective sample. For example, patients who recover after one attack are observed only during that initial attack".

The corrosive influence of this illusion upon therapeutic optimism can be readily seen in everyday clinical practice. McGlashan (1996) has recently illustrated the common effect upon the morale of the treating clinician of such experience: "I remain convinced that with them (refers to specific patients) I came upon the scene too late; most of the damage was already done. I remain convinced that with schizophrenia in its moderate to severe form, our current treatment efforts amount to palliation and damage

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control". He goes on to indicate how this experience can paradoxically help to provide momentum for a more preventive approach.

Indeed, as the concept of schizophrenia enters its second century, we are at an unusually favourable point in the understanding and clinical care of people with psychotic disorders. A building sense of optimism is heightened by the realisation that these developments are long overdue. Throughout the past hundred years, dark clouds of pessimism have cast a shadow over the prospects for people developing these disorders, particularly schizophrenia. While these originated in the reality of the serious prognosis of these illnesses at that time, prior to the discovery of effective treatments pessimism was deeply entrenched by the flawed conceptual framework devised by Kraepelin (McGorry et al. 1990; Boyle 1990). The fundamental conceptual error which was exposed during Kraepelin's own lifetime and led him to alter his opinions was the decision to allow course and outcome to substitute as an interim validating criterion in place of pathophysiological criteria. Unfortunately, the nosological model has survived essentially intact and has created a barrier to research progress, preventive efforts and good clinical care (McGorry et al. 1990). The best efforts of generations of researchers and clinicians alike have been unable to disperse the clouds of pessimism, though some sunshine has occasionally pierced the gloom with significant, often serendipitous advances such as the discovery of neuroleptic medications. Unfortunately, the clouds always regathered, since even our effective weapons, ranging from drug and psychological therapies to systems of health care, have generally been crudely or inexpertly deployed. At best, treatment has been less effective than could otherwise have been the case, and at worst it has created additional iatrogenic misery, morbidity and mortality. Examples of this include the past abuses of psychosurgery (Sachdev and Sachdev 1997; Valenstein 1986), the still widespread use of neuroleptic medications in excessively high doses (Lader 1997), the use, beyond their expiration date, of forms of psychotherapy which were ineffective in psychotic disorders (Jackson et al. 1996), and which inhibited the development of more useful and humane approaches, and the warehousing of patients (Scull 1979). The latter has been followed more recently by a well-intentioned but, in most countries, poorly planned, irresponsibly executed and inadequately funded process of deinstitutionalisation (Bachrach 1994). In many respects, the history of treatment and care of our most serious mental disordes has mirrored the natural history of the disorders themselves, and reinforced the pessimistic aura surrounding them.

Although the neuroscientific revolution has not yet truly delivered in terms of enhanced treatments, the adoption of a clinical epidemiological perspective highlighting the preventive opportunities which exist, combined with encouraging advances in psychopharmacology and psychosocial treatment, has begun to create a climate of optimism. The limitations of our societies, our concepts, our cultures of care and of the capacities of clinicians have combined to retard and prejudice the recovery process for those (mainly) young people who developed these potentially serious illnesses for many decades. As the services designed for the preneuroleptic era gradually dissolve away, we have the chance to replace them, in optimal circumstances, by better-funded and more efficient models in tune with the late twentieth century and the needs of community-based patients and their families. There have been several false dawns and the preventive seeds sown by Sullivan (1927) and Cameron (1938) did not immediately germinate within a barren ecosystem of care. Even the optimism and reform of the 1960s bypassed and ultimately failed people with schizophrenia and other serious mental illnesses. The question immediately arises: Is the current optimism more securely based? We will need to interrupt the familiar cycle of enthusiasm followed by dissipation and disappointment. Let us consider the logic, the evidence and future directions.

Early intervention in psychotic disorders is increasingly seen as having the potential to produce better outcomes in these potentially disastrous conditions, which generally strike during the critical developmental phase of adolescence or early adulthood (Wyatt 1991; Birchwood and MacMillan 1993; McGlashan 1996; Birchwood et al. 1997). This idea has logic and a substantial amount of circumstantial evidence to support it, but, to date, relatively little direct evidence. The logic translates directly from mainstream preventive medicine (Mrazek and Haggerty 1994), from which this zone of psychiatry has been effectively insulated, and rests on several pillars. Firstly, delays in initiating treatment are often prolonged, and the duration of untreated psychosis (DUP) is associated with substantial functional decline, treatment resistance and increased subsequent rates of relapse (Helgason 1990; Wyatt 1991; Loebel et al. 1992; Jones et al. 1993; Johnstone et al. 1986). Secondly, intensive and sophisticated intervention following detection during the early phase of the illness could minimise iatrogenic damage and more effectively promote recovery (McGorry et al. 1996), which frequently occurs later anyway. This is potentially critical, since such late recoveries are often seriously incomplete and seem to occur despite treatment efforts. Much of the damage is to the person's personal development, social environment and lifestyle, and is very difficult to repair after years of neglect. This is particularly poignant in people who have had a dramatic late remission in response to clozapine. Their experience is analogous to that depicted in "Awakenings" (Sacks 1982) and highlights the distinction between the core illness and its consequences. Thirdly, targeting failure of initial remission or early treatment resistance with recently developed enhanced drug and psychosocial interventions could result in a lower rate of prolonged treatment resistance, relapse and disability (Edwards et al., in press). Fourthly, maintaining remission and preventing or limiting relapse, by reducing the total duration of active psychosis and its deleterious consequences, is a post-psychotic analogue of reducing DUP (Curson et al. 1986; Johnson et al. 1983). In addition to improving outcomes for first-episode patients and those

moving through the "critical period" (Birchwood and MacMillan 1993) of the first several years after onset, it may even be possible to conceive of and offer interventions for those people who are probably experiencing the prepsychotic phase of illness. This form of preventive intervention, known as *indicated prevention*, could be closer than we think.

I now propose to briefly outline a framework for preventive interventions in psychosis and build upon this to further examine the logic and the evidence relating to the preventive clinical foci listed above.

## A practical framework for preventive intervention in psychosis

Since preventive intervention around the onset of frank psychosis has been regarded until recently as beyond our present capacities (McGlashan and Johannessen 1996), it is important to be clear about the conceptual basis for approaching it. In particular, the notion of treatment even prior to the onset of fully fledged schizophrenia attracted a previous generation of clinicians (Sullivan 1927; Cameron 1938; Meares 1959), but the conceptual and practical obstacles have not hitherto been adequately addressed.

We have examined the conceptual issues in detail elsewhere (McGorry and Singh 1995; Yung and McGorry 1996) in relation to the prepsychotic phase in schizophrenia, and they are summarised below. It is useful before doing so to consider more generally the spectrum of intervention in mental disorders (Mrazek and Haggerty 1994). Broadly, interventions can be classified into prevention, treatment and maintenance (Fig. 1).

Within prevention, drawing on the ideas of Gordon (1983), Mrazek and Haggerty subclassify interventions as universal, selective and indicated. *Universal* preventive interventions are targeted to the general public or a whole population group that has not been identified on the basis of individual risk, e.g. use of seat belts, immunisation and prevention of smoking. *Selective* preventive measures are appropriate for subgroups of the population whose risk of becoming ill is above average. Examples include special immunisations such as for people travelling to areas where yellow fever is endemic and annual mammograms for women with a positive family history of breast cancer. The subjects are clearly asymptomatic. *Indicated* preventive measures apply to those individuals who on examination are found to manifest a risk factor that identifies them, individually, as being at high risk for the future development of a disease, and as such could be the focus of screening. Gordon's (1983) view was that such individuals should be asymptomatic and "not motivated by current suffering", yet have a clinically demonstrable abnormality. An example would be asymptomatic individuals with hypertension. Mrazek and Haggerty (1994) adapted Gordon's concept as follows:

> "Indicated preventive interventions for mental disorders are targeted to high-risk individuals who are identified as having minimal but detectable signs or symptoms foreshadowing mental disorder, or biological markers indicating predisposition for mental disorder, but who do not meet DSM-III-R diagnostic levels at the current time" (p. 494).

This major definitional shift allows individuals with early and/or subthreshold features (and hence a degree of suffering and disability) to be included within the focus of indicated prevention. Some clinicians would regard this as early intervention or an early form of treatment; however, the situation with these individuals is not so clearcut. Whereas some of these cases will clearly have an early form of the disorder in question, others will not. They might, however, have other less serious disorders, and many individuals subthreshold for a potentially serious disorder such as schizophrenia may have nevertheless crossed a clinical threshold where they either require or request treatment. Eaton et al. (1995) have warned that the absence of firm data on the validity of the classification system enjoins us to be careful about conceptualising the process of disease onset. Parenthetically, many of the issues discussed here are relevant to defining caseness and

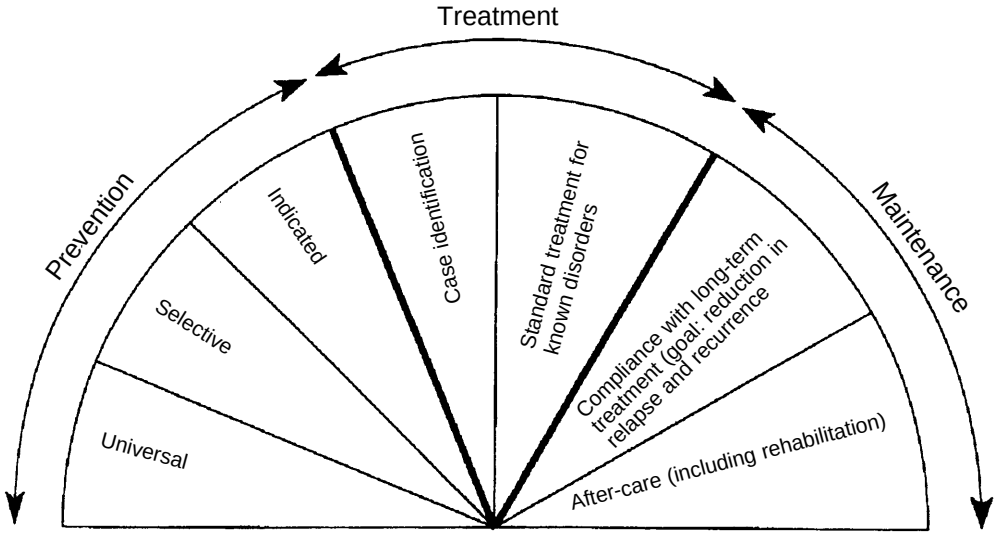


**Fig. 1** Section of preventive intervention

thresholds for initiating treatment in a range of mental disorders (Mrazek and Haggerty 1994). In schizophrenia, the threshold has been set high and requires not only the presence of positive psychotic symptoms, but also a 6-month duration of illness. This is due to a combination of historical factors, a degree of therapeutic nihilism and the social implications of the diagnosis. The height of the bar is set at a much lower level for other disorders, e.g. depression, where the above factors do not apply. The high threshold may have contributed to treatment delay (Loebel et al. 1992) and hence added to the risk of poor outcome. It may therefore be worthwhile to question the clinical threshold for treating "psychosis spectrum disorders". Ultimately, however, although we might not agree with the threshold set by DSM or ICD for receiving a diagnosis of a mental disorder such as schizophrenia, if this is the current criterion for "caseness", then an intervention aimed at preventing the further evolution of symptoms such that the threshold is reached does strictly meet the definition of indicated prevention, since it is aiming to reduce the occurrence of new cases. It we can successfully argue for interventions at this phase or level of symptoms and disability, then by current convention it should be regarded as indicated prevention and not (early) treatment per se, though this distinction may be of dubious relevance to the patient. In any case, Eaton and coworkers (1995) have emphasised that the implications of offering a preventive intervention are different from offering treatment for a fully fledged disorder, since there is a chance that, in the first instance, the person may not go on to develop the disorder in question.

Even though it is currently only just within reach, Mrazek and Haggerty (1994) state very clearly that they view the cusp of the onset phase as the current frontier of preventive effort in schizophrenia:

> "The best hope now for the prevention of schizophrenia lies with indicated preventive interventions targeted at individuals manifesting precursor signs and symptoms who have not yet met full criteria for diagnosis. The identification of individuals at this early stage, coupled with the introduction of pharmacological and psychosocial interventions, may prevent the development of the full-blown disorder" (p. 154).

Moving beyond purely preventive interventions, the framework focuses on case detection, and this involves the potential for early intervention, a form of secondary prevention under the older conceptual framework. Early intervention can be further subdivided into a series of elements, each with the potential to contribute to a secondary preventive effort. Both indicated prevention and early intervention are now considered in more detail, as dual foci for preventively oriented intervention in psychosis.

## Focus 1: Indicated prevention in psychotic disorder

What are we waiting for?

Several authors have highlighted the potential for people who ultimately develop a schizophrenic disorder to have been identified as ill prior to the onset of frank psychotic symptoms (Sullivan 1927; Cameron 1938; Meares 1959). Until recently, it was believed that given the non-specificity of prepsychotic features (Sullivan 1927), a prospective approach to the study of onset in psychosis was impossible (Häfner et al. 1995). Bleuler (1911) alluded to this as follows:

> "Thus when we speak of the initial symptoms of schizophrenia, we must limit ourselves to the first symptoms which come to notice. All too often we do not know the first real manifestations".

Häfner and colleagues (1995) have made a valiant effort to overcome this obstacle, yet residual problems clearly exist with a retrospective approach (Yung and McGorry 1996). With the advent of the framework of Mrazek and Haggerty (1994), the notion of sequential screening (Derogatis et al. 1992) or a "close-in" research strategy (Bell 1992) and the epidemiological work of Eaton and coworkers (1995), we are now able to more clearly formulate how to go about such an endeavour, and to appreciate the potential pitfalls. In retrospective studies of first-episode psychosis (e.g. Häfner et al. 1995; Yung and McGorry 1996), only those cases who have developed a psychosis are included in reconstructions of the prepsychotic phase. Hence, the predictive power of particular clinical features cannot be assessed. The prepsychotic features are described as prodromal since in this sample they are always followed by psychotic symptoms. Such features are thus regarded as the earliest manifestations as the disorder itself (even though at that point they would be below threshold for diagnosis) and hence interventions would be seen as variants of secondary prevention. Many clinicians, extending as far back as Bleuler (who actually eschewed the notion of prodrome because he believed that these early, yet highly variable features which he meticulously described were merely the initial phases of a presumably inevitably progressive disorder; Bleuler 1911) considering this clinical issue have difficulty seeing what problems could arise in treating such patients as if they have schizophrenia. Indeed, this is exactly what Ian Falloon and colleagues did in Buckingham in 1980s (Falloon 1992; Falloon et al. 1996). However, looking at the issue from a prospective standpoint reveals the dilemma. The clinical features identified retrospectively in first-episode samples are mostly non-specific (Yung and McGorry 1996; McGorry et al. 1995) and have only a limited predictive power in relation to subsequent psychosis (and thus the diagnosis of a full-fledged disorder). We have suggested the term "at risk mental state" (McGorry and Singh 1995) to denote this state of affairs, whereas Eaton (1995) has developed the notion of "precursor" features for the same purpose. These terms indicate clinical features which can be assigned a finite estimate of both relative and attributable risk for the full-fledged disorder. This means that they have a looser link with the full-fledged disorder than the notion of "prodrome", and allow for a significant false-positive rate. Drawing on the "close-in" strategy referred to above and the conceptual tools of clinical epidemiology (Kraemer et al. 1997), we have sought to iden-

tify additional risk factors and markers to improve our predictive capacity. This strategy has great potential to overcome some of the weaknesses of traditional high-risk research while retaining genuine preventive credentials.

What do we know thus far? Well, we now know that it is possible to identify and engage a sample of young people at greatly enhanced risk of early transition to psychosis. Our early findings indicate that 40–50% of such individuals identified via operational clinical criteria will develop a full-fledged psychotic disorder within 12 months of detection (Yung et al. 1996; Yung et al., in press). Admittedly, those who do make the transition are probably an unrepresentative subset of the universe of first-episode psychosis. It is also likely that some of those who do not make an early transition are nevertheless still covertly vulnerable to psychotic disorder and constitute what we have termed "false false positives" (Yung et al. 1996). This is the possibility with which the traditionalists have a problem, because they believe that schizophrenia is characterised by inevitability. Murray has characterised this loosely as "doomed from the womb" (Murray 1987). Such a model implies a "sufficient" or even a "necessary and sufficient" causal model as in Huntington's disease, a scenario we are already confident does not exist in most cases of schizophrenia.

This is a fundamental logical flaw underpinning the thinking of many clinicians, and even the intervention strategy in the Falloon study (1992), and sees the patient inevitably programmed to develop the disorder (an analogy would be with certain forms of computer virus). The alternative is a risk-factor model where a mix of potential contributory causal factors will influence the expression of the disorder. Within such a model it may ultimately be possible to identify and influence malleable causal risk factors to prevent the full expression of the disorder. In the meantime, with more accurate characterisation of risk and high-level prediction, we are approaching the stage where more intensive treatment, including time-limited, low-dose neuroleptics and psychosocial interventions, could be evaluated in a carefully controlled manner in potentially prepsychotic individuals. The latter could involve a blend of stress reduction, lifestyle restructure and enhanced coping, using modern cognitive-behavioural interventions. With this phase, however, as argued elsewhere (McGorry et al. 1996; Vaglum 1996), we simply do not yet know that interventions developed for one phase of illness are optimal or even appropriate for another.

Essentially, the answer to the question, "Why wait?", is that we have to take account of the risk/benefit ratio for patients, including issues of stigma, and carefully evaluate the optimal duration of treatments to be offered at this phase. Some people have expressed an appropriately cautious view that it could be potentially iatrogenic to treat at this phase, particularly when it comes to applying a diagnosis and using neuroleptic medication. Others have emphasised the imperative to "do something" when it is clear that a young person is in trouble, with their lifestyle and prospects collapsing around them, as, in a substantial proportion of cases, they slide into a serious psychotic disorder. This is an exciting area with huge potential for patient care and cost-effectiveness, and hence for further exploration. It is likely to yield interesting new data from a number of centres. Such data will be an essential foundation for an evidence-based clinical approach.

## Focus 2: Early intervention

### What's the hurry?

A series of recent studies have highlighted the relationship between the duration of untreated psychosis and clinical outcome in psychotic disorders (Helgasson 1990; Wyatt 1991; Loebel et al. 1992; Larsen and McGlashan 1996; McGorry et al. 1996). This is not a new idea but dates back to the 1920s (Sullivan 1927; Cameron 1938), and the delays in recognition were also described by Bleuler (Bleuler 1991). What has surprised and shocked many people, however, is the extent of the delays in treatment, even in developed countries with more than adequate psychiatric services (Larsen and McGlashan 1996). Even after the person has developed a full-fledged psychosis, the duration of the delay in obtaining treatment averages a year or even more in such developed countries. There is strong face validity to the idea that such a prolonged delay in treatment during the critical developmental phases of adolescence and early adult life could profoundly and negatively influence the capacity for psychosocial recovery, even if the biological disturbance could be successfully treated. There is an additional theory that the biological change may itself prove less responsive to treatment if it is present for a long period before the person is exposed to antipsychotic medication, and this is supported by several lines of evidence (Wyatt 1991, 1995).

Interestingly enough, despite this face-validity argument, the lines of evidence which provide partial support for the strategy and the enthusiasm generated in many parts of the world for interventions aimed at shortening this period of untreated psychosis, there is a significant degree of scepticism. Why should this be so? Firstly, it has its roots in the Kraepelinian pessimism referred to above and has been nurtured by more recent incarnations of this, such as the "doomed from the womb" notion, an unnecessarily pessimistic interpretation of the neurodevelopmental model of schizophrenia (Murray 1987; Weinberger 1987). Secondly, apart from the Camarillo study (May et al. 1976), which has its flaws, and others reviewed and reanalysed by Wyatt (1991, 1995; Wyatt et al. 1997), there are no contemporary high-grade RCTs comparing timely vs delayed intervention. Nevertheless, even those who are sceptical, or are attempting to remain so, of the early intervention paradigm, regard it as unethical to delay intervention for a first episode of psychosis (McGlashan and Johannessen 1996). This is a revealing clue to the depth of conviction of such scepticism! Other sceptics argue that brief psychoses with a short DUP which have a good outcome are somehow "a different

beast" with a different psychopathological basis and an intrinsically good prognosis. This is a variant of the notion that if you recover you did not really have schizophrenia. It is difficult to argue with such circularity and fatalism which derives, as argued, from Kraepelin's legacy, and which would find little support in other medical disciplines, where aetiopathology and outcome have been separated, e.g. nephrology.

On the other hand, a genuine reason for scepticism derives from the possibility that the relationship between DUP and outcome is at least partially explained by a third factor which contributes both to an increased risk of treatment delay *and* poor outcome, at least in an important subgroup. This could most likely occur via certain clinical features, e.g. negative symptoms of insidious onset, or persecutory delusions, which might be not only markers of poorer outcome but also mediators of delayed treatment. In light of this possible alternative explanation for the link, it therefore seems worthwhile, as McGlashan (1996) has done, to look at alternative ways (other than the RCT of delayed vs timely treatment) of testing the hypothesis that reduction of DUP results in an improvement in outcome (McGlashan 1996). Successful experimental manipulation (reduction) of the DUP variable in an experimental sample while eschewing such early detection efforts in a control sample would enable conclusions to be drawn concerning the degree of influence of this factor on course and outcome. Such samples would need to be geographically separated, and randomisation, at least at the level of the individual, would be impossible. There may be alternative possibilities, e.g. cluster randomization, though even here there would be obstacles (P. Jones and S. Lewis, pers. commun.).

## What's so special about the first episode?

This question turns of the nature and intensity of interventions offered at this phase of illness, and raises the question of how different they need to be from treatment approaches derived and delivered in later phases and more chronic subsamples of patients. Even with treatments essentially similar to those employed with patients with established illness, remission rates are excellent in first-episode psychosis, at least as far as positive symptoms are concerned (Lieberman et al. 1993). However, when one considers neurocognitive functioning, psychological recovery, relapse rates and functional outcome, the short-term prospects are probably much more guarded. This is where a careful consideration of the needs of patients and their families is critical. We have argued elsewhere that the treatment of first-episode and early-psychosis patients in general requires a highly modified approach in contrast to that offered in later phases of disorder (McGorry 1992; Edwards et al. 1994; McGorry et al. 1996). These modifications are required across the whole spectrum of treatment and challenge therapeutic errors derived from the clinician's illusion referred to above. Thus, the approaches relevant to the subgroup of cases with definite relapsing and disabling illnesses, including complex comorbidities, may be unhelpful to younger early psychosis patients. Examples of this include the nature, dose and sequence of drug therapies (McEvoy et al. 1991; McGorry and Kulkarni 1994), the content and style of psychological approaches (Jackson et al. 1996; Jackson et al., in press; McGorry et al., in press) and the approach with relatives and peers. More detail on the rationale and content of these therapeutic interventions is provided in the comprehensive Early Psychosis Training Pack (McGorry and Edwards 1997) and in a forthcoming text (McGorry and Jackson, in press).

It must be acknowledged that there is relatively little definitive evidence for the above contentions to date, apart from the data reported in McGorry et al. (1996). In this paper, significant improvements in outcome were reported over the first year following entry into treatment with a first episode of psychosis for patients treated with an enhanced phase-specific program of intervention. Patients were carefully matched on key variables known to influence outcome with historical controls treated in an earlier but less specialised program. The weaknesses of this study relate to the lack of randomly assigned or concurrent controls and hence the findings are not definitive; however, the magnitude of the effects were substantial. This study has also demonstrated substantial improvements in cost-effectiveness for the new model over the former one (McGorry et al. 1996). The improved outcomes appeared more likely to derive from more intensive and specific treatment after entry (McGlashan 1996) rather than reductions in DUP, which were relatively modest and difficult to interpret. Clearly, however, more rigorous testing of the notion that such specific phase-related interventions are more effective is required, and this should occur via a combination of specific efficacy-oriented RCTs and broader "real world" effectiveness studies including a mandatory focus on cost-effectiveness.

## Delayed remission? Treatment resistance? Why not wait and see!

A series of authors dating back to the time of Kraepelin concur that a plateau of impairment and disability is reached on average around 2–3 years following illness onset (Birchwood and MacMillan 1993; McGlashan and Johannessen 1996). Whereas this may still vary from patient to patient, and such variation is enhanced by a lack of clarity concerning the timing of illness onset, some patients may have reached this plateau by the time of first treatment; for others, there is still a time window, labelled by Birchwood the "critical period", in which at least prevention of further damage and, for some, at least a partial reversal of the process, may occur (Birchwood and MacMillan 1993). This could be conceptualised as a blend of firstly turning around a declining situation through aggressive biopsychosocial treatment – in other words, a short-term "rescue operation" – and secondly, over a longer period, maybe several years, mounting a stable "holding op-

eration" in relation to the persons's lifestyle, relationships and vocational future.

It has been argued (Edwards et al., in press) that it is important not to withhold, either by neglect or design, the full spectrum of effective treatments until treatment resistance has been confirmed and even entrenched, and the plateau of disability reached. This includes the early use of the newer antipsychotics and, following these, much earlier use of clozapine (Liebermann 1996), and of the emerging cognitively oriented forms of psychological intervention, which appear to be able to accelerate recovery from acute psychosis (Drury et al. 1996) and to reduce treatment resistance (Fowler et al. 1995). Although the latter interventions will also need to be modified for use at this phase of illness, there seems to be little logic in withholding them from patients who are slow to respond, and none in those with a clearcut treatment resistance. It may also be worthwhile to broaden the definition of treament resistance at this phase to include protracted or slow recovery, and also persistent neurocognitive impairments and negative symptoms, rather focusing exclusively on persistent positive symptoms. We have termed this treatment endeavour "recovery plus" to avoid stigmatisation and minimise early pessimism for clinicians and patients. One could well argue on ethical grounds that the question "why not wait and see?" should be replaced by an opposite one, i.e., "why wait?" Lieberman (1996) has put these contentions in the form of hypotheses which is helpful from a research standpoint. However, I would suggest that the burden of proof should be such that those advocating delays in more aggressive intervention should provide evidence that such an approach can be clinically and ethically justified. In any event, this is a rich arena for future efficacy studies using careful yet inclusive RCT methodology; however, it will probably require a multi-centre approach given the low prevalence of treatment-resistant cases, even broadly defined, in first-episode samples.

### Relapse prevention: Is it vital?

Elsewhere I have argued that to pursue the prevention of relapse as the *sole* goal of treatment, rather than as a key intervening variable influencing the overall quality of life of the patient and his or her family, can be limited and counterproductive (McGorry 1995). Many treatment studies have adopted such a narrow approach, the logical extension of which would be to overtreat all patients with high-dose neuroleptics and excessively restrictive clinical practices. Indeed, such a pattern of treatment is all too common in routine clinical care. The trade-off between maintenance neuroleptic dosage/relapse prevention and quality of life has recently been illustrated in the Treatment Strategies in Schizophrenia study (Schooler et al. 1997). On the other hand, based on the same logic as reducing the duration of untreated psychosis, it is probably equally important to reduce the proportion of time following entry to treatment that the patient suffers from ongoing psychotic symptoms. This duration of psychosis during treatment is contributed to by the time period to initial remission, i.e. the degree of initial treatment resistance, the frequency of psychotic relapse, and the degree of subsequent or emergent treatment resistance.

Once again, the frequency of relapse is another feature which appears to peak during the early years following onset (Eaton et al. 1982), particularly in those with a long DUP (Johnstone et al. 1992). Furthermore, there is also the suggestion that those who relapse demonstrate an emerging resistance to treatment as evidenced by an increasing time to remission with increasing episode number (Lieberman et al. 1996). Now this could be due to the fact that those with more severe treatment-resistant illness also have a higher vulnerability to relapse (and a long DUP); however, such emergent treatment resistance might be preventable by reducing the frequency of relapse (as well as the DUP; see above). Despite the increasing time to remission in later episodes than the initial one noted by Loebel et al. (1992), it is still not clear whether the fact that multi-episode patients require somewhat higher doses of neuroleptics for a response than first-episode patients (McEvoy et al. 1991) is due to the development of treatment resistance, the development of tolerance to neuroleptics, the concentration of the subsample of treatment-resistant patients in multi-episode samples over time, or a combination of these factors. Once again, all of these questions should be the focus of ongoing research. It seems obvious that *frequent* relapse is likely to be deleterious to the outcome of psychotic disorder and relapses are inherently risky and undesirable; hence, the question posed may once again seem like a paper tiger. However, determining whether the vulnerability to psychotic relapse is still present in the individual patient is an important task in the management of the early phases of psychosis, i.e. which patients can safely come off medication and when. Furthermore, the patient who remains relapse prone ideally needs to be convinced *personally* by whatever means that prophylactic or maintenance treatment is really necessary. In some cases this only occurs when relapse is directly experienced; in others, of course, even this fails to convince. In addition, future research needs to focus on the impact relapse has upon the illness process, the person and their families.

Finally, other aspects of persistent or intermittent comorbidity should be brought into the focus of research and treatment, which has hitherto focused largely on positive psychotic relapse.

## Conclusion

The burgeoning interest in the potential for early intervention in psychotic disorder has led to a series of seminal international conferences in recent years, many landmark publications and even the establishment of an international association to promote and encourage further advances in this area of psychiatry. Although it is most important not to inhibit rational enthusiasm, constrained for so long by corrosive scepticism, it is timely to sound a cautionary note. Many of the most potent and far-reaching

changes in service provision have been driven by powerful peripheral forces, such as economic imperatives (managed care) or ideological policies (deinstitutionalisation), and these have had "juggernaut" effects which continue to pose great risk to patient care. It is theoretically possible that early intervention, if implemented in "bushfire" mode, could come to be seen in a similar light. One way in which it could become rapidly discredited is that, if not implemented in a planned, staged, and targeted manner, it might not prove to be cost-effective, hence causing financial erosion of other valuable services. If this were to occur, the cause of prevention and early intervention would be greatly set back.

All of the exciting developments and the strategies which flow from the information outlined above ultimately must be based on sound evidence which can only arise from well-conducted clinical research. This kind of statement seems to have a pious ring to it, and certainly, in many of these areas the best evidence may follow, rather than drive, change. Some health care systems do not seem to realise this and have been paralysed in mid-reform, obsessively waiting (in vain) for rock-solid evidence to support their reform agenda. Hence, on the one hand, it is important to avoid such paralysing crises of confidence and *do something*! On the other hand, implementing changes at a pace whereby they can be evaluated and modified is sensible. Such a strategy does not need to paralyse, but may guide and provide escape routes from inappropriate pathways. This is especially true since it is becoming clearer that clinically based research, supported by neuroscientific advances, *can* strongly catalyse change in service delivery. This has certainly been our local experience.

The rise of the evidence-based paradigm is a welcome development, particularly if a range of evidence can be included to guide clinical practice. The potential of the early intervention strategy in turn creates additional responsibility for all of us to conduct sound research and evaluation, and not to overstate or oversell the results. To do otherwise could jeopardise the strategy and potentially consign us all to a further era of pessimism. The stakes are very high. The rise of a new preventive paradigm in many parts of the world, particularly in Australasia, Scandinavia, Western Europe and Canada, is very encouraging. The paradigm is attracting the interest of established and highly competent researchers who have clearly laid out blueprints for future research (Wyatt 1991; McGlashan 1996; Wyatt et al., in press). Large-scale intervention projects have been generously funded in Norway, Denmark, Sweden, the Netherlands, Australia, New Zealand and Canada, and should provide important new knowledge.

What will be required ultimately, however, is the development of funding models which support a dramatic increase in and shift of resources to the earlier phases of disorder, without disenfranchising those with more established illness. This will ultimately depend on these preventive strategies proving genuinely cost-effective and interim "hump" funding being available to cover a transitional period. This will be difficult in the era of economic rationalism and managed care, the effects of which are being felt well beyond their epicentre in the United States. These polices have the capacity to become the new clouds to shut out the preventive sunshine. Paradoxically, if their originators and those responsible for implementing them have the skill and foresight to think beyond the bottom line of the single financial year, then what is currently a threat could be turned into a synergistic force. It is likely that resources expended during the early phases of illness will prove cost-effective not only in the short term, but over the long haul for those patients who do require long-term care. The danger with this argument is that it could be implemented prematurely across the board, and even misused to support cost cutting which resulted in extensive neglect in the context of deinstitutionalisation. Clearly, patients with continuing vulnerability and or disability beyond the early phases of illness also require sophisticated and expert continuing care. This is one of the characteristics of this group, namely that effective treatment of some kind must be continued indefinitely (McGlashan and Johannessen 1996). It is hoped that the size of this group and their level of disability and need for care could be substantially reduced by earlier and intensive intervention. Perhaps the intensity of treatment could ultimately be relaxed in many people after the critical period (Birchwood et al. 1997), but we do not know this yet.

If this is to occur, it will need to be guided by extensive clinical research on at least two levels. The first of these is *efficacy* studies, essentially randomised controlled trials, to develop and refine strategies for early detection, and the various elements of treatment, namely drug therapies, psychological treatments and psychosocial interventions, as appropriate for the specific phase and developmental stage of the patients. The second is at the level of systems of care, including studies of *effectiveness*, which are intended to test the real world impact of efficacious treatments. RCTs have major limitations in this area of clinical research and need to be rethought and supplemented by a range of evidence (Thorneycroft 1996; Aveline 1997). Research and evaluation will also be crucial to enable effective systems for a range of societies and cultures to be developed. It is well known that many efficacious treatments prove less than optimally effective in "real world" situations for a variety of reasons. Examples include lithium prophylaxis in biopolar disorder and family interventions in schizophrenia. Hence, early intervention must also make sense to consumers, carers, to the average clinician, and to communities around the world, have a good "reach", and be properly funded to enable better quality of life to be achieved for those vulnerable to psychotic disorders. It is also a paradigm which, as this volume illustrates, has a potential reach across the full spectrum of potentially serious mental disorders.

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