

Early intervention in psychotic disorders: beyond debate to solving problems

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Summary The challenges of early diagnosis are similar in psychiatry to the rest of medicine. For potentially severe and persistent disorders there is great value in early diagnosis, however, only under certain conditions. Early diagnosis would not be justified if there were no efficacious treatments or if such treatments provided earlier would do more harm than good for those exposed. There is growing evidence that earlier and sustained intervention improves at least short-term outcomes. However, early intervention may be iatrogenic where systems of care are poor in quality. One thing is clear, the general pattern of care is still 'too little, too late' even in the most affluent countries. Consistent and extensive reform of health systems, with recognition of early intervention as an increasingly evidence-based 'best buy', represents one of the key priorities in international mental health.

Declaration of interest The author's early intervention studies have received partial support in the form of investigator-initiated unrestricted research grants from Janssen-Cilag.

Early diagnosis and treatment in psychiatry has been so neglected, yet is so intuitively appealing, and with increasing support from research evidence, to some it seems unnecessary, even perverse, to question it at all. However, the rise of early intervention in psychotic disorders has spawned a critique. This is an indication that a true paradigm shift is in progress, and while the critique ultimately fails to convince, it may undoubtedly influence progress in potentially positive ways.

For many people, the distress associated with the diagnosis of psychotic disorders, such as schizophrenia, is made worse by the realisation that the disorder could have been caught sooner, if only the early manifestations had been recognised. As in other complex medical disorders, these early features are often overlooked because they resemble the manifestations of benign disorders and normal experience. Patients are unlikely to seek help, and even when they do, the possibility of emerging serious disorder is rarely considered. Such delays, occurring as they typically do during the crucial life stage of adolescence and early adulthood, have long-term effects. In psychiatry the situation is analogous to that in medicine generally but is even more challenging. The emergence of the clinical phenotypes of disorder must be detected within the flux of a developing personality; the person is still an 'unknown quantity'. The young person and those close to him or her are not clear of the significance of changes in mood, experience and behaviour. The acquisition of new symptoms and their intensification are difficult to detect and interpret. Furthermore, the absence of diagnostic laboratory tests to validate clinical diagnosis and to predict future risk is another limitation. Nevertheless, the paradigm and the diagnostic challenge are identical. So, if we accept that serious mental illnesses such as schizophrenia and related psychoses are complex medical disorders affecting the central nervous

system, why should we debate the value of early diagnosis?

Well, as David Sackett has clearly described (Sackett *et al*, 1991), early diagnosis in medicine is by no means always justified. Sackett has been highly critical of over-enthusiastic preventive medicine advocates and makes many telling points (Sackett, 2002). His arguments apply principally to the presymptomatic stage of disease and the decision to undertake screening and proactive case-finding, and he sets out a number of criteria which need to be satisfied before this should be undertaken. These criteria have less relevance for early symptomatic diagnosis but are still instructive. Sackett also points out that the value of early diagnosis is dependent on the orderly progression of disease via a natural history from onset through diagnosis to outcome, and a second element, the notion of a 'critical point' in the natural history of a disease, before which therapy is either more effective or easier to apply than afterward. The latter concept also underpins the concept of staging.

FIRST-ORDER ISSUES

Sackett's criteria can be subdivided into first-order or threshold issues and second-order problems to be solved. The first-order issues can be considered in response to the question: 'When would early diagnosis not be justified?'. In simple terms, early diagnosis would not be justified if: (a) there were no efficacious treatments; or (b) treatment (if provided earlier) would do more harm than good. If there are no efficacious treatments, then early diagnosis merely labels (a potentially harmful effect, not only in psychiatry) and could be compared to providing binoculars to someone who is tied to a railway track. They can see the train coming earlier but it will still hit them at the same moment (Barnett Kramer, quoted in Marcus, 2004). Even so, some have argued that even in such situations (e.g. Huntington's and Alzheimer's diseases), early diagnosis may result in a number of benefits even though no efficacious treatments exist. Second, any effective treatment has the potential to cause harm. Early diagnosis can cause harm, particularly if benign or self-limiting forms of the disorder, including false-positive cases, are exposed to harmful treatment effects, or are stigmatised or otherwise inconvenienced. Indeed, the work of van Os and

*Paper presented at the Third International Early Psychosis Conference, Copenhagen, Denmark, September 2002.

colleagues (2001) has shown that schizophrenia represents only part of a previously poorly recognised spectrum of severity of psychosis. At best, such treatment might constitute a waste of money. At worst, early intervention in many settings would bring people into iatrogenic settings, which still abound in psychiatry. However, we do know that treating patients in real-world settings for the first time for psychotic illness results in remission for over 80% and an improvement in the Global Assessment of Functioning scale (GAF) rating from around 30 to 60–70 (Power *et al*, 1998). These are very large treatment effects. Furthermore, accumulating evidence from randomised controlled trials in early symptomatic stages of psychosis, both sub-threshold (prodromal) and full-threshold (first-episode psychosis), has demonstrated the efficacy, the relative safety and the acceptability of both drug and psychosocial treatments (McGorry *et al*, 2002; Craig *et al*, 2004; McGlashan *et al*, 2004; Morrison *et al*, 2004; Nordentoft *et al*, 2004). The concept is arguably proven, however, this does not guarantee that it will be safe to apply universally without a range of preconditions being satisfied. For example, before prepsychotic intervention is considered, high-quality phase-specific care for first-episode psychosis, severe mood disorders and other mental disorders in young people should be locally available in a low-stigma setting. It is the widespread absence of such real-world safeguards that fuels the anxieties of many critics of early intervention. These are genuine concerns but form part of the solution not the problem.

SECOND-ORDER ISSUES

Such second-order issues relate to characteristics of the disorder, its seriousness, prevalence, the technology of identification (screening and clinical case-finding), the desire of those affected to seek help, and the likelihood that interventions will prove acceptable and be adhered to. Each of these represents specific challenges to early diagnosis in general medicine – solvable problems rather than fatal flaws for the enterprise. Space does not permit a detailed discussion of these in relation to early intervention in psychosis. Critics (Warner, 2001; Pelosi & Birchwood, 2003) confuse first- and second-order issues, obfuscate boundaries between screening and clinical case-finding and presymptomatic and

symptomatic phases, and between full threshold and subthreshold illness, and misunderstand and misrepresent the results of recent key studies. The wellsprings of their arguments are an odd blend of residual antipsychiatry, a lack of confidence in the efficacy and safety of psychiatric treatment, a disconnection between psychiatry and the rest of medicine, a suspicion of and distaste for reform and change in work practice, and a genuine concern that somehow harm will come to earlier detected patients and worse neglect will befall patients with established illness. These concerns need to be balanced against the current unacceptable status quo and our capacity to change this (Garety & Jolley, 2000).

Sackett's arguments, although directed at presymptomatic disease do, however, have some cautionary lessons for earlier diagnosis in psychotic disorders, even though the latter has necessarily confined itself to early symptomatic stages. Most do, however, dissolve when we focus on help-seeking cases with symptoms. Here the onus on the clinician is quite different. For symptom-free citizens who are sought out and offered therapy, we need to be very sure that their health will improve and we will do more good than harm. With help-seeking symptomatic patients we only have to try our best and are freer to offer less evidence-based treatments and to emphasise that even well-validated treatments do not work for everyone. This dichotomy is useful, yet when we attempt to improve levels of mental health literacy (Jorm *et al*, 1997) and encourage and direct help-seeking for symptomatic distress and unmet need, it becomes less clear-cut, with the onus shifting towards the need for a firmer evidence base and greater efficacy and safety for the treatments being offered. We are operating in a grey zone where Sackett's principles can indeed guide us.

STAGING

This leads to a consideration of the concept of staging of disease. This means defining distinct clinical or clinico-pathological stages with different prognostic and treatment implications. Stages vary from asymptomatic but with elevated risk, for example, positive family history of breast cancer plus presence of specific gene profile (say stage 0), through early clinical stages to end-stage disease (stage IV). The fundamental principle of staging is that

treatments provided earlier are more benign, safer and more effective than those that are deployed later where the stakes and risk from the disease are much higher. Thus logic flows directly from Sackett's arguments. While the key shift in onus comes with the onset of early symptoms and particularly help-seeking, the principle has wider application across the full spectrum of disease stages. This framework enables the data from van Os *et al* (2001) as well as the prodromal intervention studies to be better understood.

The situation is nevertheless deceptively complex and evaluation studies need to be carefully designed. Cases detected earlier, especially by more proactive methods, may for some diseases have an intrinsically better prognosis, because (in cancer) the tumours are slow-growing (and benign) and have an increased chance of detection by screening. This is known as the 'length time bias'. It may operate quite differently in other diseases. For example, in schizophrenia, insidious onset is associated with a worse, not better, prognosis, yet such cases would have an increased chance of detection in early diagnosis strategies. Staging has been applied in other serious medical disorders, such as diabetes and rheumatoid diseases. Patients may present for the first time at any of the stages from early to late, progression across stages may or may not occur, and such progression may be influenced by treatment. It has been assumed until recently, despite significant counter-evidence, that in the case of schizophrenia and related psychoses, a pernicious intrinsic progression was inevitable and was almost unmodifiable by treatment (Hegarty *et al*, 1994; Andrews *et al*, 2004). The early intervention paradigm has helped to challenge this view and the staging concept enables better clinical trials to be designed to study the content and timing of treatments. A further important bias to be factored into such trials is the 'lead time bias', which implies the need to correct in follow-up evaluations for the period by which the onset of effective treatment was brought forward.

NEED FOR REFORM

The challenge of bringing early diagnosis to psychiatry is particularly important for the potentially serious disorders, such as the psychoses and severe mood disorders, which emerge in young people at a critical

period of life, the transition to adulthood, and frequently have lifelong and pervasive human and economic costs. Minimising the impact and burden of these illnesses and better self-management of ongoing vulnerability, even if most are not 'cured' *per se*, is an achievable public health goal. Population or primary screening of asymptomatic people is not an option yet in psychiatry. Better mental health literacy and proactive case-finding of early symptomatic patients is well worth exploring seriously. The false-positive issue can be managed by including a range of target disorders in the strategy (all with individually low incidence, but with a collectively higher incidence) and through a sequential process of clinical enrichment so that the base rate of the disorder in question rises to true positive levels of around 50%. The first step will increase coverage and reduce the missed and false-negative rate but lower the true-positive rate. The enrichment process, which needs further study, aims to increase this. All of this needs a range of appropriately resourced clinical settings with permeable filters. Existing structures function poorly and typically operate to delay intervention until it can be no longer withheld (McGorry & Yung, 2003).

Critics of the introduction of early diagnosis in psychiatry have highlighted many of these issues, often in an emotive and ingenuous manner, without reference to how these issues have been tackled in other branches of medicine. Proponents of early intervention have generally recognised the need to proceed carefully. They are mindful of the poor quality of psychiatric care even in the most advanced countries and the consequent potential for harm as well as benefit from drawing patients into such care, which may not meet their needs. This is

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why the early intervention field has placed so much emphasis on the need to reform the structure and modus operandi as well as to make the content of psychiatric treatment as stage-specific as possible. We are still at proof of concept stage but this a concept well worth the effort to prove. It is very likely, as in the rest of medicine, to represent a 'best buy' and to reduce the burden of psychiatric disease. It does not imply a disinvestment in the later stages of disorder, another false dichotomy introduced by critics, rather, new investment is required for greater health gain, cost-effectiveness and quality of life for patients and families.

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BJPpsych

The British Journal of Psychiatry

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BJP 2005, 187:s108-s110.

Access the most recent version at DOI: [10.1192/bjp.187.48.s108](https://doi.org/10.1192/bjp.187.48.s108)

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