New Targets for the Management of Schizophrenia

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ABSTRACT:

New targets for the management of schizophrenia

Schizophrenia is characterized by abnormal mental functions and disturbed behavior. The diagnosis of schizophrenia is based on criteria defined in either the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, version DSM-IV (2) or the ICD-10. Targets of treatment include positive and negative symptoms, depression, suicidal ideation and behaviors, substance use disorders, medical comorbidities, posttraumatic stress disorder, and community adjustment problems. The first-generation antipsychotics were first introduced for the treatment of schizophrenia in the 1950s. The introduction of second-generation antipsychotics (SGAs) in the last three decades improved the desired effects of these medications with a reduction of their undesirable effects such as extrapyramidal adverse effects, mortality and metabolic disorder. Medication is generally helpful in treating positive symptoms, but up to a third of people derive little benefit, and negative symptoms are difficult to treat. It has been shown that lack of efficacy and tolerability, often associated with poor compliance, results in treatment discontinuation or treatment switch. Despite critical importance of medication for patients with schizophrenia, nonadherence to treatment is an important issue worldwide. The most prominent patient-related factors associated with nonadherence included lack of insight into the need for medication, denial of illness, embarrassment and unsuitable living conditions. Although antipsychotic medications are necessary, they are not sufficient for the treatment of schizophrenia. The cognitive therapy (cognitive behavioral therapy and cognitive remediation therapy), social skills, psychoeducation programs, family intervention, training programs, and case management or assertive community treatment are the major categories of psychosocial intervention which is an important part of the disease management. The major considerations in disease management treatment include the comprehensive and continuous treatment for prolonged periods, integrated, bio-psychosocial approach to care, active collaboration with the family while planning and delivering treatment and treatment sensitive to the patient's needs and empirically titrated to the patient's response and progress.

Keywords: schizophrenia, relapse, treatment, antipsychotic

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INTRODUCTION

Schizophrenia typically manifesting in young people in their twenties, is usually lifelong and is characterized by 'positive symptoms' such as auditory hallucinations, bizarre delusions, and disrupted speech ('thought disorder') and by 'negative symptoms' such as social withdrawal, lack of motivation, self-neglect, and the appearance of flat affect. Subtle cognitive impairment is also a feature[1]. The fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) defines schizophrenia as a syndrome characterized by long duration, high relapse rate (70%), bizarre delusions and behaviors, negative symptoms, and sometimes a few mood

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problems[2]. The onset of symptoms typically occurs in adolescence and young adulthood, with a worldwide estimate of its lifetime prevalence and incidence of 1.4–4.6 and 0.16–0.42 per 1,000 persons annually, respectively[2,3]. The illness typically presents in early adulthood or late adolescence. Males have an earlier age of onset than females, and also tend to experience a more serious form of the illness with more negative symptoms, less chance of full recovery, and a generally worse outcome[4]. It is a multifactorial disorder, and the greatest risk factor is a positive family history. Regions on a number of chromosomes (e.g., 1, 6, 8, 10, 13, and 22) have been implicated as sites of potential vulnerability genes[5]. The developmental pathways that may result in schizophrenia are highly complex and poorly understood. They include family history of schizophrenia, obstetric complications and developmental difficulties, abuse, major life events, and parental loss[6]. Environmental factors (including exposure to infectious, autoimmune, toxic, or traumatic insults and stress during gestation or childhood) also play a role in the pathogenesis. Rates of schizophrenia are increased in urban, poor, immigrant and ethnic minority populations[7].

A comprehensive global survey concluded that schizophrenia accounts for 1:1% of the total disability adjusted life years and 2.8% of the years lived with disability worldwide[6]. Thus, the present paper aimed to provide an overview of the recent developments and current knowledge in the management of schizophrenia. In this context, the need for a guideline in disease management, relapse prevention strategies, and antipychotics focusing on their side effects were also reviewed.

TIME COURSE OF SCHIZOPHRENIA

Schizophrenia is characterized by abnormal mental functions and disturbed behavior. The illness can be classified clinically as the (1) premorbid, (2) prodromal, (3) progressive, and (4) residual stages. Mild deficits in social, motor, and cognitive functions during childhood and

adolescence represent the premorbid features of the disease[8]. These features have low predictive value as markers of the illness. Prodromal symptoms include attenuated positive symptoms (such as illusions, ideas of reference, magical thinking, superstitiousness), mood symptoms (e.g. anxiety, dysphoria, irritability), cognitive symptoms (e.g. distractibility, concentration difficulties), social withdrawal or obsessive behaviors[9,10]. In mosy of the cases, positive and negative symptoms develop gradually and the environmental factors that occur during this stage may act as stressors producing the behavioral symptoms that signal the onset of the disease[11]. Patients who receive appropriate therapy early in the course of their illness, a marked reduction and even remission occur in the psychotic symptoms following an initial episode with the persistence of negative and cognitive symptoms[12]. Following recovery, the majority of the patients discontinue medication and subsequently experience a relapse of psychotic symptoms. These episodes may not respond to medication; thus, repeated episodes and remissions cause clinical deterioration leading to end-stage of the illness with persistent symptoms and severe functional disabilities. Figure 1 demonstrates the typical clinical time course of the illness.

In 2007, a systematic review concluded from data published up to that time that mortality rates in schizophrenia were significantly greater than in the general population with a median standardized mortality ratio (SMR) of 2.58 (10-90% quantiles, 1.18-5.76)[13]. The meta-analysis from Brown et al.[14] reported that the contributions to excess mortality were suicide (28%), accidents (12%) and natural causes (60%). A 55-year follow up study of 319 patients published in 2008 found cancer to be the second most common cause of death (19%), with cardiovascular the most common (29%)[15].

The majority of people with schizophrenia have the potential to achieve long-term remission and functional recovery. Lieberman et al.[15] reported that 83% of patients with first episode schizophrenia experience a remission in psychotic symptoms within the first year of treatment. It was
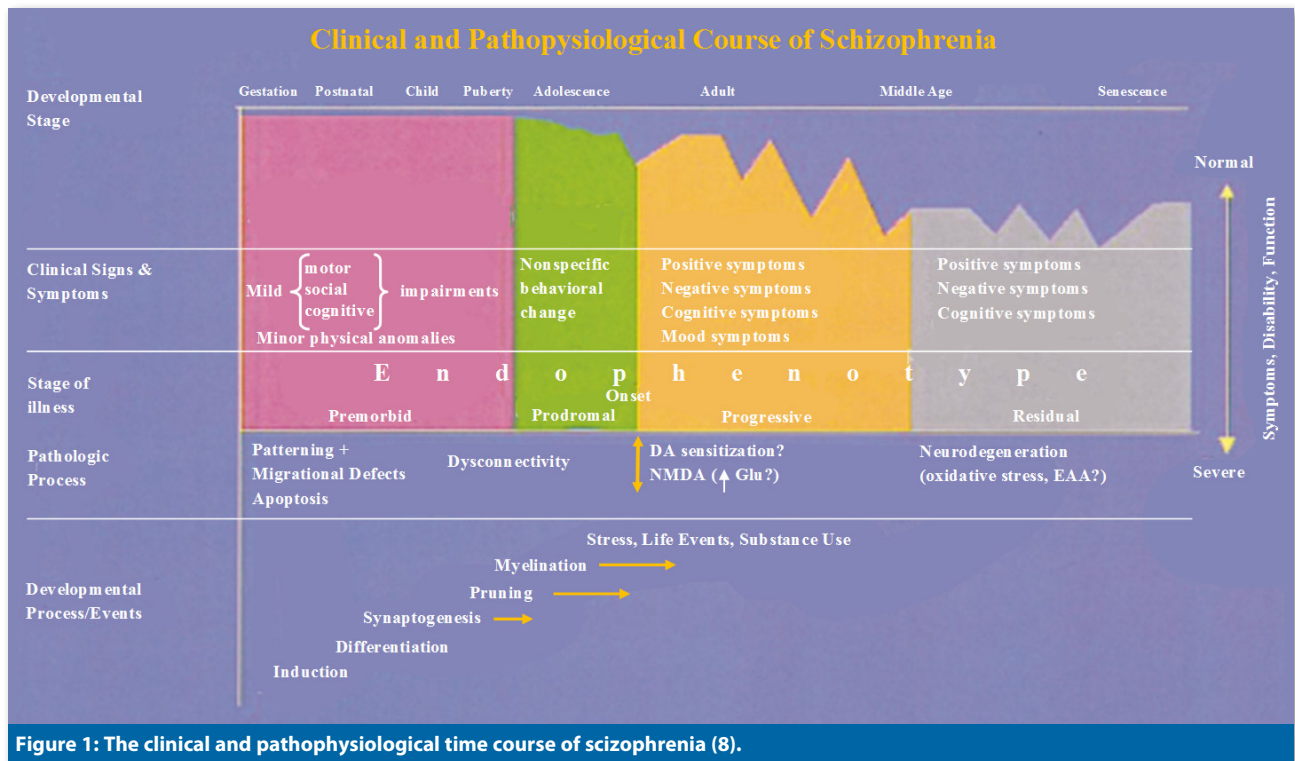
Figure 1: The clinical and pathophysiological time course of scizophrenia (8).

observed that 82% of patients who achieved a remission from their first episode schizophrenia experienced a relapse within 5 years, with comparable percentages of relapsed patients going on to have a second and third relapse[16]. Those who discontinue medications in early years are at high risk with 78% relapsing within 1 year compared with rates of 0-12% for those who remain on antipsychotic medications. On the other hand, the rates of functional recovery are lower than those of remission. The data of a systematic review by Menezes et al.[17] demonstrated that approximately 40% of patients achieved functional recovery during a follow-up period of less than or longer than 2 years. In a recent meta-analysis aiming to identify the proportion of individuals with schizophrenia and related psychoses who met recovery criteria (improvements in both clinical and social domains and evidence that improvements in at least 1 of these 2 domains had persisted for at least 2 years) and to examine if recovery was associated with factors such as gender, economic index of sites, and selected design features of the study, the median proportion

(25%-75% quantiles) who met the recovery criteria, was 13.5% (8.1%-20.0%) and there were no statistically significant differences when the estimates were stratified according to gender, midpoint of intake period, strictness of the diagnostic criteria, duration of follow-up, or other design features[18].

DIAGNOSTIC CRITERIA FOR SCHIZOPHRENIA

The diagnosis of schizophrenia is based on criteria defined in either the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, version DSM-IV[2] or the ICD-10[19]. The ICD-10 criteria are typically used in European countries and the DSM-IV criteria are used in the United States and the rest of the world, and are prevailing in research studies. The ICD-10 criteria put more emphasis on Schneiderian first-rank symptoms. In practice, agreement between the two systems is high[20].

Diagnostic criteria of schizophrenia in DSM-IV include the followings[2]:

A. Characteristic symptoms: Two or more of the

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following, each present for much of the time during a one-month period (or less, if symptoms remitted with treatment).

• Delusions
• Hallucinations
• Disorganized speech, which is a manifestation of formal thought disorder
• Grossly disorganized behavior (e.g., dressing inappropriately, crying frequently) or catatonic behavior
• Negative symptoms: Blunted affect (lack or decline in emotional response), alogia (lack or decline in speech), or avolition (lack or decline in motivation)

If the delusions are judged to be bizarre, or hallucinations consist of hearing one voice participating in a running commentary of the patient's actions or of hearing two or more voices conversing with each other, only that symptom is required above. The speech disorganization criterion is only met if it is severe enough to substantially impair communication.

B. Social or occupational dysfunction: For a significant portion of the time since the onset of the disturbance, one or more major areas of functioning such as work, interpersonal relations, or self-care, are markedly below the level achieved prior to the onset.

C. Duration: Continuous signs of the disturbance persist for at least six months. This six-month period must include at least one month of symptoms (or less, if symptoms remitted with treatment).

D. Schizoaffective and major mood disorder exclusion: Schizoaffective disorder and depressive or bipolar disorder with psychotic features have been ruled out because either (1) no major depressive or manic episodes have occurred concurrently with the active phase symptoms; or (2) if mood episodes have occurred during active-phase symptoms, their total duration has been brief relative to the duration of the active and residual periods.

E. Substance/ general mood condition exclusion: The disturbance is not attributed to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition.

F. Relationship to Global Developmental Delay or Autism Spectrum Disorder: If there is a history of autism spectrum disorder, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations are also present for at least 1 month (or less if successfully treated).

On the other hand, according to ICD-10, the symptoms are divided into groups that have special importance for the diagnosis and often occur together, such as: (a) thought echo, thought insertion or withdrawal, and thought broadcasting; (b) delusions of control, influence, or passivity, clearly referred to body or limb movements or specific thoughts, actions, or sensations; delusional perception; (c) hallucinatory voices giving a running commentary on the patient's behavior, or discussing the patient among themselves, or other types of hallucinatory voices coming from some part of the body; (d) persistent delusions of other kinds that are culturally inappropriate and completely impossible, such as religious or political identity, or superhuman powers and abilities (e.g., being able to control the weather, or being in communication with aliens from another world); (e) persistent hallucinations in any modality, when accompanied either by fleeting or half-formed delusions without clear affective content, or by persistent over-valued ideas, or when occurring every day for weeks or months on end; (f) breaks or interpolations in the train of thought, resulting in incoherence or irrelevant speech, or neologisms; (g) catatonic behavior, such as excitement, posturing, or waxy flexibility, negativism, mutism, and stupor; (h) "negative" symptoms such as marked apathy, paucity of speech, and blunting or incongruity of emotional responses, usually resulting in social withdrawal and lowering of social performance; it must be clear that these are not due to depression or to neuroleptic medication; and (i) a significant and consistent change in the overall quality of some aspects of person behavior, manifest as loss of interest, aimlessness, idleness, a self-absorbed attitude, and social withdrawal.

The normal requirement for a diagnosis of schizophrenia is that a minimum of one very clear symptom (and usually two or more if less clear-cut) belonging to any one of the groups listed as (a) to (d) above, or symptoms from at least two of the groups referred to as (e) to (h), should have been clearly present for most of the time during a period of 1 month or more.

Conditions meeting such symptomatic requirements but of duration less than 1 month (whether treated or not) should be diagnosed in the first instance as acute schizophrenia-like psychotic disorder and reclassified as schizophrenia if the symptoms persist for longer periods. Symptom (i) in the above list applies only to the diagnosis of Simple Schizophrenia and a duration of at least one year is required.

Due to the fact that, DSM-IV schizophrenia is reliably diagnosed, has fair validity and conveys useful information, the core of the DSM-IV diagnostic criteria for schizophrenia is retained in DSM-5, with modest changes proposed principally for the purpose of simplicity and incorporation of new information about the nature of the disorder accumulated over the past two decades. Most persons who did (or did not) meet the DSM-IV criteria for schizophrenia should continue to meet (or not meet) the DSM-5 criteria. In DMS-5, the six criteria (A–F) for the diagnosis of schizophrenia in DSM-IV are retained with modest changes proposed in criteria A and F. No changes are made in criteria B–E.

Major changes in the definition by DSM-5 include elimination of the classic subtypes, addition of psychopathological dimensions, elimination of special treatment of Schnederian first rank symptoms, better delineation of the illness from schizoaffective disorder, and clarification of the relationship of schizophrenia to catatonia. All these modifications aim to improve diagnosis and facilitate treatment. Similar to all previous definitions, major concerns are (1) the Kraepelinian emphasis on avolition, chronicity and poor outcome[21]; (2) incorporation of the Bleulerian view that dissociative pathology is primary and fundamental and accent on negative symptoms[22];

and (3) the Schneiderian stress on reality distortion or positive symptoms[23]. Five symptoms for the diagnosis of schizophrenia with the requirement that at least two of them being present for a month will be retained in DSM-5. Three changes include the elimination of the special treatment of bizarre delusions and Schneiderian "first rank" hallucinations, clarification of the definition of negative symptoms and the addition of a requirement that at least one of the minimum two characteristic symptoms must be delusions, hallucinations or disorganized speech. Thus, the DSM-IV subtypes of schizophrenia provide a poor description of the heterogeneity of the illness and have low diagnostic stability. Except for the paranoid and undifferentiated subtypes, other rarely seen subtypes were eliminated from DSM-5. The use of psychopathological dimensions in DSM-5 should provide a better description of the heterogeneity of the illness and thus, facilitate appropriate treatment[24]. Although ICD-11 has not been finalized, it is likely to include the changes made for DSM-5 (deletion of subtypes, addition of dimensions, elimination of special treatment of Schneiderian first rank symptoms, treatment of catatonia as a specifier and use of the same course specifiers). The differences between the two systems in terms of minimum duration of illness (6 months in DSM and 1 month in ICD) and inclusion of impairment as a criterion of illness (included in DSM and not included in ICD) are likely to remain.

THE NEED FOR A GUIDELINE IN DISEASE MANAGEMENT

Variation in service provision and in individual service user's outcomes suggest there is a need for evidence based recommendations on treatment of schizophrenia and to improve service users engagement with treatment. Medication is generally helpful in treating positive symptoms, but up to a third of people derive little benefit, and negative symptoms are difficult to treat.

Despite increasing evidence of the efficacy of discrete psychological interventions and therapies such as family intervention and cognitive

behavioral therapy, delivery of such interventions has been difficult to realize in practice. Thus, through providing recommendations for best practice the guidelines have an important role in ensuring that all individuals with schizophrenia and their families and friends have the best opportunity to engage in evidence based treatments focused on maximizing recovery and well-being.

Once a diagnosis has been established, it is important to identify the targets of each treatment. Targets of treatment may include positive and negative symptoms, depression, suicidal ideation and behaviors, substance use disorders, medical comorbidities, posttraumatic stress disorder, and community adjustment problems. Therefore, a treatment plan is formulated considering the diagnosis and clinical and psychosocial circumstances of the patient. An active collaboration with the family while planning and delivering treatment is almost always required. Management should be sensitive to the patient's needs and empirically titrated to the patient's response and progress. To summarize, the major considerations in treatment are comprehensive and continuous treatment for prolonged periods, integrated, bio-psychosocial approach to care, active collaboration with the family while planning and delivering treatment and treatment sensitive to the patient's needs and empirically titrated to the patient's response and progress.

In the acute phase of the illness during which patients exhibit symptoms such as delusions or hallucinations, disorganized thinking, behavioral disturbances, the principal tasks of treatment are reducing symptoms and risk of harm, and improvement of functioning. Their functioning is severely impaired, they are unable to care for themselves, and can be at risk of harming themselves or others. In the stable phase during when the negative symptoms may predominate and deficits in social and occupational functioning become more apparent, maintaining or improving level of functioning and prevention of recurrences are the major aims of treatment. Independently of the disease phase, the goals of treatment, or social

and cultural circumstances, the basic principles of treatment which are applicable to most, if not all patients include the followings:

1. Comprehensive assessment – A systematic and comprehensive assessment of the patient's problems (e.g., an evaluation of psychiatric, physical, psychosocial and cultural aspects) is the essential first step of implementing treatment.
2. Implementing a treatment plan – Every patient should have a treatment plan which should be prepared in consultation with the relatives/care givers.
3. Monitoring – Continuous monitoring of clinical status, response to treatment, adverse effects etc. is necessary to prevent relapses.
4. Forming a therapeutic alliance – A supportive therapeutic alliance with the patient forms the foundation on which treatment is carried out.
5. Collaborating with the family – Alliance with the family is also part of the treatment.
6. Ensuring adherence to treatment – A large percentage of patients do not comply with treatment or drop out at various stages. Modifying treatment accordingly can help in minimizing non-compliance and its consequences.

TREATMENT STRATEGIES FOR RELAPSE PREVENTION

The first- and second-generation antipsychotic drugs share a similar pharmacological mechanism in blocking the dopamine D2 receptors. The first-generation antipsychotics (FGAs) were first introduced for the treatment of schizophrenia in the 1950s. The introduction of second-generation antipsychotics (SGAs) in the last three decades further improved the desired effects of these medications with a reduction of their undesirable effects such as extrapyramidal adverse effects, mortality and metabolic disorder. The SGAs (atypical antipsychotics) were marketed as offering greater efficacy in reducing psychotic symptoms while reducing side effects (and extrapyramidal symptoms in particular) than typical medications.

These drugs (e.g., risperidone and paliperidone palmitate) are also available and under use in our country for the treatment of schizophrenia.

Nonadherence to antipsychotic medication is one of the most important risk factors for relapse and hospitalization in patients receiving treatment for schizophrenia. A study demonstrated that the median time to all-cause discontinuation of medication was less than 4 months for the majority of oral SGAs[25]. Another study showed that more than 75% of patients with schizophrenia eventually became nonadherent within 2 years of being discharged from hospital[26]. Up to 50% of medical costs of psychiatric hospitalization were attributed to nonadherence with antipsychotic medication[27,28]. For these reasons, strategies to reduce hospitalization by improve medication adherence are becoming the focus of treatment in these patients.

Long-acting injectable (LAI) antipsychotics are likely to be useful for treating patients with poor medication adherence. They have been shown to be superior to oral antipsychotics in preventing hospitalizations[29]. The main benefits of these agents are: more consistent bioavailability, more predictable correlation between dosage and plasma levels, reduced peak-trough plasma levels, improved patient outcomes, improved patient and physician satisfaction, lower relapse rates than oral therapy. Both SGA and FGA medications are now available as long-acting preparations. Recent investigations suggest a therapeutically beneficial response to dose reduction and alternate day dosing in the early stages of first-episode psychosis[30].

On the other hand, the main disadvantage of long-acting antipsychotics relates to the slow dose titration and the long time required to achieve steady state levels which is most evident in acutely ill individuals who need dose titration within days of initiating treatment[31]. Moreover, making dose adjustments is often difficult as attainment of steady state plasma levels may take more than 2 months after a dose change. For these reasons, the initiation of long-acting antipsychotics has generally been confined to certain conditions when patients are stabilized on their existing treatment.

The Electronic Schizophrenia Treatment Adherence Registry (e-STAR) assess the use of LAIs in a total of 1,659 patients with schizophrenia or schizoaffective disorder. At 12 months after switching from oral to long-acting antipsychotics, the percentage of patients who did not require hospitalization (89.1% vs 67.0%) and did not relapse (85.4% vs 47.8%) was higher with long-acting antipsychotics than with oral antipsychotics[32]. Compared to the baseline period, those on LAIs had significantly greater reductions in the number and days of hospitalization. At 24 months, only 15% of patients had discontinued LAIs for insufficient response (28.5%), patient/family choice (26.1%), adverse events (9.6%), and unacceptable tolerability (6.0%)[33]. In a study by Offord et al.[34], at the 12-month follow-up, in patients initiating long-acting antipsychotics versus oral antipsychotics had significant reductions in the number of all-cause hospitalizations, schizophrenia-related hospitalizations, and length of hospital stay. Similarly, Peng et al.[35] found that hospitalization rate declined from 49.7% to 22.4% and the duration of hospitalization declined from 7.3 to 4.7 days after starting long-acting antipsychotics in patients with schizophrenia.

A recent study analyzed four short-term, randomized, double-blind, placebo-controlled trials investigating the efficacy of paliperidone palmitate- a long-acting antipsychotic- in acute exacerbation of schizophrenia and as a maintenance treatment to prevent or delay relapse in stable schizophrenia. According to data, the drug offers several advantages relative to other available LAI antipsychotics: it can be used as an acute treatment in the outpatient setting, and it has been shown to be well tolerated by patients. Also, it does not require overlapping oral antipsychotic supplementation while it is being initiated, and it offers the convenience of once-monthly administration. The injection volume is small and it offers dosing flexibility[36].

On the other hand, few controlled trials

compared SGAs with FGAs in terms of relapse prevention in schizophrenia. In a very recent systematic review/meta-analysis of randomized trials, lasting ≥6 months comparing SGAs with FGAs in schizophrenia, SGAs prevented relapse more than FGAs (29.0 versus 37.5%, RR=0.80, CI: 0.70-0.91, p=0.0007, I2=37%; NNT=17, CI: 10-50, p=0.003). SGAs were also found superior regarding relapse at 3, 6, and 12 months (p=0.04, p<0.0001, p=0.0001), treatment failure (p=0.003) and hospitalization (p=0.004). SGAs showed trend-level superiority for dropout owing to intolerability (p=0.05). Superiority of SGAs regarding relapse was modest (NNT=17), but confirmed in double-blind trials, first- and multi-episode patients, using preferentially or exclusively raw or estimated relapse rates, and for different haloperidol equivalent comparator doses[37].

One particularly noteworthy factor is the duration of untreated psychosis. Patients with schizophrenia who are given antipsychotic medications early in their illness have better outcomes than those for whom treatment is delayed. Studies have shown that the duration of untreated psychosis is an independent predictor of and a possible influence on outcome. Thus, initiation of treatment soon after the onset of the first episode of psychosis could lead to better outcome. In a study on 88 patients showed that cognitive deterioration was positively correlated with the length of untreated illness[38]. A prospective study of 70 patients with schizophrenia and schizo-affective disorder treated for the first episode of psychosis and average duration of untreated psychosis of 51.9 weeks demonstrated that a longer duration of untreated psychosis was associated with lower frequency of and longer time to remission[39]. Based on the evidence that patients experiencing their first episode of schizophrenic pychosis are more responsive to antipsychotic medication with the need of relatively low doses of antipsychotic drugs than during subsequent episodes it has been suggested that untreated psychosis may have negative effects on brain functioning[40]. A longer period of illness is associated with increasing negative symptoms and cognitive and behavioral deficits[41]. Thus, evaluating the potential benefits of early intervention for psychosis must be a higher priority.

Early Psychosis Prevention and Intervention Centre (EPPIC) encourages referral at early stage with an aim of early reintegration of patients into the community[42]. McGorry et al.[42] compared the outcome of 51 patients with first-episode psychosis who were treated using the EPPIC program and whom treated with a standard program and reported that EPPIC program had a lower number of hospital admissions, shorter length of stay in hospital, lower levels of negative symptoms, lower dose of neuroleptics and higher scores of quality of life measures.

Medication Adherence

Despite critical importance of medication for patients with schizophrenia, nonadherence to treatment is an important issue worldwide. Nonadherence to medication has a negative impact on the course of illness resulting in relapse, rehospitalization, longer time to remission and suicide. Moreover, the consequences of nonadherence contribute to the high costs of the disease to healthcare systems. As reducing nonadherence to antipsychotic medications may reduce psychiatric morbidity and costs of care, it is important to determine the key factors contributing to nonadherence and their consequences in schizophrenia.

A systematic review of 37 papers identified a wide range of factors and consequences of poor adherence in schizophrenia[43]. According to the results of the review, the key factors for nonadherence included lack of insight, medication beliefs and susbstance abuse and the key consequences of nonadherence were greater risk of relapse, hospitalization and suicide. The main factors that were positivitely related to adherence were a good therapeutic relationship with physician and perception of benefits of medication. Other factors that influence adherence positively were family or social support, and greater social

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activities. On the other, stigma of taking medication and lack of social support were found to negatively influence adherence.

a. Patient-related factors

In a study of 153 patients with schizophrenia, the most common patient-specific factors for nonadherence were stigma related to taking medications, adverse drug reactions, forgetting to taking drugs and lack of social support[44]. Nonadherence to prescribed medication is generally associated with symptom relapse increased hospitalizations, and increased health care costs[45,46]. In a survey of 688 psychiatrists treating 5,729 patients with schizophrenia, lack of insight into the need for medication (68%), denial of illness (63-66%), embarrassment about taking medication (62%) and living conditions were the major factors associated with partial adherence[47]. Patients with schizophrenia are frequently unemployed which may also contribute to nonadherence caused by the financial burden of medication[48]. Other barriers to treatment adherence may include issues with transportation, access to care, and ability to afford medication payments.

b. Physician-related factors

Poor clinician–patient relationship is a significant predictor of nonadherence. The data of a cross-sectional study by Rettenbacher et al.[49] revealed that 41% of adherent patients were asked about drug intake most frequently by their psychiatrist while none of the nonadherent patients reported this (p=0.074). Among nonadherent patients, a higher proportion (60% vs 9% of adherent patients) stated that their relatives inquired most often about their drug intake.

c. Medication-related factors

Survey data from psychiatrists treating patients with schizophrenia suggest that more than two thirds of patients exhibit nonadherence to prescribed medications[47]. Treatment-related factors include adverse events, type of antipsychotic regimen and dosing regimen. A prospective study found that approximately 35% of patients reported adverse drug reactions to be a barrier to medication adherence[44]. Another prospective study found that 50% of patients reported side effects as a reason for noncompliance[50]. Similarly, the expert survey rated distress associated with side effects (especially weight gain in women and excessive sedation) to be important contributors to adherence problems[51].

Potential side effects of the antipsychotic drugs
Antipsycotic medications have long been the primary component of effective treatment for schizophrenia and chlorpromazine was the first drug used for the treatment of psychotic symptoms. Thereafter, thioridazine, fluphenazine, haloperidol and thiothixene were marketed; thus, conventional antipsychotics have been the mainstay of treatment for schizophrenia for 30 years. In 1989, the Food and Drug Administration (FDA) approved clozapine, the first of a new class of antipsychotic drugs named the SGAs. These drugs differed primarily by producing minimal or no extrapyramidal side effects[52]. The introduction of clozapine was followed by the approval of risperidone, olanzapine, quetiapine, and ziprasidone. By 1999, 60% of all patients with schizophrenia who received an antipsychotic in the U.S. were prescribed an SGA, and this proportion increased to 82% by 2002[53].

The appropriate treatment of adverse effects of antipsychotics is relevant in the overall management of schizophrenia as these may interfere with treatment adherence, functional capacity, well-being, quality of life, and life expectancy. With regard to antipsychotics, key side effects that should be monitored regularly include sedation, sleep difficulties, sexual problems, extrapyramidal side effects and involuntary movements, weight change, as well as abnormalities in blood pressure and in blood lipid and glucose levels.

Neurologic adverse effects, ranging from acute dystonic reactions to akathisia, parkinsonism, and tardive dyskinesia are the major concerns because

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of their potential severity, persistence, and psychosocial consequences. Extrapyramidal side effects (EPS), including akathisia, dystonia and pseudoparkinsonism are the major adverse effects associated with traditional antipsychotic therapy. Akathisia is the most frequent adverse effect. Tardive dyskinesia usually occurs after at least three months of neuroleptic treatment with an average prevalence of 20% (13-36%). The incidence of new cases with conventional antipsychotics is approximately 5%[54]. According to clinical data, clozapine is associated with little to no EPS and quetiapine has no greater rates of EPS than placebo. Olanzapine and risperidone cause less EPS than traditional antipsychotics. Risperidone was shown to cause parkinsonism at rates similar to placebo in doses under 6 mg/day while causing EPS at a rate of 20% or in doses higher that 6 mg/day. Parkinsonism with olanzapine is similar to placebo with doses up to 10 mg/day. Akathisia with olanzapine is significantly higher than placebo at doses greater than 10 mg/day. The incidence with all of the SGAs appear to be minimal and much lower than the risk on traditional antipsychotics. In a double-blind study, olanzapine and haloperidol were compared in over 1,600 subjects for up to 2.6 years and the relative risk of tardive dyskinesia over one was reported was 7.5% with haloperidol and 0.5% with olenzapine[54].

Weight gain is highly variable among antipsychotics. Olanzapine and clozapine were reported to be associated with the highest degree of weight gain in short-term trials (4-4.5 kg over 10 weeks)[55]. Hummer et al.[56] reported that 36% of subjects gained more than 10% of their initial body weight after one year of clozapine treatment with the average of 3.5 kg. On the other hand, olanzapine at doses of 12.5-17.5 mg/day has been found to cause an average weight gain of 12 kg after one year of use[57]. Weight gain with olanzapine appears to peak after 40 weeks of treatment and is greater than that is due to clozapine[58]. Weight gain with risperidone reaches a plateau early and remain at about 2-3 kg at one year[59]. Studies of quetiapine and ziprasidone reported weight gains of 1-2 kg over at least one year[60-62]. Thus, according to current data, weight gain is generally not dose-dependent with SGAs.

Other major factor contributing to non-compliance with antipsychotics is sexual dysfunction. It is known that approximately 50% of patients have reported sexual dysfunction during treatment with conventional antipsychotic treatment[63]. Sexual dysfunction during antipsychotic therapy can be attributed to excessive sedation, weight gain, EPS, or elevated prolactin levels. High prolactin levels have been associated with sexual dysfunction and its normalization has been shown to restore sexual functioning[63]. In a study comparing risperidone, olanzapine, quetiapine and haloperidol reported rates of sexual dysfunction between 35-43% risperidone, olanzapine, and haloperidol and 18% for quetiapine[64]. Clozapine has a negligible effect on plasma prolactin levels[65]. Of all the SGAs, risperidone has the highest effect to elevate plasma prolactin levels in a dose-related fashion[66]. Olanzapine causes transient and slight elevations in plasma prolactin levels in about one third of patients[67]. In large trials of quetiapine, prolactin levels were shown to decrease from baseline during therapy[68]. Ziprasidone was shown to lead to slight elevations in plasma prolactin levels[61] while apripiprazole decreases prolactin levels from baseline in all doses[62].

Published literature examining the safety and tolerability of paliperidone so far demonstrated that paliperidone seems to be well tolerated and safe to use for the treatment of schizophrenia. Its primary limitations are prolactin elevation and extrapyramidal symptoms, both of which seem to be dose-related. Weight gain increases are also verifiable, but less pronounced, than with other SGAs such as olanzapine or quetiapine. Patients who have responded to risperidone in the past, but are unable to continue on it because of compliance issues, extrapyramidal side effects, or hepatic impairment, may benefit from paliperidone[69].

Lack of efficacy and drug switching strategies
The antipsychotic treatment should aim to achieve clinical stabilization after achieving remission of

symptoms in the acute phase, thus reducing the risk for progressive cognitive deterioration, functional disabilities, comorbidities, and poor quality of life. It has been shown that lack of efficacy and tolerability, often associated with poor compliance, results in treatment discontinuation or treatment switch[16,70]. As a substantial proportion of patients with schizophrenia remains symptomatic and functionally impaired, develop intolerability to medication or dissatisfied with their treatment, switching between medications is not rare. In the clinical setting, the current psychosocial conditions, level of support and symptomatic status, presence of comorbidities should be considered when planning a change in the regimen.

Poor treatment adherence and high discontinuation rates often lead to treatment changes. It is generally accepted that subjects who are not responding to a psychotropic drug or who experience adverse events may show a better response to another agent of the same or other therapeutic class[71,72]. Switching to improve efficacy and/or tolerability has been studied in several clinical trials. A significant improvement in the Positive and Negative Syndrome Scale (PANSS) scores as well as in patients' metabolic profile has been observed by switching from conventional antipsychotics, olanzapine, or risperidone to ziprasidone over a 6-week clinical study[73]. Cognitive function has been shown to improve by switching from conventional or atypical antipsychotics to ziprasidone[74] or to olanzapine[75]. Switching from other antipsychotics to quetiapine XR was shown to be associated with an improved efficacy and tolerability profile[76]. Switching to quetiapine from typical or atypical antipsychotics has been found to significantly reduce extrapyramidal symptoms[77], and switching to quetiapine from another atypical agent has been proposed in cases of new-onset tardive dyskinesia[78,79]. A major issue that should be considered when switching between atypical antipsychotics is the occurrence of side effects or withdrawal symptoms, many of which are attributed to receptor profiles and antimuscarinic or antihistaminic blockade[80].

For switching the antipsychotic drug, it is recommended to taper off the dose of the first antipsychotic gradually while simultaneously the dose of the second one is titrated up gradually to its target dose ('crossover titration'). Alternatively, the dose of the first antipsychotic can be maintained at the same dose while the dose of the second compound is increased gradually to a therapeutic level and only then the dose of the first agent will be decreased ('overlap and taper')[80,81].

As a part of the switching strategy, it seems preferable to choose a new compound with a different receptor-binding profile compared to the first agent. In phase 1b study of the 'Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE)'[16], non-responders to perphenazine benefited significantly more from a switch to olanzapine or quetiapine compared to risperidone; probably because both perphenazine and risperidone are characterized by high antidopaminergic properties.

The important issue is that the switching strategy must be tailored to the individual patient characteristics and environmental factors. The transition period is crucial, as side effects to the new agent may be transient and withdrawal symptoms may occur; thus, both the clinician and the family should support the patient encouraging adherence and persistence to treatment.

UNMET NEEDS: TREATMENT APPROACH FOR NEGATIVE AND COGNITIVE SYMPTOMS

Negative symptoms of schizophrenia represent impairment of normal emotional responses, thought processes, and behaviors affecting communication and social interaction. The symptoms range from expressive deficits such as blunting or flattening of affect and alogia/aprosody, to motivational deficits characterized by avolition/apathy, anticipatory anhedonia, and asociality. Persistent negative symptoms are present in more than a quarter of patients and lead to poorer outcome, particularly if present in early psychosis, and contribute to a greater degree than positive symptoms to poorer quality of life.

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Treatments for negative and cognitive symptoms remain an unmet need in schizophrenia. No medications are currently approved by the US Food and Drug Administration (FDA) to treat persistent negative symptoms or cognitive dysfunction in patients with schizophrenia. Hence, negative and cognitive symptoms may persist even when positive symptoms are successfully treated. While antagonism or partial agonism at the dopamine D2 receptor and, in the case of second-generation antipsychotics, antagonism at the serotonin 5-HT2A receptor are under use to alleviate positive symptoms, antipsychotic combinations and adjunctive use of nonantipsychotic agents, have been attempted to treat patients with persistent negative symptoms or cognitive impairments. Many studies have examined adjunctive antidepressants with antipsychotics for the treatment of chronic schizophrenia. In a meta-analysis of 23 trials comparing the effect of add-on antidepressants versus placebo for negative symptoms in schizophrenia, the effect size was moderate (-0.48) for antidepressants[82]. However, current evidence is insufficient to support any augmentation strategy as a standard treatment recommendation for negative symptoms[83].

The British Association for Psychopharmacology (BAP), in their 2011 guidelines for the treatment of schizophrenia, recommends addressing the secondary causes of negative symptoms first, followed by a trial of an antidepressant[84]. The use of antipsychotic agents to treat persistent negative symptoms beyond acute inpatient hospitalization does not seem to be effective except the use of amisulpride. A meta-analysis of five double-blind, placebo-controlled studies of amisulpride in patients with predominant negative symptoms of schizophrenia found a positive correlation between the severity based on the mean SANS score at baseline and mean improvement at end point[85,86].

Several studies have provided preliminary evidence that increasing NMDA receptor activation through glycine-site agonists improves negative symptoms in schizophrenia. Among these, sarcosine is a nonselective glycine reuptake inhibitor which has been found to improve negative symptoms in several studies[87]. Metabotropic glutamatergic receptors agonists, specifically, subtype 2 (mGluR2) may also be used. However, pomaglumetad methionil (LY2140023), an mGluR2/3 agonist, appeared promising but ultimately provided disappointing results as an adjunctive agent for patients with prominent negative symptoms[88]. Agents active at alpha-7 nicotinic receptors are currently being developed as add-on therapies. In a Phase IIb study, EVP-6124 met the primary end point on cognition and demonstrated improvement of negative symptoms (a secondary end point)[89]. A meta-analysis of adjunctive pharmacotherapies in schizophrenia found that five studies with acetylcholinesterase inhibitors (two studies with galantamine and three studies with donepezil) demonstrated a greater effect on negative symptoms than cognition[90]. On the other hand, the data of clinical studies using the psychostimulants (e.g. methylphenidate, amphetamine, modafinil, armodafinil) do not conclusively support the use of modafinil/armodafinil as add-on treatment in schizophrenia for negative symptoms[91]. Studies with other medications such as nonsteroidal anti-inflammatory drugs, corticosteroids, N-acetyl cysteine (NAC), estrogens, melatonin, davunetide, and fatty acids concluded that only aspirin and NAC showed significant effects[92]. A systematic review and meta-analysis of selective serotonin-3 (5-HT3) receptor antagonists, including ondansetron, granisetron, and tropisetron, revealed that when used as add-on therapy, they conferred greater benefit for negative symptoms than positive symptoms[93]. Finally, adjunctive therapy with pregnenolone demonstrated significantly greater improvement in negative symptoms which was supported by two additional studies[94,95].

PSYCHOLOGICAL INTERVENTIONS

Antipsychotic medications are a necessary but not sufficient treatment for schizophrenia. The major objectives of treatment include reducing the

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frequency and severity of episodes of psychotic exacerbation as well as improving the functional capacity and quality of lives of the individuals. In the early '60s, major role therapy and family psychoeducation were introduced based on the interpersonal and family theories of psychosis. With further research in the field, more disease-specific psychotherapies started to develop in the '80s and '90s. Five major categories of psychosocial intervention have been used in the treatment of patients with schizophrenia. These categories include the cognitive therapy (cognitive behavioral therapy and cognitive remediation therapy), social skills, psychoeducation programs, family intervention, training programs, and case management or assertive community treatment[96].

Cognitive behavioral therapy (CBT) is a highly structured and standardized therapy to help patients with schizophrenia cope with their psychotic symptoms by examining and reevaluating their thoughts and perceptions of experiences. In CBT, the patient would be encouraged to actively participate by examining the evidence for and against the distressing belief, challenging the habitual patterns of thinking about the belief, and using reasoning and personal experiences to develop rational and acceptable alternative explanations and interpretations for coping, problem solving, and self-management of the illness and its symptoms. Although some studies have found CBT to have positive benefits in terms of reduction of positive symptoms and recovery time over the course of 9–12 months in comparison with standard care and a few psychological approaches, it has not yet shown promising evidence of reduction of negative and persistent severe psychotic symptoms for people with schizophrenia, particularly over a longer-term (i.e., 2-year) follow-up[97,98].

Previous prospective, nonrandomized controlled trials of CBT for schizophrenia in the '90s indicated several limitations, including small sample sizes (e.g., 3–30 patients per group), lack of other psychosocial interventions for comparison, lack of blinding, and lack of validity and fidelity checking of the intervention sessions. Although

the effect sizes for improving the positive symptoms in more recent randomized controlled trials (2000–2006) were mainly very low to medium (i.e., 0.02–0.62; mean weight effect size, 0.37), there were no significant differences in target symptoms (both positive and negative) between individual and group CBT[90-102]. Controlled trials of CBT for relapse prevention reported inconsistent findings. Gumley et al.[103] showed the significant effect of CBT in identifying prodromal signs of relapse from schizophrenia during a 12-month follow-up, whereas Durham et al.[104] found a modest effect in relapse prevention and reduction of positive symptoms. Although there are differences in duration, number of sessions, comparative treatment, and outcomes in controlled trials, recent systematic reviews of these trials reported a similar significant positive effect of CBT on improving psychotic symptoms over the course of 6–12 months follow-up when compared with standard psychiatric care[103,104]. In seven controlled trials reviewed by Gould et al.[105], CBT was found to produce a large effect size in residual or persistent positive symptoms immediately after the intervention (effect size, 0.65) and within 1 year (effect size, 0.93). Tarrier et al.[99] conducted a multicenter randomized controlled trial with an 18-month follow-up of CBT for inpatients with acute schizophrenia and reported that CBT was more effective in symptom control than routine care. However, there were no significant differences on relapse, rehospitalization, or level of functioning between groups. When compared with supportive psychotherapy and psychoeducation, CBT for schizophrenia showed relatively lower effects on relapse, reduction of rehospitalization, and mental state both medium term (6 weeks–3 months) and long term (>3 months–1 year)[97,106]. As suggested by Barrowclough et al.[107] and Addington et al.[108] CBT could be used as an adjunct to other psychosocial interventions to improve symptoms or psychosocial functioning, particularly for young people with a high risk for psychosis or for those with a dual diagnosis and/or substance abuse.

Cognitive remediation therapy (CRT) is a computer-based intervention that was originally

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designed to improve deficient cognitive abilities (e.g., attention, memory, and executive function) in people with traumatic brain injury[109]; then, it was found beneficial for people with depression[110], eating disorders[111], and schizophrenia[110]. Although CRT by itself has no effect on improving negative symptoms[112], the combination of CRT with SST, groups, and problem solving has been found to be promising[113]. The data of recent controlled trials using cognitive remediation for cognitive rehabilitation of people with schizophrenia and showed its medium-sized effects (effect size, 0.30–0.48) in improving attention, processing and working memory, and executive functioning[114]. Despite the inconsistent and questionable generalizability and durability of the benefits found in cognitive and other functional outcomes, a recent meta-analysis of 26 controlled trials (involving 1,150 patients) proposed that cognitive remediation could significantly improve cognitive performance (effect size, 0.41), psychosocial functioning (effect size, 0.36), and psychotic symptoms (effect size, 0.28) in people with schizophrenia during a short-term (e.g., 1 year) follow-up[114].

A lack of social skills is one of the major deficits in psychosocial functioning among people with schizophrenia. It can provoke stressful interactions with the social environment and lead to social withdrawal and isolation. Social skill training (SST) originated from the social skills model of Liberman et al.[115] and consists of three main components: receiving skills (social perception), processing skills (social cognition), and sending information skills (behavioral responding or expression). SST is based on a behavioral model that targets the improvement of a person's ability to function skillfully in social situations. SST has been found to improve both positive and negative symptoms[116]. This training, practiced mostly in groups, aims to enhance patients' social competence in terms of interpersonal and communication skills, illness management, community reintegration, workplace social kills, and instrumental activities of daily life. The common set of training strategies included goal setting, behaviorally based instruction, role modeling, behavioral rehearsal, corrective

feedback, positive reinforcement, and homework to foster generalization of skills[117]. Social skills compliance gained by SST may also expand patients' participation and partnership in treatment decisions and partnership. By learning how to properly use medication, the patients become more in control of their own illness, experience greater responsibility for their treatment, and achieve greater insight into their illness[118]. Three critical reviews of more than 50 controlled trials of social SST for schizophrenia suggest that participants retain their improvements in knowledge and behaviors for up to a 2-year follow-up[119-121]. However, the results of most studies during the last three decades are discouraging for transferring the learned social skills (particularly those complex steps/procedures and high stimulus gradients) to participants' real environments. Therefore, recent studies suggest that creating opportunities for using the skills in the living environment would increase the likelihood of skill transfer to everyday life situations[121]. One recent meta-analysis of 22 randomized controlled trials conducted between 1973 and 2007 concluded that these training programs can produce a significant improvement in social functioning (effect size, 0.41–0.52) and negative symptoms (effect size, 0.40–0.47) of people with schizophrenia, and reduce rehospitalization rates over the course of 1–2 years of follow-up[117]. By using performance-based measures, the participants' mastery of social skills and daily living skills (effect size, 0.48–0.52) could be consistently and sustainably maintained during the follow-up period. However, these training programs could not demonstrate any significant effect on improvement in general psychopathology, relapse prevention and positive symptoms, and cognitive functions[115].

Because family members are the main caregivers for patients in the community, the effect of caring for patients is often described as burdensome and includes the different subjective and objective aspects of physical, emotional, or psychological and socioeconomic health problems[122]. Pharoah et al.[123] suggested the terms psychosocial, psychoeducation, and behavioral management

approaches to family interventions generally refer to those interventions in an individual or group format, in which patient and family members meet together. The primary aim of the program is to reduce patient relapse and readmission. However, family education, consultation, support, and counseling and relatives' groups usually refer to interventions directed at family members alone (excluding the patient).

There are several other reasons for providing interventions to families of people with schizophrenia. First, studies revealed that family dynamics and emotional environment affect the recurrence of positive symptoms, and therefore the course of the illness[124]. Although a supportive and caring family environment can be induced through family education and partnership in treatment planning and implementation, an enhanced competence and ability of the families to detect and notify mental health professionals about any warning signs of relapse are crucial for relapse prevention[125]. Reducing caregiver burden is an important goal of family support and care. Finally, high levels of emotion and perceived burden within a family can have a negative effect on a patient's illness, increasing their vulnerability to relapse[126]. The intimate relationship and interactions between patients and their family members warrant the application of family-centered interventions to improve both the families' and patients' ability to cope with the illness management. Recent reviews of more than 50 controlled trials (>4,800 patients) of family-based intervention from 1980 to 2010,[127] revealed that family intervention, as an adjunct to drug treatment, significantly family members' knowledge about the illness, reduce family burden and patients' relapse up to 2 years, and improve patients' compliance. Both single-family and/or multiple-family group programs, lasting from 3 months to 3 years and consisting of psychotherapeutic techniques, were associated with fewer patient relapses and rehospitalizations, with rates about half those of patients receiving routine psychiatric care[128].

Family psychoeducation, which has been derived from stress reduction and coping models and other psychological theories such as cognitive–behavioral, social learning, and crisis theories[128,97] is the most frequently used model of family-based intervention for people with schizophrenia in both Western and Asian countries. As these psychoeducation programs mainly focused on the patient's mental condition, the studies paid little attention to the family's burden or the family members' perceptions of their problems and needs. Behavioral family management is another frequently used approach to family-based intervention for schizophrenia. Developed by McFarlane et al.[129], the program uses family education, training in communication skills, and practice in problem solving via 10 sessions during a 3-month period[130-132]. It has been shown to be effective in reducing patients' symptoms, promoting remission, strengthening social functioning, and reducing family burden.

Studies in China[132,133], Europe[134], and the United States[129,135] have consistently demonstrated that family psychoeducation and/or behavioral approaches to intervention at least 10 sessions over the course of 6 months are more effective and have a relatively long-lasting effect (i.e., >2 years) in terms of preventing patient relapse than individual psychosocial treatment or medication alone. The common elements in several of the more effective family psychoeducation programs include social support, education about the illness and its treatment, guidance and resources during a crisis, and training in problem solving[136]. However, little is known about the major therapeutic components of psychoeducation and other psychosocial family-based interventions for schizophrenia.

Anderson and Adams[137] and Drake et al.[138] have suggested there are difficulties in employing family intervention in everyday clinical practice, with groups of patients with schizophrenia in receipt of community care because of inadequate mental health care services, staff training, and resources. Stanley et al.[139] suggest that an integrated therapeutic approach to family-based intervention consisting of components such as pharmacotherapy, psychosocial therapies, and

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spiritual therapy is more successful in improving the mental status and psychosocial functioning of people with schizophrenia, together with reducing family burden and increasing quality of life in their family caregivers.

Assertive community treatment (ACT) offers a multidisciplinary approach that is usually combined with SST, CBT, or any personal support. Teams include peer support specialists and practitioners with expertise in psychiatry, substance abuse treatment, and employment. Although ACT reduces time in the hospital for mental illnesses in general[140], it seems specifically to improve housing stability[141] and reduce hospitalization rates, especially in patients with higher baseline hospitalization rates[141]. ACT is a persistent, intensive case management model that targets refractory schizophrenia. This treatment approach was found to be particularly effective for those who make particularly high use of inpatient services, have a history of poor engagement with services leading to frequent relapse and/or social breakdown or need immediate access to assistance[141]. These treatment teams are characterized by very low staff-to-patient ratios (e.g., 1:10), high frequency of contacts/visits, provision of comprehensive medical and social advice in a home or supervised care environment, and multidisciplinary care. Although frequent home visits can facilitate medication compliance, crisis intervention, and establishment of therapeutic relationships, health assessment of patients and their families is more accurate because treatment team members can observe patients' behaviors directly rather than depending on patients' self-reporting. Bond et al.[143] suggested that every community have ACT teams with a capacity to serve 0.1% of the general population or 20% of all patients with severe mental illness. In the '90s, ACT conducted in the United States was shown to reduce patients' hospitalization and increase community service use at a reduced cost[144,145]. Bond et al.'s study[143] in Australia reported that ACT not only reduced patients' symptoms and rehospitalizations but also improved their housing and quality of life. The United Kingdom studies

indicated that ACT did not demonstrate any positive effect on social adjustment and functioning. Clarke et al.,[146] in their review on 25 randomized controlled trials with 3–36 months' follow-up, suggest that ACT can substantially reduce psychiatric hospitalization by 78%, increase housing stability (67%), and moderately improve positive symptoms (44%) and quality of life (58%) among patients with schizophrenia. In contrast, it has been suggested that ACT has little effect on patients' social and vocational functioning, substance use, and satisfaction with services. As ACT targets individualized management and intensive care for difficult-to-engage or refractory patients with schizophrenia, one of the major barriers may be the absence of valid methods to determine these patients' health needs[143,144].

Personal therapy was developed on the basis of supportive psychotherapy[145]. It is one of the few approaches that was designed specifically for people suffering from schizophrenia and combines SST with some common elements of CBT. Personal therapy is modeled to the phases of recovery; thus, it is a long-term endeavor and seems to decrease the probability of relapse[146].

Taken together, CBT may be particularly beneficial for those with residual psychotic symptoms and cognitive remediation, SST for those with cognitive or social cognition deficits or both, and ACT for those at risk for frequent hospitalizations or those who have had recent homelessness. There is increasing emphasis on tailoring psychotherapeutic interventions to the phase of the illness as the goals of intervention might vary according to the phases. More research is needed, to identify the synergistic effects of combinations of interventions that are hypothesis-driven and cost-effective.

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