Early detection and intervention in psychosis:
an ethical paradigm shift*

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Summary This paper will first posit the rationale for intervention before onset, then outline the current usual practice of treating schizophrenia and the determinants of that practice. Recent developments that permit or demand a change in this practice will then be elaborated. The article concludes with an elaboration of the currently known risks and benefits of early intervention research. The ethics of early intervention are undergoing a paradigm shift, a shift that supports early intervention research as being necessary to bring empirical balance to territory that is currently overpopulated with zealous opinions.

Declaration of interest None.

EARLY INTERVENTION

The specific rational for early intervention research comes from the fact that although current treatments control positive symptoms, they do not affect the unknown neurobiological processes that create lifelong, usually irreversible deficits in mental and emotional capacity. These processes appear to be most active usually between 1 and 3 years prior to and following onset of disorder. Because of this, special attention and concentrated study, including treatment trials, should target this period.

Early intervention was not a serious consideration until the mid 1990s. Before this, it was considered clinically and ethically correct not to use antipsychotic pharmacotherapy until a diagnosis of psychosis could be made. The standard practice with prodromal symptoms was to wait until psychosis was cleanly present before applying psychosis-specific treatments. Diagnosis and treatment of schizophrenia was delayed for four reasons. First, antipsychotic medications were known to control positive symptoms of schizophrenia and to prevent or delay relapse, but no one thought they might also alter its natural history, much less prevent or delay the disorder itself. Second, neuroleptics had side-effects that could be unpleasant, disabling and even irreversibly damaging. There was little reason to expose patients to such risks unless their use was demonstrably necessary. Third, the so-called prodromal signs of schizophrenia were quite non-specific, making prediction too inexact to be useful for pre-emptive intervention. As such, identified ‘at-risk’ groups invariably contained high proportions of ‘false-positive prodromals’; i.e. persons whose ‘prodromal’ symptoms turned out to precede or to portend some disorder other than psychosis. Poor predictability exposed far too many of such individuals to unnecessary risks. Fourth, the diagnosis of schizophrenia was delayed until it could no longer be denied in order to avoid the stigma associated with the label.

The points made here are largely based on a paper published in 2001 (McGlashan, 2001).

RECENT DEVELOPMENTS

The 1990s saw new data and developments that impacted on each of the above reasons supporting delayed intervention in schizophrenia. First, evidence emerged suggesting that existing treatments for psychosis might also affect the natural history of the disorder. This included numerous studies of first-episode schizophrenia demonstrating a correlation between a shorter duration of untreated psychosis (DUP) and better prognosis. These data have been reviewed extensively and will not be detailed here (McGlashan, 1996a, 1999, 2000). The evidence is positive but equivocal insofar as several studies have not replicated this correlation. Furthermore, even if this correlation between earlier intervention and better course proves to be solid, a causal relationship has yet to be demonstrated (McGlashan, 1999). To do so with the greatest scientific credibility would require randomising a group of patients with first-episode psychosis to delayed treatment, which would be unethical. An ethical effort is underway to test for causality using a quasi-experimental design (McGlashan, 1996b; Johannessen et al, 2001). Until a causal direction can be delineated, the alternate hypothesis cannot be dismissed that the DUP effect is a byproduct of innate (premorbid) prognosis, i.e. patients who are destined to be among the most ill also present at onset in ways that result in a long DUP (McGlashan, 1999).

The evidence that early treatment may affect the natural history of the psychosis also comes from two studies of treatment prior to onset. In a pioneering investigation, Falloon (1992) applied home-based stress management to prodromally symptomatic, high-risk individuals identified by primary care practitioners in a small county in Britain. The intervention may have prevented psychosis and reduced the incidence of schizophrenia, but the results are limited in their significance because of the small sample size. The second study by McGorry et al (2002) involved randomising operationally defined prodromally symptomatic patients at high risk to open label treatments, one being an atypical neuroleptic plus enriched psychosocial intervention, and the other being standard supportive psychosocial intervention without neuroleptics. The results are significant and support the hypothesis that prodromal phase intervention can delay or prevent the onset of psychosis.

The second development in the 1990s leading to a paradigm shift in the ethics of early intervention was the introduction of novel neuroleptics, such as clozapine, risperidone and olanzapine. These agents proved to have equal efficacy to traditional neuroleptics and had fewer side-effects. Particularly auspicious has been the relative scarcity of extrapyramidal side-effects: akathisia, neuroleptic malignant syndrome and tardive dyskinesia (Beasley et al, 1996, 1999; Glazer, 2000a,b; Tollefson et al, 1997a,b). These agents have their own set of undesirable side-effects, such as...
weight gain and somnolence, and we do not yet know about their long-term safety. Nevertheless, the benefit:risks ratio of the 'novel' medications is currently superior to the standard neuroleptics, which impacts, in turn, on the benefit:risks ratio of early intervention.

Perhaps the most important development in the 1990s altering the conservative status quo about early intervention was the demonstration by McGorry et al. that subgroups of patients with 'prodromal' symptoms could be identified who possessed a very high risk of 'converting' to psychosis in the near future, i.e. within the ensuing year. The criteria included clinical, functional and demographic phenomenologies that were easy to identify and operationalise. The Australian team found that between 20 and 41% of patients so defined became psychotic within 1 year (Yung et al., 1996, 1998; McGorry, 1998).

The Australian criteria were incorporated by the author and colleagues into a Scale of Prodromal Symptoms (SOPS) and a Structured Interview of Prodromal Symptoms (SIPS) (Miller et al., 1999). This scale has identified prodromal persons for a study of early intervention in the Prevention through Risk Identification, Management, and Education (PRIME) prodromal clinic in the US. In individuals identified as prodromal by the SIPS, the rate of conversion to psychosis has been comparable to that of the Australian populations (Miller et al., 2003), thus validating the high predictability of these criteria in another sample from another research centre in another country.

Such high predictability is new to the field of pre-onset markers of vulnerability and needs replication. Nevertheless, the results thus far are significant enough to call into question the ethics of the conservative 'wait and see' practice, i.e. the status quo. Such behaviour on the part of clinicians may be protecting 60% of a prodromal sample (the false-positives) from unnecessary treatment, but it may also be keeping 40% of the sample (the true positives) from the knowledge of a risk that is real and potentially treatable. The treatability of psychosis in the prodromal phase is largely unknown but is being tested in ongoing clinical trials. Should treatment prove to be effective in delaying or preventing the onset of psychosis, then a 'wait and see' attitude could be regarded as unprotective, if not unethical.

A further argument against early identification is exposure to the stigma of being labelled as at risk for psychosis. This risk is especially onerous to false-positive prodromal patients who receive no benefit from the label in the form of appropriate treatments to offset the risk. But what is the risk of stigma? No one has yet attempted to define stigma or to measure its negative impact. For example, we are not aware of any research suggesting that being in a psychiatric clinic stigmatises anyone. It is vital to clarify that the populations being studied in the Australian and North American prodromal clinics are actively symptomatic and treatment-seeking. Study 'individuals' are mental health consumers or patients, not asymptomatic citizens (even if at high risk). They come to the study recognising that something is wrong or not 'quite right'. They come already accepting the role of patient, if not the label.

**RISKS AND BENEFITS OF EARLY INTERVENTION**

What are the risks and benefits of pre-onset detection and intervention research as illustrated by the PRIME clinic protocol in the context of contemporary psychiatric practice in America?

Risk revolves primarily around two issues: drug side-effects and stigma. Concerning drug side-effects, the immediate side-effects associated with atypical neuroleptics are modest in frequency and very modest in serious adverse effects. Long-term side-effects are not yet known. Currently, benefits are substantial and known risks in the absence of weight gain are modest.

The potential risk of stigmatising participants as psychotic and doomed to chronic illness is certainly present and should be recognised. In practice, however, we have found that this risk can be managed with a judicious balance of education about psychosis and counselling about probability and the uncertainty of prediction. We do not continually confront or challenge a patient who denies our assessment and judgement about risk for psychosis, but we also do not collude with their 'not knowing'. Although it may be tempting to keep information of risk from a person to avoid distress, such 'protection' can also be seen as violating that person's civil liberties and right to know. Preliminary results suggest the criteria indicating imminent risk have a sensitivity of 40%, meaning the level of predictability is no longer negligible. We feel a person who meets these criteria has a right to know the risks. Such persons certainly have a right to deny the reality of risk, but we have no right to deny it for them.

The main benefit of participating in such research lies mainly in learning one's actual risk for psychosis or other mental illnesses over time. For patients with prodromal symptoms who are false-positives, participation helps to clarify risk and shed light on what actually is wrong (if anything) and what contributed to the person's prodromal-like symptoms initially. For patients who are true positives, participation will clarify this as well, with the additional benefit that such patients will receive active treatment sooner than is usually the case for first-episode psychosis.

An 'indirect' benefit of treatment research in the prodromal phase of psychosis is that research participants are more likely to possess intact capacities to provide informed consent. Compromised competency in schizophrenia research or treatment usually accompanies the later stages of the disorder.

To conclude, the data informing the benefit:risks ratio are insufficient to justify prodromal intervention as standard practice at the present time, but the data are sufficient to justify prodromal intervention research. In short, we need to stop shadow-boxing with our own projections of doom and illuminate our current gloom of ignorance with high-quality scientific investigation.

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**REFERENCES**


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