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Conventional and alternative preventive treatments in the first stages of schizophrenia

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ABSTRACT – *Background and Objectives:* Schizophrenia is a progressive disorder that moves through multiple stages starting from non-specific risk factors to at-risk mental state (ARMS) (also known as ultra-high risk of psychosis or UHR) to first episode of psychosis (FEP) to chronic course marred by frequent relapses and varying degrees of disability. In order to prevent a deteriorating course, treatments designed to address and possibly even correct the abnormal neuronal system functioning and psychosocial deficits need to be implemented early before potentially irreversible and maladaptive changes take place.

Methods: A literature search was conducted in the electronic databases Pub-Med and MEDLINE for relevant empirical and review articles published in peer reviewed journals.

Results: The review of literature suggests that a range of pharmacological and psychosocial interventions are being used and trialled in treatment of early stages of schizophrenia with varying degrees of success.

Conclusions: There is a variety of therapies for schizophrenia ranging in scope from improving symptom profiles to functional recovery and a good rationale for their use early in the course of illness. Treatments that focus on integrating pharmacological, psychological and psychosocial interventions with a strong evidence base for effectiveness need to be integrated for the best chance to avert or hinder schizophrenia. Schizophrenia research is moving towards a notion that early intervention can interact with existing and intact neuroplasticity mechanisms that can be harnessed in an adaptive manner to promote healthier neural system functioning and increased stress resiliency, which will in turn lead to symptom reduction and functional recovery.

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Introduction

Schizophrenia is a syndrome that includes signs and symptoms of unknown aetiology¹. The early course of schizophrenia has been found to predict longitudinal course of the illness^{2,3}. Early intervention services, introduced in the 1990s, have been established to reduce treatment delay and provide phase specific care^{4,5}. Based on the staging model of mental illness⁶, schizophrenia is a progressive disorder that moves through multiple stages starting from non-specific risk factors to at-risk mental state (ARMS) (also known as ultra-high risk of psychosis or UHR) to first episode of psychosis (FEP) to chronic course marred by frequent relapses and varying degrees of disability. As a syndrome, schizophrenia is characterised by FEP whereby sufficient symptoms are present to differentiate an illness⁷. This corresponds to the concept of “early period” introduced by Birchwood and colleagues⁸, which focuses on the ARMS and FEP and implies that it is imperative to intervene during this “critical period” and thereby alter the early course of illness by lowering morbidity, disability and cost associated with schizophrenia^{9,10}. This represents a paradigm shift from management of long term disability to an expectation that interventions in the early stages of schizophrenia will result in improved psychosocial outcomes.

Intervention research in the early stages of schizophrenia now focuses on not only treatments of existing symptomatology and disability but also on reducing duration of untreated psychosis and prevention of psychotic relapse. This shift has been driven by phase specific research, both retrospective and prospective, that indicates dysfunction in a number of brain systems in schizophrenia prodrome and ARMS. One of the largest longitudinal studies of volumetric brain changes in schizophrenia over time reported decreases in

multiple grey and white matter regions, which were most evident two years following FEP¹¹. Loss of brain volume was similarly noted in ARMS individuals who transitioned to psychosis compared to those who did not transition and healthy volunteers¹². That is, the brain and psychosocial functioning in the early stages of schizophrenia are compromised. In order to prevent a deteriorating course, treatments designed to address and possibly even correct the abnormal neuronal system functioning and psychosocial deficits need to be implemented early before potentially irreversible and maladaptive changes take place^{5,6,13}.

To date, a number of randomised controlled trials (RCTs) testing a range of psychological, pharmacological, nutritional and multicomponent psychosocial treatments have been conducted. The current paper presents an overview of most utilised and researched treatments, both conventional and alternative, in the early stages of schizophrenia with an emphasis on the FEP.

Methods

A literature search was conducted in the electronic databases Pub-Med and MEDLINE for relevant empirical and review articles published in peer reviewed journals using the following keywords: *early schizophrenia, early psychosis, ultra-high risk, clinical high risk, treatment, therapy*. Selected articles were further cross-checked for additional references. Chosen articles were reviewed for information regarding treatment initiatives, which are summarised in the following sections. Treatments were defined as deliverable interventions aiming to relieve psychotic symptomatology or to improve functional outcomes in early schizophrenia¹⁴.

Indicated and novel pharmacological treatments

Current biological treatment options for established schizophrenia have predominantly centred on the dopamine theory and treatment with dopamine antagonists such as antipsychotics. In the ARMS, antipsychotics are generally avoided and are instead reserved for later stages of psychotic illness. In FEP, antipsychotics are used as the first line treatment to mitigate psychotic symptoms. The response rate is reportedly in the range of 40–90%^{15,16,17,18} with time to response ranging from one to ten weeks of treatment^{17,18}. Despite this variability, patients with FEP show positive treatment outcomes as a result of antipsychotic treatment compared to those with the chronic course of illness¹⁸. Second-generation antipsychotics (SGAs) reportedly have superior efficacy in relapse prevention and in reducing psychotic symptoms compared to first generation antipsychotics (FGAs)^{16,19}. However, this advantageous efficacy is not as clear when individual SGAs are compared to individual FGAs¹⁹.

Besides side-effects, antipsychotics are not efficacious in treatment of negative and cognitive symptoms of schizophrenia, or psychosocial functioning, which has triggered a search for alternative pharmacological therapies. There is now a body of evidence to support a role for both inflammation and oxidative stress in the pathophysiology of psychotic disorders^{20,21}. Environmental factors such as inflammation, obstetric complications, viral infections and stress have been associated with an increase in oxidative stress and are also considered risk factors for schizophrenia²². Oxidative stress, a state where the levels of available antioxidants is reduced, or the levels of oxidative species is increased, is well documented in schizophrenia and re-

lated psychoses²⁰. Furthermore, there is consistent evidence of increased blood concentrations of inflammatory cytokines in patients with schizophrenia²³. Given that inflammatory abnormalities are present in drug-naive individuals in early schizophrenia, which are comparable to those reported in patients with the chronic course of the disorder, suggests an association independent of antipsychotic medication²⁴. Inflammation and oxidative stress also reciprocally induce each other in a positive feedback manner²⁵. Recent research suggests that the supplementation with omega-3 poly unsaturated fatty acids (PUFAs) appears to be a promising treatment in the early stages of schizophrenia^{26,27}. In the ARMS, omega-3 PUFAs were effective in reducing transition to psychosis²⁶. According to a recent Cochrane Review, doses of antipsychotics can be reduced in schizophrenia patients who are on omega-3 supplements²⁸. Although omega-3 supplements are promising across all stages of illness evidence to date suggests that they may be most useful in the ARMS where they may have a neuroprotective role²⁶. Several large clinical trials are currently being conducted to determine the mechanism and the role that omega-3 PUFAs play in the prevention and treatment of schizophrenia. One of the trials is being conducted in a large ARMS cohort by our group (ANZ CTR ID: ACTRN12608000475347).

Additionally, evidence suggests that aspirin may also be effective in treating psychotic symptoms²⁹. Besides its anti-inflammatory and antioxidant properties, aspirin has been shown to have antidepressant effects in preclinical studies and reduces risk of depression in epidemiological studies^{30,31}. Given that depression is a common feature in all phases of schizophrenia, these antidepressant effects provide further rationale for using aspirin. Low-dose aspirin has been shown to be both anti-inflammatory and neu-

roprotective in humans and animal models³². Aspirin can also reduce oxidative stress and protect against oxidative damage³³ and it has been reported as a safe, tolerable and less time-consuming treatment option. Studies on efficacy of aspirin symptom management early in the course of schizophrenia are just starting, and to date there is one registered trial of aspirin in an ARMS sample (ClinicalTrials.gov ID: NCT02047539).

Psychological therapies

Psychological therapies in all phases of schizophrenia have aimed to target symptoms of illness, such as positive and negative symptoms, as well as cognitive deficits⁷. In later phases of illness, they are used as adjuncts to pharmacological treatments rather as stand-alone treatments. However, recent evidence suggests that some psychological treatments such as cognitive behavioural therapy (CBT) may be effective on their own^{34,35}. A range of psychological therapies have been developed over the years of which CBT and family interventions have been recommended in clinical guidelines for early schizophrenia³⁶. Additionally, there has been a rise in demand for cognitive remediation in this stage of illness as there are reports that some forms of it are beneficial. Psychological therapies are benign treatments used as first line interventions in the ARMS, and to a large extent in FEP.

CBT, which is based on cognitive models of psychosis, has been implemented in all stages of schizophrenia. This model posits that dysfunctional interpretations of anomalous experiences contribute, against a background of pre-existing biopsychosocial vulnerability, to the emergence and maintenance of psychotic symptoms^{37,38}. Results from trials of CBT in the ARMS and early schizo-

phrenia suggest that the therapy is moderately effective in reducing transitions to psychosis^{39,40,41}, reducing relapse rates⁴², speeding recovery⁴³, reducing subclinical and clinical positive symptom severity^{39,40,44} and improving perceived quality of life⁴⁵. However, durability of CBT in absence of continued treatment is unclear with reports of both durable effects in the ARMS³⁹ and lack thereof in FEP^{42,44,45}. Lack of sustained effect of CBT may in part be due to the limited duration of treatment and more longitudinal trials with longer duration of CBT treatment are therefore needed^{7,42}.

Family interventions have likewise been extensively researched, and tend to range from traditional family therapy to psychoeducational therapies⁷. Based on this research, there is evidence for a range of benefits of family therapy in FEP and more advanced stages of illness, such as increased medication compliance and reduced hospitalisation as well as relapse^{46,47}. However, effectiveness of family therapy in the ARMS is yet to be established and a group of US researchers is currently trialling this^{48,49}. This is especially important given that patients in the ARMS and FEP tend to have greater interaction with their families compared to patients with a chronic course of the disorder who are generally older, which means that the effect of family therapy early in the illness may be stronger⁷.

Cognitive remediation therapy

Given a wide range of cognitive deficits across all stages of schizophrenia, including the ARMS, compared to healthy persons and other psychiatric groups, there has been a rise in demand for treatments that directly target cognitive dysfunction. Cognitive deficits are strongly related to poor functioning in areas of

work, social relationships and independent living^{50,51}, which is why there is a notion that improving cognition and the ability to learn may enable individuals to engage in broader rehabilitation efforts and hence improve their functional outcomes⁵². Initiatives targeting cognition, cognitive remediation treatments (CRT), are divided into cognition-enhancing and compensatory approaches. While cognition-enhancing approaches have been designed to improve specific abilities in different cognitive domains (e.g. learning, memory, attention) through a set of specified training modules⁵⁰, compensatory approaches attempt to bypass cognitive impairments and teach strategies to “compensate” for these impairments by relying on environmental aids or similar processes^{50,53,54}. To date, the success of both cognition-enhancing and compensatory methods at improving cognition and functional outcomes of people with schizophrenia has been encouraging. Additionally, given that people in early schizophrenia experience impairments in cognition and functioning similar or equivalent to those evidenced by individuals in the later stages of their illness, it is thought beneficial to implement CRT as early in the course of illness as possible. Only a handful of studies examining efficacy and durability of CRT in the ARMS^{55,56} and FEP^{53,54,57,58} have been done to date with early evidence suggesting favourable effects.

Psychosocial therapies

Psychosocial therapies have been designed to aid functional recovery by targeting areas implicated in the development of disability, such as impaired social and role functioning, but which are not directly linked with symptoms of illness⁷. They have been reported to improve treatment adherence and promote bet-

ter occupational and social functioning in established schizophrenia^{59,60}. Given that schizophrenia typically occurs in late adolescence and early adulthood, which are critical phases of life for social and occupational development, these areas of functioning are often the first to show marked decrease from premorbid levels. Despite wanting to stay at school or work, almost half of people in early schizophrenia are out of school or unemployed^{7,61}.

It is now widely accepted that functional recovery is just as important as symptomatic recovery. Functional disability is the most costly aspect of psychotic illness and functional recovery is valued by patients above symptomatic recovery⁶². Therapies such as vocational rehabilitation, including return to study for younger patients, have been designed to minimise functional disability and improve long-term occupational functioning. The most evidence-based model of vocational recovery broadly, and supported employment specifically, is the Individual Placement and Support (IPS) model. Studies of IPS in early schizophrenia have reported achieved employment or education rates as high as 85%^{63,64}. However, maintaining occupational roles has been identified as a challenge in this cohort suggesting that other factors, such as cognitive function, are involved in successful vocational rehabilitation⁶⁵. Therefore, there are now recommendations for adjunctive interventions to vocational therapy^{65,66} in order to enhance its effects.

Reflective of the technological developments and their utility in other areas of health, internet and mobile based therapies are being developed for treatment delivery in all stages of schizophrenia⁶⁷. Given that young people are amongst the biggest users of these technologies, it is intuitive that interventions are turning to these resources for support. Preliminary research in this area to date has found beneficial effects of computer and mo-

bile phone based psychoeducation on rate of relapse, hospitalization, socialisation and medication adherence of patients with established schizophrenia^{59,60}. A new wave of research on internet based therapies is currently underway, and a recent study by our group has shown it to be feasible and beneficial in terms of perceived social connectedness and empowerment in FEP⁶⁸. To our knowledge, there is no current empirical evidence exploring appropriate vocational interventions for the ARMS although similar principles are likely to be relevant³⁶.

Conclusions

A variety of therapies now exist for schizophrenia ranging in scope from improving symptom profiles to functional recovery, and there is a good rationale for their use early in the course of illness. Such therapies in early schizophrenia are qualitatively different from preventing future cases of the disorder or from early symptom identification, but may nevertheless help reduce morbidity in those who continue through to the more chronic course⁶⁹. Combining therapies such as psychological or psychosocial with novel pharmacological treatments is an approach that needs to be evaluated further as different treatments, sequences and durations of therapy may be needed for sustained benefits^{70,71}. Longitudinal follow-up studies suggest that most of treatment benefits early in the course of schizophrenia are seen in the first 2 years and are generally not sustained at the 5 year follow-up⁷⁰. That said, it may be that a combination of longer interventions administered longitudinally, over the illness course and as a part of standard therapy, is needed to produce the most efficacious, long term benefits. After all, treatment development at all stages

of schizophrenia is undergoing a shift from conceptualising schizophrenia as a neurodegenerative disease with an inevitably poor outcome to a manageable disease. Treatments that focus on integrating pharmacological, psychological and psychosocial interventions, which have a strong evidence base for effectiveness, need to be integrated for the best chance to avert or hinder schizophrenia¹. A perspective that early intervention can interact with existing and intact neuroplasticity mechanisms that can be harnessed in an adaptive manner to promote healthier neural system functioning and increased stress resiliency, which will lead to symptom reduction and functional recovery, is becoming increasingly popular¹³.

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