

IS PRE-PSYCHOTIC INTERVENTION OF SCHIZOPHRENIA REALISTIC ?

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Background

Schizophrenia is a serious disorder that often affects young people in their early twenties. The outcome is often poor, associated costs and burdens are extensive. Almost 15% of schizophrenics end up with frequent admission and require long-term residential care (1). Recently, the idea of early detection and intervention has been launched as a new and promising approach.

The starting point for consideration regarding early intervention strategies is the observation that most patients who develop schizophrenia have had a period with non-specific, non-psychotic prodromal symptoms before the onset of psychosis (2,3). The prodromal period has been reported to last, on average, 1 – 2 years. Another finding across studies is that the period from onset of a manifest psychosis to onset of adequate treatment (duration of untreated psychosis DUP) is long. The mean duration of DUP is 1-2 years with a median of approximately 26 weeks. The majority of studies show a statistically significant correlation between long DUP and poor outcome (4,5), although others have not found the correlation (6,7).

Genes that Contribute to Schizophrenia

Many theories have been offered to explain the genetic mechanisms that produce schizophrenia. One hypothesis is that schizophrenia has a homogeneous pathogenic genotype with pleiotropic effects. Individuals with schizophrenia may present with a variety of symptoms. Yet the preponderance of evidence argues against the possibility that most cases of schizophrenia are caused by a common gene

(8). In particular, single major gene models do not explain familiar pattern of illness accurately, in either families or twins; multi-factorial polygenic models explain such data better. In a model version of this view, the schizophrenia phenotype results from the additive effect of multiple genes and environmental factors. Each factors contributes effects until a critical threshold level is reached and the critical symptoms are manifested. In this model, common genes of small effect may be involved, rather than rare genes of much larger effect, as is more likely in single major gene models. Although models like these account best for family patterns of transmission, we will not know their accuracy with certainty until we identify the actual genes that are involved in schizophrenia.

The important implication of multi-factorial polygenic models is that genetic heterogeneity at least partly accounts for phenotypic heterogeneity. While most cases of schizophrenia are accounted for best by polygenic models, some may indeed result from the effects of one or several genes of moderate to large effects. In some cases for example, family transmission patterns are predicted about as well by oligogenic models (a type of model that points to relatively small number of aetiological genes that have moderate or larger effects) as they are by multi-factorial polygenic ones (8)

In contrast to the high genetic 'loading' apparent in many familiar cases of schizophrenia, sporadic or non-familiar cases of schizophrenia may result primarily from factors other than schizophrenia genes. Psychosocial causes, amphetamine misuse, schizophrenia-like psychosis or epilepsy and other brain trauma, brain disorders, infection in utero and /or complication of pregnancy

are among the variable likely to contribute to the development of such cases. Finally, some isolated cases may be due to gross chromosomal abnormalities (9)

In the light of the high heritability estimates for schizophrenia, the discovery of genes that cause the disorder has been eagerly anticipated since the 1980s, spurred in part by the development of polymorphic DNA markers that can detect multiple forms of a gene (alleles) in chromosomal locations. While several forms of molecular genetic analyses are in use, linkage analyses provide a particularly versatile procedure that is helping to explain the familial basis of schizophrenia. Results from linkage studies depend on a variety of factors, including the presumption of the mode of inheritance, the involvement of genes whose effects are large enough to be detected and /or the extent to which family members are diagnosed accurately. Since all these factors (and others, such as the importance of statistical power) are in some way problematic; it is not surprising that linkage studies have thus far been less than conclusive, and have yet to identify the genes that causes schizophrenia.

In the last few years, evidence for the presence of susceptibility genes have been shown by linkage studies. A study in 1995 provided evidence of such genes in chromosome 6p and 8p (10). Additional sites have been identified including chromosome 10p (11), 13q (12) 15q (13) and 22q (14). However although these loci have been identified, the actual genes involved in schizophrenia have yet to be positively.

Early Intervention after the onset of psychosis

Until recently most preventive work in schizophrenia and related disorders has been of secondary nature, aiming to minimise disability, relapses and co-morbidity, and to maximise recovery in those with already diagnosed disorders. The approach means that treatment is given as soon as possible after the psychosis is detected. This leads to a shortening of DUP (duration of untreated psychosis) and should reduce the prevalence of the disorder. However, these measures are too late for most patients, because damage is already extensive.

The onset of psychosis could be defined as related not only to positive and negative symptoms, but also the onset of a syndrome with specific criteria of symptoms combination and duration. The onset

of positive symptoms has been reported to be more reliable than negative symptoms (15), but through studies of the early course of illness have shown that about 70% of the patient with schizophrenia develop negative symptoms before positive symptoms (16). The literature generally recommend the use of positive symptoms to define the onset of psychosis (17), but the possibility of using other definitions should be recognised.

Early Intervention in the Prodromal Period

Identifying and treating symptoms that are precursors to a more serious disease in order to prevent outbreak of the disease is called primary prevention. This should lead to a decrease in the incidence of the disorder. In this context treatment of prodromal symptoms of schizophrenia may be labeled as primary prevention. This is because the treatment is targeted to those who are symptomatic but who do not yet have a fully developed disorder.

The first step in planning indicated prevention is therefore to acquire accurate knowledge of the various 'symptoms foreshadowing mental disorder'. One example where this model has been applied is the treatment for individuals with mild depressive symptoms who would be seen as being at risks for the development of a major depressive episode (18). The same indicated prevention principle can be applied to the area of psychiatric disorder in which the prodrome, the period of change from the person's premorbid state immediately precedes a first psychotic episode.

What are the prodromal features in psychotic disorders which we should detect in people in order to plan the prevention?. Yung and McGorry (19) in their literature review found that prodromal psychopathology is extremely diverse and includes many non-specific symptoms such as depression and anxiety. The prominence of these non-specific features highlights the fact that the presence of an apparent prodromal syndrome does not make subsequent development of disorder inevitable. Prospectively, it is unclear whether or not a person presenting with a cluster of symptoms characteristic of a psychotic prodrome will make the transition to psychosis or not.

Uncertainty about whether a particular mental state (the prodrome) will be followed by diagnosable disorder raises both terminology and practical issues. The term 'prodrome' implies that this syndrome will always be followed by the disorder. Hence, it can

only be 'diagnosed' accurately in retrospect. Prospectively, a more appropriate term would be 'precursor syndrome (18) or 'at risk mental state' (20), both of which emphasise that the particular mental state places the individual at risk for the disorder at that time point but the transition to a fully developed disorder is not invariable.

Studies of the psychotic prodrome, particularly of the features which seem to occur just prior to the development of full blown psychosis, and early symptoms of psychotic disorders have led to suggestion that some sub-threshold forms of psychotic symptoms and transient isolated psychotic experiences may precede the development of a psychotic disorder (21). This has led to another approach to identifying high-risk individuals which involves defining symptoms which may indicate 'psychotic-proneness'. For example 'psychotic-like symptoms' (attenuated form of psychotic symptoms) and isolated psychotic symptoms (22), or other definitions of prodromal features (23) have all been suggested as candidate psychopathological indicators of vulnerability to psychosis. Individuals with these symptoms may or may not have a genetic risk.

The fact that an at-risk mental state may or may not progress to psychosis (i.e. the problem of false positives) raises several important logistic and ethical dilemmas in relation to the indicated prevention model. There are attempts to minimise the 'false positive problem' by adding in further risk factors to enhance prediction and minimise false positives. This involves combining other risk factors such as trait-risk factors (family history of schizophrenia and related disorders) and state-risk factors (prodromal symptoms, attenuated and transient psychotic symptoms). Other studies are investigating the predictive power of a number of other putative risk factors for schizophrenia such as attention and other cognitive deficits (24), neuropsychological soft signs (25) and structural brain abnormalities (26).

High-risk Studies

A few research groups throughout the world set out to combine multiple strategies for identifying high-risk individuals, including modification of the above approaches. Their main objective is to identify a group at high risk of transition to psychosis within a brief follow-up period, that is a group at risk of impending psychosis. Identification of those at risk of transition to psychosis in short term would enable

detailed and frequent prospective assessment of the at-risk individuals and therefore psychological mapping of the process of becoming psychotic.

This could enable identification of precursor features which occur just prior to psychosis. The specificity of these features can be examined and their utility in predicting psychosis studied. Ultimately they could be used as 'warning signs' indicative of impending psychosis. Thus the underlying objective is to be able to predict with a reasonable degree of specificity which high-risk individuals, will in the absence of treatment, become psychotic in the short term.

The Buckingham Project

The Buckingham study from 1984 to 1988 (23,27) is a pioneer study in primary prevention. It is claimed to be the first study to organise a very early detection of psychosis. The study was carried out in the country of Buckinghamshire, England.

The project teams established a mental health service system with close connection to the existing primary health services. 16 general practitioners in the area (population 35,000) were trained in detecting early cases of psychosis with the use of a checklist for prodromal symptoms similar to the prodromal symptoms in DSM-III R (28). Patients with possible prodromal symptoms were referred immediately to specialist mental health team for assessment and treatment.

During this 4-year period, 16 patients with prodromal symptoms were detected; only one of these definitely had schizophrenia and she was treated with low-dose neuroleptics. Epidemiological studies carried out 10 years earlier indicated that an incidence of 2.5 new cases per year. The investigators draw the conclusions that a 10-fold reduction in the annual incidence of schizophrenia from 7.4/100,000 to 0.75/100,000 total population, had been achieved.

Despite several methodological shortcomings and ambiguous evidence that primary prevention can be achieved through identification of prodromal states, the Buckingham study could be classified as a prospective clinical trial according to the APA coding system. The most remarkable finding in this study is that no first-episode cases with long DUP were identified had been heavily criticised. Most other studies of first-episode schizophrenia that about 50% of the patient have been psychotic for quite a long time at the time of inclusion.

The 'PACE' Study

The Personal Assessment and Crisis Evaluation Service (PACE) is a clinical service established in Melbourne, Australia in connection with the Early Psychosis Prevention and Intervention Centre (EPPIC) Services. The focus of PACE is to look for predisposing factors which occur just prior to psychosis, i.e. to try to identify individuals who in the absence of treatment run a high risk of becoming psychotic in the short term (29). Three types of prodromal states are defined: attenuated and transient psychotic symptoms; and trait plus state risk factors for psychosis (genetic risk).

The PACE service is located at a generalist out-patient services and health promotion centre for adolescent. All patients are help-seeking and experience some kind of psychiatric symptoms. Patients between the ages of 16-30 with one or more of the predefined prodromal states are followed-up with monthly ratings of psychopathology in order to detect the transition to psychosis.

During the first 16-month period, 119 referrals were assessed and 49 patients met the criteria for prodromal syndromes. 20 patients had been follow-up for at least 6 months, 40% of those developed psychosis; 5% within the first month of follow-up (30). A comparison between those who develop psychosis (n=8) and those who did not (n=12) showed that the psychotic group initially had significantly higher BPRS total scores, more negative symptoms and signs of depression and poorer quality of life and lower GAF scores. This study also has several methodological weaknesses. The statement that 40% of the patients identified in a possible prodromal stage of psychosis developed psychosis within the first year of follow-up had been heavily criticised.

Other Project on Primary Prevention

The 'Born Early Recognition' study which was conducted in Germany found that 81% of 96 patients included in the study had at least one early or basic symptom (BS) of schizophrenia at baseline (31). At 8-year follow up, 58% had developed schizophrenia. One-quarter of the patients with early symptoms of schizophrenia did not develop schizophrenia. Statistically significant predictors of the transition to schizophrenia were the BS's 'cognitive thought, perception and motor disturbances' and additionally the presence of schizotypal personality disorder.

There are a number of ongoing projects on the primary prevention of psychosis (32) such as a) The PRIME (Prevention through Risk Identification, Management and Education) Clinic, located at the Yale Medical School in New Haven, Connecticut, United States; b) The TOPP (early Treatment Of Prepsychosis Project) which is being carried out at Rogaland Psychiatric Hospital, Stavanger, Norway as part of an ongoing international multi-site study testing the efficacy of Early Treatment and Intervention in Psychosis (TIPS) and c) The DEEP (Detection of Early Psychosis) project is being carried out in Turku, Finland.

Ethical Issues

Several ethical issues arise when attempting to intervene in a group who, although defined as high risk, are not psychotic and in whom transition to psychosis is not inevitable.

Stigma

The use of psychiatric services and labelling a person as a psychiatric case is stigmatising (33). In addition, the definition of a person as being 'high risk' can result in a change in the way he or she is perceived by others. Despite rigorous public psychology education campaigns, there is still a prevailing view that psychotic disorder have poor prognoses with inevitably deteriorating courses such as gloomy out-looks could result in demoralisation and even depression in individuals labelled as 'high risk'. The situation would be compounded if such a nihilistic view were reinforced by family members, general practitioners and others significant persons.

Given all of these ethical pitfalls, should we promote psychiatric treatment for putatively high risk people?. Experience with PACE patients (29) have shown that many are aware of their increased risk and often wish to discuss this with a clinician. Young people presenting with transient psychotic experiences often want to know if these will occur again and whether they may progress to something more serious. The discussion must be carried out in a sensitive manner. It is also important not only to communicate the idea of risk, but also offer a possible solution. At the end patients and their families will decide whether to receive treatment or not. We should respect their decisions.

Treatment of High Risk Cases

A further issue of concern is what treatment to provide for those putatively high risk people. Is use of neuroleptics justified to prevent later development?. Of course the false positive issue is relevant again as some cases would then be in danger of receiving the medication unnecessarily, with all the implications of short and long term side-effects and stigma. The opposing view point has also been expressed, with suggestions that neuroleptic treatment should not be withheld from those obviously at the point of imminent onset of psychosis. However even if such a particular point could be defined, such as level of symptoms, type of symptoms, number of risk factors, the question arises of which antipsychotic treatment should begin and how long should medication continue?

Few would argue with providing treatment for those presenting with particular symptoms or problem, particularly when symptoms have been long lasting and unlikely to resolve spontaneously. The problem arises in deciding whether to start antipsychotics or not for those with prodromal symptoms. Falloon (23) commented that both psychosocial treatment and low dose of neuroleptics seemed to be of benefit for people experiencing the possible prodromal symptoms of schizophrenia. In order to avoid treating a false positive, some center (29) withhold antipsychotic medication for prodromal symptoms; they just treated them symptomatically targeting at the specific symptoms. Finally, the cost/benefit ratio of the treatment needs to be considered such as side-effects of atypical antipsychotics, decreased cost of treatment and increased benefit of neuroleptics if the cases progress to psychosis.

Conclusions

Early intervention programmes for schizophrenia are difficult to organise and expensive to carry out. For the time being, no research projects have shown beyond reasonable doubt that primary prevention in psychosis is possible. Several ongoing studies describe characteristic of prodromal states which indicate increased risk of transition to psychosis. However the issue of false positive remained unresolved because the conversion rate reported from the early phases of these studies lie between 33 and 58% (32). Even though these findings are encouraging, the specificity of prodromal states is still ambiguous and caution must

be taken to avoid unnecessary stigmatisation. Despite carrying the risks of somatic or psychological side-effects due to the use of antipsychotic medications or labelling such as 'early schizophrenia' or 'prepsychosis' we believe that patients who worry over their symptoms and wish to receive treatment should be treated without further delay.

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