The recognition and optimal management of early psychosis: an evidence-based reform

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The quality of health care for schizophrenia and other psychoses around the world remains unacceptably poor (1-3). Serious under-resourcing of mental health care is a major factor in most countries, but even when this is less of a problem (e.g., parts of Western Europe), there is still a large gap between efficacy (what can be achieved under optimal conditions) and effectiveness (what can be achieved under routine conditions). Typically, Falloon recognised this in conceiving the optimal treatment project (OTP) for schizophrenia (4). Many factors are responsible for this efficacy-effectiveness gap, including community-wide stigma and pessimistic beliefs about outcome, the low status of psychiatry in the health care system with consequent under-funding and poor workforce quality, the failure in the developed world to fully implement, resource and sustain the reforms associated with deinstitutionalisation, and the lack of translation of genuine advances in treatment into clinical settings (5). In fact, reform and the evidence base actually are not as closely related as might be expected, and while the former tends to lag well behind the latter, sometimes the opposite occurs based on fashion or enthusiasm alone. In psychiatry, given our fragile position in the health care system and a legacy of errors and scandal, this rightly concerns us. Hence our desire to get it right. We remain unclear as to how much evidence is required before reform is justified, and even what kind of evidence is necessary. There is also the key practical issue that to produce evidence, a certain amount of reform needs to be carried out anyway.

EARLY PSYCHOSIS: A NEW REFORM PARADIGM

According to Milan Kundera (6), “The best progressive ideas are those that include a strong enough dose of provocation to make its supporters feel proud of being original, but at the same time attract so many adherents that the risk of being an isolated exception is immediately averted by the noisy approval of a triumphant crowd”. Over the past decade, there has been a growing sense of optimism about the prospects for better outcomes for schizophrenia and related psychoses, and this has achieved the status of a ‘progressive idea’. This has disturbed some (7), who have urged caution in proceeding with reform. However, while there is a sociopolitical dimension to all successful reform, this one has an increasingly solid basis in evidence. Clinicians and policy makers in particular are enthusiastic about reform based on this idea because of the sound logic behind it and the unacceptably poor access and quality of care previously available to young people with early psychosis, and are encouraged by the increasing evidence that better outcomes can be achieved. The rationale for, and extent of, this reform is described in Edwards and McGorry (8) and the latest evidence reviewed in a balanced manner by Malla and Norman (9). The present article will summarise this evidence and provide guidelines for its clinical application.

A key driver of this paradigm is the special clinical needs of young people at this phase of illness, the iatrogenic effects of standard care and a range of secondary preventive opportunities (10). This is especially clear when the clinical care of the first episode and recent onset patients is streamed separately from chronic patients, something which is still difficult to engineer and sustain (11). The key failures in care are prolonged delays in accessing effective treatment, which usually occurs in the context of a severe behavioural crisis; crude, typically traumatic and alienating initial treatment strategies; and subsequent poor continuity of care and engagement of the patient with treatment. Young people have to demonstrate severe risk to themselves or others to gain access and a relapsing and chronically disabling pattern of illness to ‘deserve’ ongoing care. These features are highly prevalent in most systems of mental health care, even in developed countries with reasonable levels of spending in mental health.

The increasing devolution of mental health care into community settings has provided further momentum, as has a genuine renaissance in biological and psychological treatments for psychosis. An exponential growth in interest in neuroscientific research in schizophrenia has
injected further optimism into the field, with a new generation of clinician-researchers coming to the fore. Several countries have developed national mental health strategies or frameworks which catalyse and guide major reform and mandate a preventive mindset and linked reform (1,12). Around the world, an increasingly large number of groups have established clinical programs and research initiatives focusing on early psychosis, and it now constitutes a growth point in clinical care as well as research (8). It differs fundamentally from previous reforms (e.g., deinstitutionalisation) in being much more evidence-based, and also in its integration of biological, psychosocial and structural elements of intervention.

Early intervention means early detection of new cases, shortening delays in effective treatment, and providing optimal and sustained treatment in the early ‘critical period’ of the first few years of illness (9). Even with existing knowledge, substantial reductions in prevalence and improved quality of life are possible for patients, provided societies are prepared to pay for it. However, this has not occurred, despite the development of effective treatments (2,13), because we have so far failed to translate these advances to the real world beyond the randomised controlled trial. Early intervention, with its promise of more efficient treatment through an enhanced focus on the early phases of illness, is an additional prevalence and burden reduction strategy, which is now available to be widely tested and, if cost-effective, to be widely implemented. This is hardly a radical goal and would be non-controversial in other areas of health care, where primary prevention remains out of reach, e.g. diabetes, many cancers.

While evidence is a critical element, how much evidence is required before a change in practice is warranted? In deciding where the onus of proof should lie, we should also remember that the alternative to early and optimal intervention is delayed and substandard treatment with all its human (and inhumane) consequences (10,14). Even in developed countries, as consumers and carers will readily attest, the timing and quality of standard care is relatively poor, very much a case of ‘too little, too late’. In developing countries, a significant proportion of cases never receive treatment (15). While we do need evidence, there are obvious additional clinical and commonsense drivers for the provision of more timely and widespread treatment of better quality.

**EARLY INTERVENTION IN THE REAL WORLD: CONCEPTS, EVIDENCE AND CLINICAL GUIDELINES**

Mrazek and Haggerty (16) have recently developed a more sophisticated framework for conceptualizing, implementing and evaluating preventive interventions for mental disorders which supersedes the primary, secondary and tertiary prevention model.

*Universal* preventive interventions are focused upon the whole population, while *selective* preventive measures are aimed at asymptomatic high risk subgroups of the population.

*Indicated* prevention is concerned with subthreshold symptoms which confer enhanced risk for a more severe disorder. ‘Early intervention’ can be defined as indicated prevention, early case detection and optimal management of the first episode of illness and the subsequent ‘critical period’.

**Prepsychotic intervention**

Prepsychotic intervention is a form of indicated prevention and is currently the earliest possible phase for preventive intervention in psychosis (16). However, at present it remains a research focus, even though clinical guidelines have been developed to underpin a safe and appropriate clinical response to young people presenting for treatment with potentially subthreshold or prodromal symptoms (10), since these are distressing and disabling (17,18). Much of the disability and collateral damage associated with psychotic disorders develops during this complex and confusing period and sets a ceiling for recovery, thus influencing the social course of the disorder (17). In fact, subthreshold symptoms constitute a risk factor in their own right for more severe disorder (19). Since universal and selective prevention remain out of reach at present, indicated prevention marks the current frontier of prevention research in psychotic disorders (16). Notwithstanding the neurodevelopmental theory of schizophrenia, the illness is relatively quiescent during childhood (20), with the emergence in adolescence or early adult life of symptoms and disability which can be used to predict full-threshold disorder (21,22). The idea of intervening at this stage of illness raises conflicting concerns. With the passage of time, some of these cases will be seen to have been manifesting an early form of the disorder in question, and the subthreshold clinical features will then turn out to have been ‘prodromal’, a retrospective term. On the other hand, others will not undergo transition, and will therefore constitute ‘false positives’ for the disorder in question. This has caused concerns about the effects of labelling and unnecessary treatment (23,24).

Following a series of initial naturalistic studies which created more accurate operational criteria for ultra high risk (21), a recent randomised controlled trial in this clinical population has shown a significant reduction in transition rate to psychosis for patients receiving more specific treatment - very low dose risperidone (1-2 mg/day) and cognitive therapy - in comparison to non-specific treatment - supportive psychotherapy and symptomatic treatment (25). Such patients must be distinguished from a subgroup of the general population who report isolated psychotic symptoms in the apparent absence of distress, disability or progressive change, and who do not desire assistance (24,26).

Further research is urgently required to clarify the range
of treatments which will alleviate distress and disability and reduce the risk of subsequent psychosis in help-seeking ultra high risk patients. While this evidence is being assembled, if people present with a potentially incipient psychosis, there may often be a need for a clinical response. What should the clinician do when approached by a young person, or by the family of a young person, who appears to be at ultra high risk?

For those meeting the criteria for ultra high risk (21,25), the offer, at least, of initial psychosocial treatment, including the emerging range of cognitive therapies aimed at the relief of such distress and disability in young people, with or without syndrome-based drug treatments, such as antidepressants, seems justifiable. What the patient and family should be told about the level of risk of future psychosis has been debated. However, in our experience, an open approach of disclosure, guided by the curiosity of the patient and family, has worked well, especially since many are well aware of this risk and are already concerned. An optimistic attitude to treatment and recovery in schizophrenia and psychosis generally should be strongly communicated (27).

If this offer of intervention is initially refused, as it may well be in this age group, this can usually be accepted, although some kind of assertive monitoring or follow-up may be also justifiable, combined with family contact. This is important and necessary, because, in addition to the risk of psychosis, there is a higher than expected rate of substance abuse, deliberate self-harm and suicide in this potentially prespsychotic population (25).

Not uncommonly, the parents of the young person will be very concerned, but unable to persuade him/her to attend for assessment. Since this is partly due to stigma and self-stigmatisation, the young person should ideally be assessed and offered help in a low stigma setting. This can be accomplished through home visits by the family doctor, by the school counsellor, or, where these exist, by mobile youth mental health teams linked to specialist mental health services. Naturally, a good understanding of the range of normal psychology of adolescents and young adults, and of appropriate interviewing and engagement strategies, is invaluable.

Even if psychosis does emerge and the symptoms cross the threshold for antipsychotic therapy, a key advantage of this focus on vulnerable, prespsychotic or potentially prodromal young people, in a youth oriented setting, is that a therapeutic relationship has been securely established. The young person is usually more accessible to therapeutic relationships generally and this means that recommendations concerning drug therapy are more likely to be accepted when they are made, and hospitalisation can be avoided, hence reducing the costs and secondary trauma (28). Furthermore, the duration of untreated psychosis (DUP) is reduced to an absolute minimum. Even if only a minority of first episode cases can be engaged prior to psychosis and no transitions to psychosis can be prevented, the advantages are still potentially great. Treatment will be commenced ‘on the right foot’, in an atmosphere of trust rather than fear and disruption, and with fewer complications.

The final clinical issue in this phase of illness is whether there is a role for antipsychotic medications prior to reaching the threshold for diagnosis of a frank psychotic disorder. Despite the lower risks of some disabling side effects and better efficacy of the novel antipsychotic drugs (29), and positive early research findings (25), caution is required here. Novel antipsychotic medications are clearly not a benign intervention and have increasingly recognised side effects of a different kind. If the indications for broadening the use of antipsychotic medications beyond frank and persistent psychosis are not very carefully defined and supported by high quality research, then it is likely that much harm could be done. Treatments in the early phase of illness may not only be different but more benign. While antipsychotics may ultimately not be the appropriate treatment for this phase of illness, at least for some, it is the advent of more benign antipsychotic medications that has helped to catalyse interest in intervening this early.

In the future, a range of other strategies may prove to worth trying, such as cognitive remediation, cognitive behaviour therapy, and putative neuroprotective agents (30). The safety, acceptability and efficacy of all interventions need to be thoroughly tested through further clinical research. The value of such research cannot be overestimated, given the critical nature of this phase of illness in relation to outcomes for patients. However, in most clinical settings, because of the lack of streamed first episode psychosis programs, very few of these patients get anywhere near mental health services. Hence this is a focus which is still a long way off in terms of reform priorities.

Early case detection in first episode psychosis

Once the currently accepted threshold for treatment with antipsychotic medication - the first clear and sustained emergence of psychotic features - is reached, there is a firm foundation for early intervention. Despite this, and the severity of these disorders, for a substantial proportion of people, such treatment is surprisingly delayed, often for very prolonged periods (31,32). Indeed for others, especially in the developing world (15), treatment is never accessed. This focus is concerned with the timing of intervention.

The DUP, as a marker of delay in delivering effective specific treatment, is a potentially important variable in relation to efforts to improve outcome in first episode schizophrenia, and more widely in first episode psychosis (31,32).

DUP is important because, unlike other prognostic variables such as genetic vulnerability, gender and age of onset, it is a potentially malleable variable which can become the focus of intervention strategies. Psychosis may be an easier and less conflicted target to detect than schiz-
opheephrenia (33). Schizophrenia, which requires a period of frank psychotic features for diagnosis, may take time to emerge as a stable diagnosis, and our primary treatment target is positive psychotic symptoms, for which we prescribe antipsychotic medications (notwithstanding their effects on other symptom domains). A strong and extensive literature supports a correlational link, albeit moderate, between DUP and both short and long term outcome (31,32), although two recent studies have cast doubt on the link (34,35).

Assuming the link is as robust as it seems, there is a further question. Is the association causal? That is, is delay (prolonged DUP) in treatment a risk factor for worse outcome? Or is the link due to a common underlying factor, namely a more severe form of illness, which has a more insidious onset, with more negative symptoms, more paranoid ideation, less salience and awareness of change and less willingness to seek and accept treatment? Even if this is so, DUP may still be a key intervening variable through which these clinical features influence outcome, and hence reducing it may mitigate their effect (36).

In addition to the evidence-based argument (32), there is a strong clinical appreciation, derived from patients and families directly, of the destructive effects of delay and the range of negative psychosocial outcomes which accumulate during the period of untreated psychosis. These include vocational failure, self-harm, offending behaviour, family distress and dysfunction, aggression, substance abuse, and victimization by others (10). Even those who have questioned the relationship between DUP and outcome are either extremely vague about how long one should wait to intervene in cases of clearcut psychotic disorder (7) or strongly support the idea of intervening as soon as a diagnosable psychotic disorder emerges which is impacting on functioning or quality of life (34). Since we do have effective treatments available, therapeutic nihilism, the underlying premise of a ‘wait and see’ attitude, is not justified.

Mental health services, in partnership with local communities, primary care and individual clinicians, should therefore embark upon a range of strategies to reduce delays in treatment onset (37). This is not a process which has been seen as part of the mandate of clinicians or clinical services, where resources are insufficient or scarce. It is more common, understandable and possibly even necessary, for the latter to regulate their workload by restricting access to new patients. There may be a natural reluctance to widen access because of a lack of resources, due to inadequate funding, to cope with a feared influx of referrals. Indeed, the effect of early detection strategies in community psychiatry settings (e.g., community education and mobile detection teams) will probably be twofold, as witnessed in recent studies (36,38).

Firstly, if intensive efforts are made to improve mental health literacy in the general community, improve recognition skills among general practitioners through training and consultation-liaison, and improve access to, and engagement with, specialist mental health services, then the DUP for the average case should be substantially reduced, especially the relatively small subgroup with a very long DUP. This should make the work of the service easier and result in a reduced need for inpatient care and involuntary treatment (37). Secondly, there will be an increase in treated incidence of psychosis and hence workload, and a corresponding reduction in the prevalence of hidden psychiatric morbidity in the community (36). More resources will be required for services to become proactive in this way, to undertake the detection role and cope with the additional caseloads. Such a role should be built into part of the mandate of modern community-based mental health services and hence adequately funded.

**Optimal and intensive phase-specific intervention in first episode psychosis and the ‘critical period’**

The third and most robustly evidence-based preventive focus is enhancing the quality of treatment. As Malla and Norman put it, there is a lot more to early intervention than intervening early (9). The notion that optimal treatment of the early phase of disorder could shorten the duration of illness and thus reduce the prevalence of the disorder, and further have a positive medium to long term effect on the course and outcome, is an attractive idea. However, the treatment should be phase-specific. This introduces the idea of ‘staging’ into psychiatric treatment, an idea which has been rarely applied. It implies that the treatment in earlier phases of illness should be different, more benign and potentially more effective than in later phases. The best examples of this lie in the cancer field (39).

The idea of a ‘critical period’ during which the disorder is more responsive to intervention has recently been developed for psychotic disorders and fits with the patterns of illness severity found in recent follow-up studies, as well as the developmental stage of life in which these illnesses emerge (27,40,41).

Since it does not require as much of a change in role as the previous two preventive foci, more intensive phase-specific treatment during the first episode of psychosis, and beyond into the critical period, is the most feasible proposition for most clinicians and researchers interested in secondary prevention.

In general, there is some evidence that such intensive treatment of young people at this phase of illness is effective (11,42), and cost-effective (43) in real world settings at least in the short term, though more research is certainly required to examine the longer term impact and to determine the most appropriate service models.

Whether it is possible to reduce the intensity of treatment over a longer time frame or not, is an important secondary research question. Recent studies would suggest that treatment intensity should not be reduced within the first 5 years for the majority of patients (44-46).
**First episode psychosis**

The key elements of management in first episode psychosis are summarised as follows.

**Access and engagement**

Most people, though not all, who develop psychotic disorders are young people with little or no experience of mental health services. They lack knowledge and carry the same fears and prejudices as the rest of the community regarding mental illness and will generally be reluctant to seek or accept help. This is exaggerated by the sense of invulnerability which is part of normal adolescence and by the presence of psychotic symptoms. Access and engagement with services are processes that can be markedly enhanced by the way services are designed and operated. Mobile assessment available around the clock in a setting that suits the individual patient and family is a key advance in improving access to care. This should ideally be offered even prior to a crisis or high risk situation having developed, so that a calm and careful process of assessment and initial management can be undertaken.

Engagement with services is made more difficult if a traumatic crisis and involuntary treatment is the initial experience of the young patient and family. While inadequate resources are typically a structural obstacle, many services still shield themselves behind convenient interpretations of local mental health legislation, requiring patients who are not actively seeking help on their own behalf or who reject it, especially first episode cases, to develop suicidal or violent behaviour before even direct assessment is offered. Although crises cannot always be avoided, the frequency can be reduced substantially if resources are devoted to a mobile early detection and assessment service (41).

**Assessment**

The initial assessment should focus on the major diagnostic issues and levels of risk of harm to self or others. The rest can be pieced together over time. A key issue is to determine whether the patient is clearly psychotic, and if so whether there is also a major mood syndrome present. This can be difficult. Substance abuse and dependence are frequently comorbid with positive psychotic symptoms, and should not lead to exclusion of the patient from treatment.

As early detection strategies begin to bite, it is also likely that more subthreshold cases, including those with isolated psychotic symptoms (26), will be assessed. Some of these patients have psychotic symptoms that are not typical of the textbook or diagnostic manual and may confuse clinicians. Many of these patients do request and require treatment, and further research is required to carefully define the range of appropriate treatment for such patients, though the onset of cut and sustained positive psychotic symptoms represents a watershed for any given patient.

Although the novel antipsychotics have broader effects than on positive symptoms alone, the clear emergence of frank and sustained positive symptoms is currently a necessary step to considering their use in clinical settings. Hence, in detection and diagnosis, (first episode) psychosis is an appropriate target which is a necessary waystation en route to schizophrenia as currently defined. Secondary targets within the psychosis spectrum include mania, depression, post-traumatic stress disorder and a range of other comorbid syndromes, rather than DSM or ICD diagnoses per se, because they constitute a better guide to drug therapy.

**Acute treatment**

The initial decision is whether inpatient care is required. This will be influenced by patient factors, the degree of family and social support, and by the range of services available and local policies. Where this is possible, home-based acute care is preferred for a range of reasons and can be achieved in over 50% of cases with a highly structured and intensive approach (41). An antipsychotic-free period of at least 48 hours is usually advisable, during which benzodiazepines only are prescribed to alleviate the distressing symptoms of agitation, anxiety and insomnia. If sustained psychosis is confirmed, then antipsychotic medication may be commenced. Reversible medical illnesses and drug intoxications should also be identified during this period.

Second generation or novel antipsychotics are indicated where possible as first, second and even third line therapy, because of their better tolerability and greater efficacy. The starting dose should be very low and be increased to an initial ‘step’ or target dose and held there for the effect to be evaluated. Further increases should only occur in the setting of poor response and only then at intervals of approximately 3 weeks, to allow the effect of the change in dose to become clear. More rapid increases in dose in first episode psychosis lead to greater risk of side effects, especially extrapyramidal features, with no clear benefit. This because we now know that low dosages are able to produce sufficient levels of D2 blockade in the central nervous system to bring about a clinical response, and that the threshold for clinical response is lower, albeit narrowly so, than the threshold at which neurological and other side effects begin to manifest (47,48).

These low doses of antipsychotics are not intended or expected to deal immediately with the behavioural disturbances and associated symptoms frequently seen in this acute phase. The latter should be managed if at all possible with benzodiazepines and psychosocial strategies during this period, since the use of parenteral or sedating oral typical neuroleptics will inevitably produce aversive side effects and can be achieved in over 50% of cases with a highly structured and intensive approach (41).
effects and undermine, perhaps terminally, an already fragile process of engagement and adherence to treatment.

Emergency situations requiring urgent sedation can be managed with intramuscular benzodiazepines such as midazolam or lorazepam in most cases. In occasional cases this will be ineffective and a short-acting sedating neuroleptic is the next best option. Repeated injections are rarely required with good nursing care, a supportive milieu and liberal use of benzodiazepines in the acute phase.

Naturally intensive psychosocial support is essential for the patient and family during this highly stressful period, though services are often unable to provide this due to inadequate funding, low morale and poor skills, combined with an unfortunate lack of awareness or acknowledgement of its critical role. This is a deficiency in urgent need of reform.

Home-based care is less stressful for the patient in particular and usually results in a reduced need for acute medication. It is more likely to be feasible with earlier intervention. However, the presence of manic features makes it more difficult to carry out home-based intervention. Indeed, the identification and treatment of the major affective syndromes, especially mania, is a key issue in the treatment of first episode psychosis. A manic syndrome is present in up to 20% of cases of first episode psychosis and should be rapidly treated with a mood stabiliser, ideally lithium carbonate or alternatively sodium valproate, to promote full recovery while minimising antipsychotic dosages. Subsyndromal manic features are even more frequent. Depression, unless clearly dominating the clinical picture, commonly resolves in parallel with the positive psychotic symptoms; however, if it persists or worsens during the post-psychotic period, it should be actively treated with a combination of antidepressants and psychological intervention. More detailed descriptions of the principles and practice of acute care can be found elsewhere (8,41).

The recovery phase

Up to 85-90% of first episode patients will achieve a remission or partial remission of their positive psychotic symptoms within the 12 months following entry to treatment, though some potentially responsive patients will fail to engage with treatment or rapidly cease adherence to medication. This is balanced by the persistence of the vulnerability in most patients and the tendency to recurrence, which may be subtle (45). A range of psychosocial strategies can augment and broaden the scope and depth of the recovery process, and these include psychological interventions, family interventions and group based recovery programs (9). Some of these will increase the remission rate for positive symptoms and they all aim to improve negative symptoms, functioning and quality of life. Rapid discharge of responding patients following an acute first episode of psychosis to unsupported general practitioners is poor practice. It represents a missed opportunity for maximising and consolidating recovery and for secondary prevention. An integrated shared care model with the general practitioner and other agencies is likely to prove more beneficial in minimising relapse and promoting more complete recovery.

The ‘critical period’

This term can be regarded as covering the period following recovery from a first episode of psychosis and extending for up to five years subsequently. This is based on the notion that this is the phase of maximum vulnerability (40). A number of recent research studies have focused on the treated course of early psychosis (9,45,46). These have shown that the early course of illness for both schizophrenia and affective psychosis is turbulent and relapse prone, with up to 80% of patients relapsing within a five year period, and between acute relapses there may be additional persistence of subclinical, yet disabling clinical features. These findings suggest that, if possible, drug therapy should be continued for most if not all patients for longer than 12 months after recovery from a first psychotic episode.

However, it should be remembered that a subsample, at least 20%, never relapse, that some will not relapse for a prolonged period, and that relapse prevention is not the sole consideration in treatment but rather a means to an end. Adaptation to illness is a challenging, often overwhelming task for these young people and they usually need to be given time and special help to come to an acceptance of the need for maintenance treatment (49,50). A concerted effort should be made to maintain the engagement of most patients with clinical care during the early years after onset and to have in place a written relapse plan, so that action can be taken if symptoms reemerge whether on or off medication. A good therapeutic and personal relationship with the patient and family is the key to success and should be nurtured, though continuity of care is at a premium in public psychiatry in developed countries. This deficiency is the Achilles’ heel of the system, leaving patients, who often have significant problems with trust and in forming social relationships, with no safety net. Even with standard care, however, it has been shown that outcome at 13 years is much more positive than expected, supporting the notion of an early critical period, which may be turbulent, but this turbulence seems to abate after 2-5 years (27). With optimal care such outcomes could be substantially improved (4). “If early detection provides one safety net to limit the psychosocial damage of these illnesses, then optimal and sustained treatment during this critical period when the vulnerability is at its peak can act as a second one, providing an additional degree of ‘damage control’.” This strategy is supported by the fact that the level of disability attained within the
CONCLUSIONS

Despite and partly because of the poor quality of standard treatment for schizophrenia and other psychoses in real world settings in both developed and developing countries (1), there is growing support for a more preventive stance in treatment. Primary prevention, specifically universal and selective preventive interventions, is beyond our capacities at the present stage of knowledge. However, indicated prevention for subthreshold symptoms has been endorsed as the frontier of prevention research in schizophrenia (41), while early detection and optimal early treatment are clearly within the mandate of clinicians and services, and can be justified despite predictable academic skepticism. This skepticism must be appropriately addressed through rigorous clinical research, but it may prove difficult to fully dissipate, and should not be allowed to snuff out precious therapeutic optimism, which can improve morale within services as well as patient outcomes. Realistic optimism has been in short supply in the treatment of schizophrenia and this deficiency has contributed to the serious gap between efficacy and effectiveness in treatment, as well as suicide rates (51-53). Evidence will be a vital guide, because a range of new clinical and ethical issues are being brought to light as the frontier advances (though they are essentially the same as in the rest of medicine), and it is important that changes in mental health care are based on solid foundations, not shifting sands, as so often in the past. Nevertheless, dispersing the mists of pessimism which have shrouded the clinical care of people with schizophrenia, fuelled suicide and enhanced stigma, is an overdue and worthwhile endeavour. The treatment objectives and approaches reviewed here characterise recent steps in this direction, in the confident belief that further progress will occur.

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