# Prevention of Schizophrenia: A Review

Yatan Pal Singh BALHARA

**SUMMARY**

Research over the years has introduced multiple interventions for schizophrenia. Notwithstanding the nature of intervention pharmacological or psychological a complete cure for the condition remains a much-desired, yet unachieved goal. What is required is an exploration of alternative intervention strategies for treating schizophrenia a preventive approach is such an option. The chronic nature of schizophrenia and its associated disabilities have a tremendously negative affect the quality of life of patients, their families, and communities. Among the preferred approaches to reducing the negative consequences associated with the disorder is the prevention of its emergence. This review aimed to present the available data on the prevention of schizophrenia data that suggest some pharmacological and non-pharmacological interventions have a potential role in the prevention of schizophrenia. Nonetheless, the findings are restricted to a few sites and are at best preliminary; as such, the findings must be replicated in new studies that include large samples and different settings.

**Keywords:** Schizophrenia, prevention, antipsychotics

## INTRODUCTION

Schizophrenia is a leading contributor to the global burden of disease (WHO 2001) and is among the top 10 contributors to years lived with disability (YLD), both among men and women. In terms of the global burden of disease, schizophrenia is the 7th leading cause of YLD, accounting for 2.8% of total global YLD (Mathers et al. 2006). Schizophrenia is responsible for enormous costs to the healthcare budget of many countries. Up to 3% of the total healthcare budget in developed countries like the US is spent on the management of schizophrenia (Knapp et al. 2004). The chronic nature of schizophrenia and the lack of an effective cure mean that the relative contribution to the disability is likely to be more by such cases owing to their early onset and likely longer total duration of illness. Furthermore, the impact is greater when treatment services are inadequate, in terms of availability, accessibility, and acceptability.

### The Concept of Prevention Used Herein

Prevention can occur at different stages of the disease course. Prevention can be performed prior to the onset of disease risk factors (primordial prevention), after the onset of such risk factors, but before the onset of disease (primary prevention), after the onset of disease with the aim of diagnosing and intervening as early as possible (secondary prevention), and after the onset of disease with the aim of reducing or minimizing disease-associated disability (tertiary prevention). Preventive intervention, as per the Institute of Medicine (IOM) Committee on Prevention of Mental Disorders classification, is restricted to interventions provided before a patient receives a psychiatric diagnosis (Mrazek and Mrezak 2004), which is the definition used relative to the present review, which is concerned with primordial and primary prevention of schizophrenia.

**Received:** 05.12.2011 - **Accepted:** 06.07.2012

Assist. Prof. of Psychiatry, National Drug Dependence Treatment Centre (NDDTC), All India Institute of Medical Sciences (AIIMS), New Delhi, India.

E-mail: *ypsbalhara@gmail.com*

## Is It Possible to Prevent Schizophrenia: A Window of Opportunity?

In order to prevent the onset of a condition (disease) one should have a reasonable degree of understanding of the causative factors. Additionally, interventions must be made put into effect at an appropriate time, i.e. either prior to the emergence of causal factors or after the emergence of causal factors, but prior to the onset of the condition. If appropriate preventive measures are put in place during the appropriate time period they are likely to prevent onset of the condition. This model is applicable to various medical conditions, especially infectious diseases.

Although the causal factors of schizophrenia are not fully known, advancements have been made in our understanding of the risk factors that contribute to its development (King et al. 2005). Thus, preventive interventions can be planned based on these factors. Moreover, the concept of prodrome in schizophrenia (a phase that can last for years) provides an opportunity to act prior to the onset of observable psychotic signs and symptoms (Hafner et al. 2006). In fact, the presence of an identifiable pre-psychotic phase in schizophrenia has generated great interest as a potential preventive strategy. As such, preventive measures could be applicable to schizophrenia.

Of the various prevention approaches, emphasis has been directed towards indicated prevention for schizophrenia (Killackey and Yung 2007). Indicated prevention focuses on those with some of the early signs and symptoms of schizophrenia, and as such are likely to be relatively resource efficient. The universal prevention approach targets a relatively larger section of the population. The issue of viability and cost-effectiveness plays a major role in such situations. The base rate of schizophrenia is very low; hence, a universal prevention approach is unlikely to be viable (McGorry et al. 2005).

## Detection of the Pre-Psychotic Phase

Detection of the pre-psychotic phase of schizophrenia is central to the concept of its prevention. The aim is to detect those at risk of developing the condition as early as possible and then to administer appropriate interventions targeting specific risk and protective factors.

Different approaches have been used to determine the pre-psychotic phase and to define the high-risk group. These include the close-in approach (Bell 1992), basic symptom approach, and clinical high-risk approach (Cornblatt et al. 2002).

According to the close-in approach, individuals must meet a number of conditions in order to be included in the high-risk group. This approach includes the behavioral difficulties in adolescence while assessing the ultra high-risk group. Multiple gate screening and close-in follow-up of individuals considered at risk for developing psychosis aims to minimize the false positive rate. While multiple gate screening involves use of numerous screening measures, close-in follow-up involves closely spaced follow-up assessments. Individuals assessed using this approach are likely to be those seeking help for themselves or those referred for treatment by their family; as such, they are likely to exhibit clinical problems (McGorry et al. 2003). This approach has been used in many studies referred to as ultra high-risk studies. One of the earliest uses of this approach was at the Personal Assessment and Crisis Evaluation (PACE) Clinic (McGorry and Singh, 1995; Yung et al. 1995), which led to the development of the Early Psychosis Prevention and Intervention Center (EPPIC) program (Edwards et al. 1994; McGorry 1993).

The basic symptom approach emphasizes the importance of assessment of the basic symptoms, and is based on the premise that the cognitive, affective, and social disturbances associated with schizophrenia occur years before the first psychotic episode, and that such disturbances are often recognized by the affected individual during this early stage. The detection of the prodrome, thus, should be based on observation of these features. The Bonn long-term study (Huber et al. 1979), age-beginning-course study (Hafner et al. 2002), and Cologne early detection study (Klosterkotter et al. 2001) have used this approach.

The clinical high-risk approach emphasizes the importance of clinical psychotic features in identifying the prodromal phase. This approach relies on observation of the attenuated positive psychotic features or specific combinations of cognitive, academic, and social impairment, as well as disorganization/odd behavior (represented by the acronym CASID). The onset of schizophrenia, rather than the first episode of psychosis, is the target of prevention in this approach. As a result, even frankly psychotic features could be treated as a sub-threshold form of schizophrenia. The Hillside Recognition and Prevention (H-RAP) Program uses this approach (Phillips et al. 2005). The ultra high-risk and basic symptom approaches are increasingly considered to be complementary.

## Defining the High-Risk Prodromal Group

In order to develop and administer preventive services for schizophrenia it is essential that the target population be defined. As discussed in the previous section, due to the low base rate for schizophrenia in the general population universal and selective prevention strategies are unviable; therefore, indicated prevention should be the aim (Killackey and Yung 2007). Specific criteria to identify this subgroup of high-risk individuals in the general population have been developed by several researchers and although there is some overlap between the different approaches they are not the same.

In order to avoid any confusion associated with use of the term prodrome and to incorporate the prospective approach into preventive measures the term at-risk mental states has been advocated (Mason et al. 2004; McGorry and Singh, 1995; Yung et al. 1995), which indicates a prospectively defined syndrome that appears to be consistent with the schizophrenia prodrome, but by definition is not necessarily a harbinger of psychosis (Compton et al. 2007). Similarly, others have referred to this period as the clinical high-risk period, because the prodrome label implies a greater likelihood of developing schizophrenia than that can be definitively established (Comblatt et al. 2002).

McGorry et al. (2003) defined 3 prodromal syndrome types for determining high-risk groups for the development of schizophrenia: attenuated positive symptom syndrome (APSS), brief intermittent psychotic syndrome (BIPS), and genetic risk plus functional deterioration (G/D). The diagnostic criteria for these syndromes are shown in Table 1.

McGlashan et al.'s criteria are also closely based on these criteria and are referred to as criteria of prodromal syndromes (COPS). Cornblatt et al. described the clinical high-risk (CHR) status in terms of 2 categories: CHR– (attenuated negative/disorganized symptoms) and CHR+ (attenuated positive symptoms in addition to attenuated negative/disorganized symptoms (Cornblatt and Auther 2007; Cornblatt et al. 2002).

In order to improve the predictive power of such assessment tools additional premorbid risk factors have been used together with traditional high-risk criteria. This approach circumvents the possibility of prolonged duration of exposure to risk factors if a prolonged observation period with the same set of features was used as the strategy to increase predictive power. These criteria are referred to as ultra high-risk (UHR) criteria and include the following: 1. Attenuated and brief, limited intermittent psychotic symptoms (BLIPS); 2. A decrease in the Global Assessment of Functioning (GAF) score ≥30 points within a 6-week period, plus a family history of schizophrenia or schizotypal personality (Yung et al. 2003).

## Assessment of High-Risk States

Numerous scales and interview schedules have been develop in order to facilitate the assessment of high-risk states. Some of the commonly used assessment tools are the Comprehensive Assessment of At-Risk Mental States (CAARMS), Scale of Prodromal Symptoms (SOPS), Structured Interview of Prodromal Symptoms (SIPS), DSM-III-R Prodromal Symptoms of Schizophrenia, Bonn Scale for the Assessment of Basic Symptoms (BSABS), and Youth Psychosis at Risk Questionnaire (Y-PARQ) (Ord et al. 2004).

CAARMS is a semi-structured interview for assessing prepsychotic (prodromal) symptomatology. CAARMS considers the intensity, frequency, and duration of symptoms. It is designed to track small changes in an individual's symptoms and experiences. The dimensions measured by this scale are disorders of thought content, perceptual abnormalities, conceptual disorganization, motor disturbances, disorders of emotion and affect, impaired energy, and impaired tolerance to normal stress. The CAARMS is reported to have good-to-excellent inter-rater reliability and predictive validity (McGorry and Singh, 1995).

BSABS is a 66-item scale that assesses disturbances in thought, language, perception, bodily sensations, stress tolerance, affect, energy, concentration, memory, emotional reactivity, social contacts, and non-verbal expression (Miller et al. 2002).

SIPS is a semi-structured interview originally based on CAARMS and the Positive and Negative Symptom Scale (PANSS). Ratings are made on the SOPS. These instruments were developed by the PRIME group. SIPS/SOPS measures a group of 5 psychotic symptoms, a group of 6 negative symptoms, and a group of 4 disorganization symptoms on

**Table 1**. High-risk groups for the development of schizophrenia, according to McGorry et al.

| Attenuated Positive Symptom Syndrome (APSS) | Brief Intermittent Psychotic Syndrome (BIPS) | Genetic risk plus Functional deterioration (G/D) |
|---|---|---|
| Abnormal unusual thought content, suspiciousness, grandiosity, perceptual abnormalities, and/or organization of communication that is below the threshold of frank psychosis.<br>+<br>These symptoms began or exacerbated during the previous past year.<br>+<br>These symptoms occurred at least once each week during the previous month.<br>+<br>Psychosis is ruled out. | Frankly psychotic unusual thought content, suspiciousness, grandiosity, perceptual abnormalities, and/or organization of communication.<br>+<br>These symptoms began during the previous 3 months.<br>+<br>The symptoms currently occur for at least several minutes each day and at least once each month.<br>+<br>Psychosis is ruled out | First-degree relative with a history of any psychotic disorder, or<br>schizotypal personality disorder in patient.<br>+<br>Substantial functional decline during the previous year.<br>+<br>Psychosis is ruled out. |

a 6-point severity scale. Additionally, the severity of current symptoms (6 points) and that of pre-psychotic symptoms (5 points) are measured.

The Schizophrenia Prediction Instrument-Adult Version (SPI-A) was developed by Schultze-Lutter and Klosterkötter and is based on BSABS. SPI-A is used to assess 7 groups of basic symptoms: overstrain, emotional deficits, cognitive impairment, cognitive disturbances, body perception disturbances, perception and motor disturbances, and estrangements (Schultze-Lutter and Klosterkötter 2004).

DSM III criteria for prodrome of schizophrenia were modified by Yung and Jackson (1999) for assessing the at-risk mental state. The criteria include social isolation or withdrawal, impaired role functioning, peculiar behavior, impaired personal hygiene, blunted or inappropriate affect, digressive speech or poverty of ideas, odd beliefs or magical thinking, unusual perceptual experiences, and lack of initiative, interests, or energy. Some additional at-risk indicators were added to these features to facilitate more comprehensive assessment and include attention or cognitive symptoms, neurological soft signs, structural brain abnormalities, transient psychotic symptoms, and family history of psychosis.

## Available Prevention Interventions

Since the past decade interest in preventive interventions for schizophrenia have been increasing. Several research groups have been active in assessing the effectiveness and applicability of different interventions. The prevention strategies that have been assessed include both pharmacological and non-pharmacological interventions. The primary aim of preventive interventions is two-fold. The first is to reduce distressing symptoms experienced by young people that meet the high-risk criteria, and the second is to prevent these symptoms from exacerbating and developing into acute psychosis. The underlying basis for these approaches is the stress-vulnerability model of psychosis.

Non-pharmacological approaches to prevention include psychoeducation, supportive therapy, interpersonal therapy, family therapy, group therapy, and social skills and stress management groups. Cognitive behavior therapy (CBT)-based interventions have been employed at the PACE clinic (McGorry and Singh 1995) and make use of modified CBT techniques for treating psychosis. The technique emphasizes close collaboration between the therapist and client, individualized intervention, and gaining an understanding of the experiences and strategies necessary for coping with and/or reducing the symptoms. Additionally, assistance for liaising with housing, education, employment, or other services is also carried out.

Other programs like early detection and intervention evaluation (EDIE) for people at high-risk of psychosis in Manchester, UK, are based on cognitive therapy (Morrison et al. 2004) and aim to assist at-risk young people to cope with their symptoms, and reduce the risk of and possibly prevent the onset of acute psychosis. These interventions target the symptoms that cause distress and disability, and are structured according to a formulation of the affected individual's life experiences, environment, self and social knowledge, and intrusions, as well as their interpretations of intrusions, and their emotional, behavioral, cognitive, and physiological responses. The underlying principle of such approaches is change state-strategies, which focuses on normalization of experiences and evaluation of alternative explanations.

The role of pharmacological agents in the prevention of schizophrenia is debatable and the optimal approach remains unknown. The rationale cited for use of medications is their efficacy in individuals with established psychotic illnesses. This effect is likely to extend to those in the pre-psychotic phase of schizophrenia. Randomized controlled trials have been conducted with olanzapine and risperidone (Salokangas and McGlashan 2008) (Table 2). Open-label trials with amisulpride (Ruhrmann et al. 2006. 2005), risperidone and haloperidol (Keri et al. 2006), and aripiprazole (Walsh et al. 2006) have reported positive results, including a reduction in attenuated psychotic and negative symptoms, a reduced rate of conversion to psychosis, and improvement in functioning in those receiving the active drug; however, concerns remain over the safety of their use in children. It was reported that younger patients might be more sensitive to the extra pyramidal side effects (EPSEs) of antipsychotic medication than adults. In addition, the high false positive rates of the assessment tools used to identify those at high-risk results in a much higher number of children taking antipsychotics than is necessary (Lewis 1998).

Other medications used to prevent the onset of schizophrenia include neuroprotective agents, antidepressants, corticotrophin-releasing hormone receptor agonists, and estrogen (Phillips et al. 2005). Use of neuroprotective agents is based on the premise that dysregulation of neuronal cell production and degeneration in some brain regions might result in neurodevelopmental abnormalities observed in psychosis and that intervening at this level could prevent the onset of the disorder (Berger et al. 2003). Drugs of this class that have been used include lithium (Berger and McGorry 2002; Manji et al. 1999), eicosapentaenoic acid (EPA) (Fenton et al. 2000), and glycine (Javitt et al. 2001); however, evidence of the effectiveness of all neuroprotective agents is limited.

Antidepressants have also been used for preventive interventions in an effort address the potentially troublesome side effects associated with antipsychotics. In fact, some preliminary research has shown that they are comparable in efficacy to antipsychotics; however, as most current at-risk mental state assessment criteria are based on the emergence of attenuated

**Table 2**. Published RCTs on the prevention of schizophrenia.

| STUDY | TYPE | INTERVENTION | N | RESULTS |
|---|---|---|---|---|
| Amminger et al. 2010 | RCT | Omega-3 PUFA vs. placebo | 76 | 2 of 41 individuals (4.9%) in the omega-3 PUFA group and 11 of 40 (27.5%) in the placebo group had transitioned to psychotic disorder (P = 0.007). Omega-3 PUFA significantly reduced positive symptoms (P = 0.01), negative symptoms (P = 0.02), and general symptoms (P = 0.01), and improved functioning (P = 0.002), as compared to placebo. |
| McGorry et al. 2003 (at PACE clinic) | RCT | Combined intensive cognitive treatment and risperidone 1-2 mg $d^{-1}$ (SPI), vs. need-based intervention (NBI) | | At month 6 more participants in the NBI group developed acute psychosis (P < 0.05) |
| McGlashan et al. 2004 (at PRIME clinic) | Db RCT | Olanzapine vs. placebo | 60 | Psychosis at 12 months: 16% of active; 38% of controls (P = 0.09) |
| Morrison et al. 2004 | RCT | Cognitive therapy vs. treatment as usual | 58 | Psychosis over the course of 12 months: 6% in the CT group; 22% of controls |
| Bechdolf et al. 2006 | RCT | Comprehensive cognitive-behavioral therapy vs. supportive counseling | 128 | By month 12 transition to sub-threshold psychotic symptoms (38% vs. 17.3%; P = 0.024) and schizophrenia (1.9 vs. 12.1; P = 0.041) was lower in the cognitive therapy group |

PUFA: Polyunsaturated fatty acid; PACE: personal assessment and crisis evaluation.

or brief psychotic features, there is little rationale for their use. A randomized controlled trial (RCT) of omega-3 polyunsaturated fatty acids reported encouraging results, in terms of preventing progression to frank psychosis (Amminger et al. 2010). RCTs on schizophrenia prevention strategies are summarized in Table 2.

Only a few relevant trials have been conducted and at present there is little conclusive evidence regarding the protective effects of antipsychotic medication in patients with childhood schizophrenia. Additionally, there s concern about the side effects of these medications (Morrison et al. 2004). A Cochrane review of early intervention for psychosis concluded that there was an insufficient number of trials to draw any definitive conclusions (Marshall et al. 2006). Moreover, the available RCTs are not free of limitations. For instance, a study by McGorry et al. (2002) was not blind, and the active treatment was a combination of psychosocial and pharmacotherapeutic methods. Additionally, Morrison et al.'s (2004) study did not use blinding and their findings are no longer significant because patients that were retrospectively determined to have been psychotic at the time of intake were not dropped from the cognitive therapy group. McGlashan et al. (2004) reported that drug-placebo difference in conversion rates was only trend-level significant and the risks of medication (e.g. weight gain) proved to be substantial (McGlashan et al. 2007).

## Schizophrenia Prevention Programs

Research groups located primarily in USA, UK, and Australia are involved in schizophrenia prevention programs, and are involved in providing clinical care services as well. The main objectives of these programs/services are as follows, as described by Phillips et al. (2005):

To improve our understanding of the neurobiological and psychosocial processes that occur during the pre-psychotic phase, and contribute to the onset of acute and persistent psychosis.

To improve our understanding of the processes that protect against progression, and promote recovery and resolution of symptoms and impairment.

To develop and evaluate a range of psychosocial and biological interventions for treating current syndromes, and to prevent future disorders from fully manifesting.

To establish a clinical paradigm that is highly accessible and acceptable to young people in the ultra-high risk of psychosis group.

These programs have a lot in common. The aims, approaches, assessments, and interventions used by these programs are described in Table 3, and some of these programs are presented in Table 4.

**Table 3**. Main features of schizophrenia prevention.

| | |
|---|---|
| AIMS | Identification of young people at high risk of developing first-episode psychosis in the near future |
| Target Population | Services provided to help-seeking young people.<br>Those that do not wish to be treated are not to be compelled to participate.<br>Services do not actively promote care to those that are asymptomatic, not distressed, or not seeking help. |
| Assessment Approach | A combination of mental state risk factors, and genetic or trait risk factors is used. |
| Focus of Services | Management of current difficulties.<br>Monitoring and possible prevention or attenuation of emerging psychosis. |
| Nature of Services | Provide a clinical, as well as research or evaluative component. |
| Policy on use of Antipsychotics | Services using very low doses of antipsychotic medication. |
| Continuity of Care | Services that are linked with early psychosis services or are able to provide management of first-episode psychosis. |

## Universal Prevention Approach

The preventive approaches described previously are categorized as selective prevention. These prevention strategies target individuals known to have some risk factors for the development of schizophrenia. Their cost effectiveness and viability support their use (Killackey and Yung 2007); however, universal prevention of schizophrenia has been employed in some countries. Universal prevention strategies cater to the general population and thus avoid overlooking anyone in need of the necessary services, as can be the case with indicated prevention. A Norwegian study based on the universal prevention model used an extensive public information campaign to educate the general population, schools, and healthcare professionals regarding the signs and symptoms associated with early psychosis and the long-term benefits of early referral, diagnosis, and treatment (Ueland and Rund 2005). As compared with the period prior to the campaign, the incidence of reported psychotic illness increased to approximately 40%. Additionally, there was an associated reduction in the time from to initiation of treatment or DUP.

## Hurdles in the Prevention of Schizophrenia

As mentioned above, in order to develop a preventive intervention for any disorder there must be a window of opportunity (the time to intervene) and a set of identifiable risk and/or protective factors. Preventive interventions for schizophrenia, as described herein, aim at identification of at-risk individuals; thus, accurate identification of this population is a major limiting factor in carrying out any prevention intervention. There remains no consensus on the concept of the prodrome phase of schizophrenia; in fact, whereas the prodrome was mentioned the DSM III (1980), it is not included in the current version of DSM IV (1994). The signs and symptoms used to describe prodrome are non-specific and could be the harbinger of other disorders. The prodrome of schizophrenia can be confused with the early stages of affective disorders, pervasive developmental disorders, substance use disorders, personality disorders, cognitive disorders, PTSD, and certain non-psychiatric conditions. Moreover, prodrome can be definitively diagnosed in retrospect when the clinical picture has evolved into schizophrenia. In order to address these issues

**Table 4**. Schizophrenia prevention programs.

| SERVICE/ PROGRAM | LOCATION |
|---|---|
| Personal Assessment and Crisis Evaluation (PACE) Clinic | Melbourne, Australia |
| Prevention via Risk Identification, Management and Education (PRIME) Clinic | Yale University, USA |
| H-RAP Program | New York, USA |
| Psychological Assistance Service (PAS) | Newcastle, Australia |
| Early Treatment of Pre-Psychosis (TOPP) clinic | Norway |
| Early Identification and Intervention Evaluation (EDIE) trial | Manchester, UK |
| Early Recognition and Intervention Center | Germany |
| OASIS | South London, UK |
| The Cognitive Assessment and Risk Evaluation (CARE) Program | University of California, San Diego, USA |
| Center for the Assessment and Prevention of Prodromal States | University of California, Los Angeles, USA |

the concept of at-risk mental state has been used in research on the prevention of schizophrenia with increasing frequency. This term has been coined to avoid the confusion surrounding prodrome and to give a prospective notion to the concept (Bell 1992).

Despite some of the advantages associated with the concept of at-risk mental state, it is not entirely free of shortcomings. The rate of transition of the at-risk mental state to acute psychosis varies according to study. The rate of transition over a 12-month period in 1 study varied from a high of 70% to a low of 9.4% (Cadenhead 2002). Possible causes of this variability include variation in the underlying proportions of true- and false-positives that were referred for treatment. Yung et al. reported a 34% transition rate among those clinically identified as prodromal. On the other hand, only 10% of those clinically identified as possibly prodromal that met the ultra high-risk criteria for psychosis progressed to psychosis over a 6-month period (Yung et al. 2006). Moreover, differences in the base rate of psychosis in different source samples may have accounted for the differences in the transition rate. It has been observed that the population from which participants are drawn affects the predictive validity of the intake criteria. In addition, as the prevalence of a disorder decreases the positive predictive value decreases. Inter-center variability is not only due to differences in the criteria for the at-risk mental state; despite of use of similar approaches, use of different scales can also affect the detection rate and transition rate. Other factors contributing to these limitations include recall bias, cognitive deficits, and the presence of depression/anxiety symptoms and attenuated symptoms. Furthermore, the retrospective nature of some studies is associated with inherent limitations.

Concerns have been raised over the effectiveness of such approaches. It has been estimated that the prevalence and incidence of pre psychosis are 10%-20% and 1%-2%, respectively (van Os and Delespaul 2005; Cadenhead, 2002). Additionally, high-risk individuals have a 50% transition rate to a psychotic disorder over a 3-6-month period (Yung et al. 2003; Miller et al. 2002;). van Os and Delespaul (2005) reported that with these figures 99% of cases would be rated false-positive based on the incidence of subclinical psychotic experiences and about 95% would be rated as false-positive based on the prevalence of subclinical psychotic experiences. Thusly, the predictive value of current approaches does not exceed 5%. With this predictive value and a treatment success rate of 25%, the NNT would be 80. Even if the treatment success rate increases to 50%, the NNT would reach a high of 40 (van Vos and Delespaul, 2005).

## The Future

In order to overcome the limitations of the current approaches and improve the effectiveness of preventive interventions numerous recommendations have been made, which include strengthening and augmentation of current approaches, as well as the introduction of approaches based on new paradigms. In addition, the sample enrichment technique can be used to improve sampling for preventive intervention programs, which also improves sensitivity as well as specificity. A two-tiered strategy in which initial screening is followed by detailed screening, or a series of selection processes is likely to be beneficial. Use of post hoc criteria to pick small developmental differences has also been recommended. In addition, sampling from an appropriate site can also reduce false-positive/negative rates, and hence increase the positive predictive value (PPV). Whereas in the general population the prevalence of schizophrenia is 0.6% the basic symptoms have a 1.4% PPV; a specialized department with special interest in schizophrenia (having a prevalence of 50%) could provide a PPV of basic symptoms as high as 70% (Klosterkotter et al. 2001). Furthermore, use of combinations of multiple predictors can increase the predictive value. Subclinical psychotic experiences and family history of schizophrenia –when used alone– have a 1-year predictive value of 4% and 0.5%, respectively; however, if both are used in combination the 2-year predictive value increases to 25% (van Os and Delespaul, 2005).

The reviewed preventative approaches aim to augment the detection of schizophrenia and subsequent preventive interventions via at-risk metal state strategies. Some approaches address other issues as well and target modifiable risk and protective factors for schizophrenia. Research has shown the potential role of multiple risk and protective factors in the development of schizophrenia (King et al. 2005). The strength of the association between individual risk factors and schizophrenia vary. Some of these have been studied in greater detail. Family history of schizophrenia has a relative risk (RR) of 7.3-59.7 for development of schizophrenia (Mortensen et al. 1999); other risk factors include head injury (RR of 2) (AbdelMalik et al. 2003), a preference for solitary play (RR of 2) (Jones et al. 1994), and obstetrical complications (RR of 1.38) (Geddes et al. 1999). The risk factors that are modifiable and have a strong association with the development of schizophrenia can be targeted via specific preventive interventions.

Brown et al. (2001) reported that 21% of their birth cohort with congenital rubella met the criteria for a schizophrenia spectrum disorder during assessment over 30 years. Thus, immunization of women of reproductive age could be a potential preventive intervention strategy for reducing the emergence of congenital rubella. Maternal deficiency of folate as well as other micronutrients is hypothesized to play a role in the etiology of at least some cases of schizophrenia (Mattson and Shea 2003); hence, dietary folate supplementation could be an effective prevention intervention. A similar approach by

the USFDA for the prevention of neural tube defects in newborns resulted in a 31% reduction in the prevalence of spina bifida and a 16% reduction of in the prevalence of anencephaly, following fortification of cereal grain products with folate (Williams et al. 2005). An association between head injury, especially in childhood, and the risk of subsequent schizophrenia has been observed (AbdelMalik et al. 2003). Use of preventive strategies like educational and public safety interventions, including the construction of safe playgrounds, could reduce the incidence of head injuries. Such an approach by the Harlem Hospital Injury Prevention Program in New York City resulted in a 45% decline in head injuries (Durkin 1999). Similarly, cognitive and behavioral abnormalities observed during the pre-morbid stages of schizophrenia could be subjected to remediation; such an approach has shown promising results in terms of the cognitive and behavioral precursors of other childhood mental and behavioral conditions (Rebok et al. 1996; Mrazek and Haggerty 1994; Kellam et al. 1991). Obstetric complications most closely associated with an increased risk of developing schizophrenia include fetal oxygen deprivation (Geddes et al. 1999), prolonged labor, placental complications, premature delivery, maternal obesity prior to pregnancy (Rebok et al. 1996), and maternal respiratory infections during the second trimester of pregnancy (Brown et al. 2001). These complications can be managed by improving antenatal and perinatal services.

The examples cited above could become a part of future prevention interventions for schizophrenia; however, first they need to be subjected to additional rigorous research in order to more clearly determine their effectiveness and applicability. The prevention of childhood onset schizophrenia is challenging; yet, the issue has attracted the interest and attention of various research groups. Over the past 2 decades systematized research in this field has expanded; however, the evidence available to date has emerged from limited settings. Both pharmacological and non-pharmacological interventions have shown promise with respect to prevention of the emergence of schizophrenia in those at high risk for developing the condition. The findings published by the available studies offer promise, although more detailed and rigorous research is necessary before the findings could be put into day-to-day practice. Additionally, careful consideration of the important ethical issues associated with these approaches must be undertaken. Education of the caregivers of those at high risk for developing schizophrenia is also important for increasing the level of acceptance of such services, when available.

## REFERENCES


AbdelMalik P, Husted J, Chow EW et al (2003) Childhood head injury and expression of schizophrenia in multiply affected families. Arch Gen Psychiatry 60: 231–6.

Amminger GP, Schäfer MR, Papageorgiou K et al (2010) Long-Chain omega--3 Fatty Acids for Indicated Prevention of Psychotic Disorders: A Randomized, Placebo-Controlled Trial. Arch Gen Psychiatry 67:146-54.

Bechdolf A, Wagner M, Veith V et al (2006) A randomized controlled trail of cognitive-behavioral therapy in the early initial prodromal state of psychosis. Presentation in the 18th Biennial Winter Workshop on Schizophrenia Research, Davos, 4 February 2006. Schizophr Res 81 Suppl:22-3.

Bell RQ (1192) Multiple-risk cohorts and segmenting risk as solutions to the problem of false positives in risk for the major psychoses. Psychiatry 55:370-81.

Bentall RP, Morrison AP (2002) More harm than good: The case against using antipsychotic drugs to prevent severe mental illness. J Ment Health 11: 351-65.

Berger G, Wood SJ, McGorry PD (2003) Incipient neurovulnerability and neuroprotection in early psychosis. Psychopharmacology Bulletin 37:79-101.

Berger GE, McGorry PD (2002) "Neuroprotection in Early Psychosis—A New Avenue to Explore?" Paper presented at the XII World Congress of Psychiatry, Yokohama, Japan.

Brown AS, Cohena P, Harkavy-Friedmana J et al (2001) Prenatal rubella, premorbid abnormalities, and adult schizophrenia. Biol Psychiat 49: 473-86.

Cadenhead K (2002) Vulnerability markers in the schizophrenia spectrum: implications for phenomenology, genetics and the identification of the schizophrenia prodrome. Psychiat Clin N Am 25: 837-53.

Compton MT, McGlashan TH, McGorry PD (2007) Toward Prevention Approaches for Schizophrenia: An Overview of Prodromal States, the Duration of Untreated Psychosis, and Early Intervention Paradigms. Psychiat Ann 37:340-8.

Cornblatt B, Lencz T, Obuchowski M (2002) The schizophrenia prodrome: Treatment and highrisk perspectives. Schizophr Res 54:177-86.

Cornblatt BA, Auther AM (2005) Treating early psychosis: Who, what, and when? Dialogues Clin Neurosci 7:39-49.

Durkin MS, Laraque D, Lubman I et al (1999) Epidemiology and prevention of traffic injuries to urban children and adolescents. Pediatrics 103.

Edwards J, Francey SM, McGorry PD et al (1994) Early psychosis prevention and intervention: Evolution of a comprehensive community-based specialised service. Behave Change ll:223-33.

Fenton WS, Hibbeln J, Knable M (2000) Essential fatty acids, lipid membrane abnormalities, and the diagnosis and treatment of schizophrenia. Biol Psychiat 47: 8-21.

Geddes JR, Verdoux H, Takei N et al (1999) Schizophrenia and complications of pregnancy and labour: an individual patient data meta-analysis. Schizophrenia Bull 25: 413 -23.

Hafner H, Maurer K (2006) Early detection of schizophrenia: current evidence and future perspectives. World Psychiatry 5:3.

Hafner H, Maurer K, Loffler W, et al (2002) The early course of schizophrenia. In Risk and Protective Factors in Schizophrenia:Towards a Conceptual Model of the Disease Process (ed. H. Hafner), pp. 207-228. Darmstadt: Steinkopff.

Hanssen M, Bak M, Bijl R et al (2004) The incidence and outcome of subclinical psychotic experiences in the general population. Br J Clin Psychol. In press.

Hawkins KA, McGlashan TH, Quinlan D et al (2004) Factorial structure of the Scale of Prodromal Symptoms. Schizophr Res 68:339-47.

Huber G, Gross G, Schuttler R (1979) Schizophrenie.Verlaufsund sozialpsychiatrische Langzeituntersuchungen anden 1945-1959 in Bonn hospitalisierten schizophrenen Kranken. Bonn: Springer.

Javitt DC, Silipo G, Cienfuegos A (2001) Adjunctive high-dose glycine in the treatment of schizophrenia. Int J Neuropsychopharmacol 4:385-91.

Jones P, Rodgers B, Murray R, et al (1994) Child development risk factors for adult schizophrenia in the British 1946 birth cohort. Lancet 344: 1398–402.

Kellam SG, Werthamer-Larsson L, Dolan LJ et al (1991) Developmental epidemiologically based preventive trials: Baseline modeling of early target behaviors and depressive symptoms. Am J Commun Psychol 19: 563-84.

Kennedy E, Kumar A, Datta SS (2007)Antipsychotic medication for childhood-onset schizophrenia. Cochrane Database of Systematic Reviews, Issue 3. Art. No.: CD004027. DOI: 10.1002/14651858.CD004027.pub2

Keri S, Kelemen O, Janka Z (2006)Therapy of mental states at high risk for psychosis: Preliminary results from Hungary. Orv Hetil 147:201-4.

Killackey E, and Yung AR (2007) Effectiveness of early intervention in psychosis. Curr Opin Psychiatry 20:121-5.

King S, Laplante D, Joober R (2005) Understanding putative risk factors for schizophrenia: retrospective and prospective studies J Psychiatry Neurosci 30:342-8.

Klosterkotter J, Hellmich M, Steinmeyer EM, et al (2001) Diagnosing schizophrenia in the initial prodromal phase. Archives of General Psychiatry 58, 158-64.

Knapp M, Mangalore R, Simon J (2004) The Global Costs of Schizophrenia. Schizophrenia Bull 30:279-93.

Lewis R (1998) Typical and atypical antipsychotics in adolescent schizophrenia: efficacy, tolerability, and differential sensitivity to extrapyramidal symptoms. Can J Psychiat 43:596–604.

Manji HK, Moore GJ, Chen G (1999) Lithium at 50: have the neuroprotective effects of this unique cation been overlooked? Biol Psychiat 46:929-40.

Marshall M, Rathbone J (2006) Early Intervention for psychosis. Cochrane Database of Systematic Reviews, Issue 4. Art.No.: CD004718. DOI: 10.1002/14651858.CD004718.pub2

Mason O, Startup M, Halpin S et al (2004) Risk factors for transition to fi rst episode psychosis among individuals with 'at-risk mental states.' Schizophr Res 71:227-37.

Mathers CD, Lopez AD, Murray CJL (2006)The Burden of Disease and Mortality by Condition: Data, Methods, and Results for 2001. In: Global Burden of Disease and Risk Factors. (eds) Alan D. Lopez, Colin D. Mathers, Majid Ezzati, Dean T. Jamison, Christopher J. L. Murray, Geneva, pp 552.

Mattson MP, Shea TB (2003) Folate and homocysteine metabolism in neural plasticity and neurodegenerative disorders. Trends Neurosci 26:137-46.

McGlashan TH, Addington J, Cannon T et al (2007) Recruitment and Treatment Practices for Help-Seeking "Prodromal" Patients. Schizophrenia Bull 33:715–26.

McGlashan TH, Zipursky RB, Perkins DO et al (2004) Olanzapine vs. placebo for prodromal schizophrenia. Schizophr Res 67 Suppl:6.

McGorry P, Killackey E, Lambert T et al (2005) Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for the treatment of schizophrenia and related disorders. Aust NZ J Psychiat 39: 1-30.

McGorry PD, Singh BS (1995) Schizophrenia: Risk and possibility. In: Raphael, B., and Burrows, G.D., eds. Handbook of Studies on Preventive Psychiatry. Amsterdam: Elsevier pp. 491-514.

McGorry PD, Yung AR, Phillips LJ (2003) The "Close-in" or Ultra High-Risk Model: A Safe and Effective Strategy for Research and Clinical Intervention in Prepsychotic Mental Disorder. Schizophrenia Bulletin 29:771-90.

McGorry PD (1993)Early Psychosis Prevention and Intervention Centre. Australian Psychiatry 1:32-4.

Miller TJ, McGlashan TH, Rosen JL et al (2002) Prospective diagnosis of the initial prodrome for schizophrenia based on the Structured Interview for Prodromal Symptoms: Preliminary evidence of interrater and predictive validity. Am J Psychiatry 159:863-5.

Morrison AP, French P, Walford L et al (2004) Cognitive therapy for the prevention of psychosis in people at ultra-high risk. Br J Psychiatry 185: 291-7.

Mortensen PB, Pedersen CB, Westergaard T et al (1999) Effects of family history and place and season of birth on the risk of schizophrenia. NEJM 340: 603-8.

Mrazek D, and Mrazek PJ (2004) Prevention of Psychiatric Disorders in Children and Adolescents. In: Kaplan and Sadock's Comprehensive Textbook of Psychiatry. (eds) Benjamin James Sadock, Harold I. Kaplan, Virginia A. Sadock, Eighth Edition. Lippincott, Williams and Wilkins, pp 3760.

Mrazek PJ, Haggerty RJ (1994) Reducing Risks for Mental Disorders: Frontiers for preventive intervention research. Committee on Prevention of Mental Disorders, Institute of Medicine. Washington DC: National Academy Press.

Ord LM, Myles-Worsley, Blailes F et al (2004) Screening for prodromal adolescents in an isolated high risk population. Schizophrenia Res. 71:507–8.

Phillips LJ, McGorry PD, Yung AR et al (2005) Prepsychotic phase of schizophrenia and related disorders: recent progress and future opportunities. Br J Psychiat 187 (suppl. 48), s33-s44.

Rebok GW, Hawkins WE, Krener P et al (1996) Effect of concentration problems on the malleability of children's aggressive and shy behaviors. J Am Acad Child Adolesc Psych 35:193–203.

Ruhrmann S, Hoppmann B, Theyshn S et al (2006) Acute symptomatic treatment clinically at risk for psychosis. Schizophr Res 86:S8.

Ruhrmann S, Schulze-Lutter F, Maier W et al (2005) Pharmacological intervention in the initial prodromal phase of psychosis. Eur Psychiatr 20:1-6.

Salokangas RKR, McGlashan TH (2008) Early detection and intervention of psychosis. A review. Nord J Psychiatry 62:92.

Schultze-Lutter F, Klosterkötter J (2004) Schizophrenia Prediction Instrument, Adult Version – SPI-A. Cologne: University of Cologne Department of Psychiatry and Psychotherapy.

Tien AY, Eaton WW (1992) Psychopathologic precursors and sociodemographic risk factors for the schizophrenia syndrome. Arch Gen Psychiatry. 49:37-46.

Tully EM, McGlashan TH (2006) The prodrome. In: Lieberman JA, Stroup TS, Perkins DO. Textbook of Schizophrenia. Washington, DC: American Psychiatric Publishing 341-52.

Van Os J, Delespaul P (2005) Toward a world consensus on prevention of schizophrenia. Dialogues in Clin Neurosci 7:53-67.

Walsh BC, Tully E, Thomas L et al (2006) Aripiprazole treatment of the psychosis prodrome. Schizophr Res 86:S7.

White T, Anjum A, Schulz SC (2006) The Schizophrenia Prodrome. Am J Psychiatry 163:376-380.

Williams LJ, Rasmussen SA, Flores A et al (2005) Decline in the Prevalence of Spina Bifida and Anencephaly by Race/Ethnicity: 1995–2002. Pediatrics 116: 580-6.

World Health Organisation (2001) Mental Health: New Understanding, New Hope. Geneva.

Ueland T, Rund BR (2005) Cognitive remediation for adolescents with early onset psychosis: a 1-year follow-up study. Acta Psychiatr Scand111:193-201.

Yung AR, Jackson HJ (1999) The onset of psychotic disorder: Clinical and research aspects. In: McGorry PD, and Jackson HJ eds. The Recognition and Management of Early Psychosis. Cambridge, England: Cambridge University Press pp. 27-50.

Yung AR, McGorry PD, McFarlane CA et al (1995) The PACE Clinic: Development of a clinical service for young people at high risk of psychosis. Australian Psychiatry 3:345-9.

Yung AR, Phillips LJ, Yuen HP et al (2003) Psychosis prediction: 12- month follow-up of a high-risk ("prodromal") group. Schizophr Res 60:21-32.

Yung AR, Stanford C, Cosgrave E, et al (2006) Testing the Ultra-High Risk (prodromal) criteria for the prediction of psychosis in a clinical sample of young people. Schizophr Res 84:57-66.