Early interventions in Schizophrenia: What do we know?

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The idea that intervention is needed early in Schizophrenia has been known to psychiatric field as early as 1927 when Harry Stack-Sullivan spoke of "recognizing that to leave the illness undiagnosed and untreated would lead to less favourable outcomes, necessitating a long stay in institutions". The early intervention programs were first initiated at Melbourne, Australia and Buckinghamshire, UK during the mid 1980s. It spread to the American and European countries and in recent time the programs have been initiated in Southeast Asia as well.

What is the need for Early Intervention?

The first general hypothesis is that the neurobiological processes that make schizophrenia a severe and chronic condition may be most active early in the course of the disorder. Birchwood initially proposed that the illness is stormier early in the course and intervention in the first 3 years of illness offers a window of opportunity to prevent or limit the potential decline in the outcome.[1] This was later labeled as "critical period" where intervention in 3to 5 years is considered crucial for good outcome. To support this there is group of researchers studying the relationship of brain volumes in First episode psychosis proposing the "biological toxic" theory. Neuro-imaging studies have shown significant changes in the gray matter in different areas of the brain during transition to psychosis and in the early stages of the illness with no further progression with the illness.[2]

The second area of prevalent hypotheses among early intervention advocates suggests that effective early intervention may improve outcome by reducing the secondary effects of psychosis which include social and educational/vocational disruption, substance abuse, depression, and homelessness. In this case, reducing DUP and getting proper treatment during the "critical period" functions to limit the possibility of secondary morbidity that can handicap the rehabilitation and recovery process. It has also been argued that treating first-episode patients promptly and effectively during their initial experience with the mental health care system will increase compliancy rates of both medication and psychosocial Rehabilitation.[3]

There are three reasons why early interventions should be considered. First, deterioration in psychosis occurs early and is not progressive with the illness. Prospective studies have shown that the Deterioration does not increase with the duration of the illness. The deterioration is maximum in the initial phase of the illness first 2-5 yrs. Landmark study of Eaton et al of 90 early psychosis patients followed up for 10 yrs showed that there is a steep decline to a stable 20-25% of residual positive or negative symptoms within first 2 years of onset.[4] A recent meta-analysis of longitudinal studies in first episode psychosis also confirmed that the proportion of patients with poor outcome does not increase over time.[5] Second, there is desynchrony between the recovery and the functional outcomes in schizophrenia. In first episode patients the clinical recovery is a more a norm but is disproportionate to the functional outcomes. Around 75% of first episode psychosis patients show clinical recovery but only one third show functional recovery.[5,6] Lastly, the period around the onset of the psychosis gives us a golden opportunity to intervene on several important predictors of outcome like prolonged untreated psychosis, social isolation, drug use, affective symptoms, non-adherence to medications, the presence of early negative symptoms, and cognitive dysfunction. Intervening early can potentially modify the course of the illness. [7]

What is Early Intervention?

The early Intervention should ideally look at preventing the onset of Schizophrenia in at risk population (Primary Prevention). There is presence of certain molecular, biological, and psychosocial factors at certain points in the life span, has been linked to later development of schizophrenia. Environmental risk factors for schizophrenia include prenatal exposures, obstetric complications, childhood trauma, urban birth, migrant status, and adolescent cannabis use. Identified risk factors are neither necessary nor sufficient causal factors for schizophrenia. The vast majority of people who are exposed to them do not develop schizophrenia and a majority of individuals with schizophrenia may not have had the specific exposure in question.[8]

Therefore early interventions usually aims at providing treatment to people in early stage of illness (secondary prevention), to either uncover the illness at the earliest point (prodrome) or shorten the course and decrease the severity of illness in First episode Psychosis. The two main components of early interventions are Early Detection and Phase specific treatment. Early detection focuses on individuals in Prodrome or those who are psychotic but not yet received adequate treatment. Phase specific treatment would aim at provide intense Psychosocial and clinical intervention at early stage of the illness to prevent progression to psychosis or promote recovery. Early

intervention researchers are hoping that treatment that contains a combination of anti-psychotic medication, psychosocial rehabilitation that includes both the client and his or her caregivers, and assertive community care can function to limit the progression of disability caused by schizophrenia.

The 2 main goals of early interventions in first episode psychosis are reducing the (Duration of Untreated Psychosis) DUP and providing enriched care in the critical period of the illness.[9]

The prodrome or high risk or the ultra high risk approach for early intervention has its own problems. Prodrome is usually a diagnosis in retrospect; many of the symptoms are non specific and occur in other non psychotic illness such as depression. Even though identifying prodrome can help reduce the DUP and improve outcomes along with treating co-morbid substance use and depression early and increase the engagement in treatment. It has high false positive rates and there might be false positive where cases do not develop psychosis in follow up but later convert to psychosis. The antipsychotic therapy can cause adverse effects in false positive cases and increase the stigma and anxiety in such cases. There is also a risk of medicalising a normal response of an individual to stress. The findings from the Edinburgh high risk project indicate that those with genetic loading of schizophrenia, social withdrawal, social anxiety, schizoid and schizotypal personality, behavioural problems, and cognitive impairment are more likely to develop schizophrenia. Ultra high risk study have used attenuated psychotic symptoms, Brief limited intermittent psychotic symptoms and state and trait risk factor as the criteria for selection and have found that there is a significant decline in social and occupational functioning in such case and that around one third of such patients convert to psychosis.[10]

There is some evidence from various studies that ultra high risk group approach is a valid and rational approach, as many of them have significant decline in their academic-occupational and other aspects of social functioning. Transition to psychosis was associated with deficits in the verbal fluency and memory domains, less gray matter in frontal and para hippocampal cortex, and increased presynaptic dopamine synthesis capacity.[11]

The debate over using this approach has been about the transition risk in such cases. A meta-analysis of 27 high risk studies with 2502 subjects has shown conversion rates of 18% after 6months, 22% after 1year, 29% after 2 years and 36% after 3 years of follow up.[12] However recently, especially at the more established at-risk clinics, 12-month transition rates appear to be falling.[13] In a meta-analysis of diagnostic outcome of the high risk studies , out of those who converted to psychosis, 73% of subjects converted to schizophrenia spectrum disorder (50% Schizophrenia) and 11% to mood disorders.[12] There is abundant research to validate the Ultra High risk criteria which lead to the Attenuated psychosis syndrome appearing in the appendix of DSM 5 to bring research on this group under one roof and validate the entity.[14]

Does Early Intervention work?

The studies can be broadly divided into 2 groups, studies on the Prodrome or the Ultra High risk groups and those on FEP.

There was initial enthusiasm on intervention in the prodrome phase as the PACE trial using a randomized controlled trial of low dose risperidone with cognitive behavior therapy versus supportive psychosocial therapy showed that combined pharmacological and psychosocial treatment may delay or avert the onset of psychosis at 6 months.[15] However there was no difference between the groups at 12 months and 35% converted to psychosis. A recent meta-analysis[16] of randomized prevention trials of 12 months or longer follow ups using 15 studies have reported that all interventions were effective and risk reduction was 54% at 1 year and 37% at 2to 4 years. Robust evidence was for Cognitive Behaviour Therapy. The evidence that needed to be replicated was omega-3-fatty acids, integrated therapy and antipsychotics. The question whether any psychological, pharmacological, or nutritional interventions can prevent or delay transition to psychotic disorders for people at high risk was examined in a systematic review and meta-analysis of 11 trials including 1246 participants and 8 comparisons.[17] Moderate quality Evidence was seen for effect of CBT on reducing transition to psychosis at 12 months. Very low quality evidence for omega-3 fatty acids and Low to very low quality evidence for integrated psychotherapy. There was no evidence to support the early promise of some antipsychotic drugs in delaying or preventing transition to psychosis. This study concluded that although evidence of benefits for any specific intervention is not conclusive, these findings suggest that it might be possible to delay or prevent transition to psychosis.

The studies on FEP focused on reducing the DUP. The landmark TIPS study[18] used a comprehensive education and detection system that was delivered by randomized allocation to a healthcare sector in Norway while two control sectors in Norway and Denmark delivered comparable care but without the benefit of efforts to reduce DUP. TIPS demonstrated that reducing DUP (from a median of 1.5 to 0.5 years) led to markedly improved clinical presentations and improved medium and longer term (5-year) outcomes. Recent study reporting 10 yr outcomes also showed good recovery and functionality in early detected patients.[22] However replication of these findings has been difficult exemplifying the significant logistical challenge in such studies. Four pragmatic trials(LEO Trial,[19] OPUS Tial,[20] Norwegian study[21] and STEP USA) using the integrated early interventions service model allocating

participants randomly to treatment groups in FEP showed good outcomes at the end of 1-2 years in reducing the symptoms, improving quality of life and preventing relapses. The effect was not sustained in long term in these studies.

Chocrane review[23] tried to evaluate the effects of early detection; phase-specific treatments; and specialized early intervention teams in the treatment of people with Prodromal symptoms or first episode psychosis. The review focused on randomized trial, included six Studies on prodrome and twelve on FEP. The authors concluded that there is emerging, but as yet inconclusive evidence, to suggest that people in the prodrome of psychosis can be helped by some interventions. There is some support for specialized early intervention services, but further trials would be desirable, and there is a question of whether gains are maintained. There is some support for phase-specific treatment focused on employment and family therapy, but again, this needs replicating with larger and longer trials.

A recent systematic review [24] of the effects of early interventions for psychosis on the usage of inpatient services included 15 studies of FEP that used multimodal intervention across various research designs. The main outcome used to measure the effectiveness was utilization of the inpatient services either in the form of hospitalization or inpatient bed days. Results suggested that early intervention programs are superior to standard care with respect to reducing inpatient service usage.

Concluding the evidence till now shows that, for subjects in Prodrome there are some evidence on Cognitive behaviour therapy but no evidence on usage of low dose antipsychotics. For patients in FEP, integrated therapy or psychosocial or vocational interventions show definite improvement but long term advantage of such improvements has not yet been established.

Are early interventions services worth the cost?

To address this question we need to understand the how to measure cost effectiveness of the services. Whether to measure direct and indirect costs, how measuring benefits which variables to choose? and what to compare it with? With these considerations in mind, available evidence on the potential for early interventions to deliver cost-effective care is not definitive.[25] In Sweden and Australia, specialized early interventions services were found to have lower costs (mostly because of decreased inpatient hospitalizations) and improved symptomatic and functional outcomes, although the durability of these differences remained questionable.[26,27] Extending their analysis to 8 years in a smaller sample, the Australian group subsequently found lower levels of positive symptomatology, improved remission rates and illness course, trends toward increased employment, and significantly lower direct service costs among the early interventions group.[28] This study is important in that it suggests that early interventions confers long-term advantages if more comprehensive indirect costs are taken into account. From a societal perspective even a minor reductions in the unemployment and family burden with long term implication might offset more immediate cost of early interventions.

Criticism

The main criticism for early interventions services comes from the opponents who raise important questions. Whether early interventions services are really changing the course of schizophrenia? Whether intervening in the prodrome is justified? What is so special about these interventions that a standard Community mental health team cannot address? And how long the intervention needs to be given? Is 3 yrs a valid duration for the intervention? Is the extra cost for the stand alone services worth the outcome? [29]

What do we know?

The concept of early intervention is good to focus on people at risk of developing schizophrenia and monitor them regularly. There is no evidence to intervene in at risk population at this point of time. Interventions in the prodrome still needs to be validated first in establishing the existence of a clinically identifiable syndrome like Attenuated Psychosis Syndrome and then what treatments are likely to benefit in preventing a transition to psychosis. There is strong evidence that early interventions in the critical period shows better clinical and functional outcomes but long term outcome has not yet been established.

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