

Current approaches to treatments for schizophrenia spectrum disorders, part I: an overview and medical treatments

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Abstract: During the last three decades, an increasing understanding of the etiology, psychopathology, and clinical manifestations of schizophrenia spectrum disorders, in addition to the introduction of second-generation antipsychotics, has optimized the potential for recovery from the illness. Continued development of various models of psychosocial intervention promotes the goal of schizophrenia treatment from one of symptom control and social adaptation to an optimal restoration of functioning and/or recovery. However, it is still questionable whether these new treatment approaches can address the patients' needs for treatment and services and contribute to better patient outcomes. This article provides an overview of different treatment approaches currently used in schizophrenia spectrum disorders to address complex health problems and a wide range of abnormalities and impairments resulting from the illness. There are different treatment strategies and targets for patients at different stages of the illness, ranging from prophylactic antipsychotics and cognitive-behavioral therapy in the premorbid stage to various psychosocial interventions in addition to antipsychotics for relapse prevention and rehabilitation in the later stages of the illness. The use of antipsychotics alone as the main treatment modality may be limited not only in being unable to tackle the frequently occurring negative symptoms and cognitive impairments but also in producing a wide variety of adverse effects to the body or organ functioning. Because of varied pharmacokinetics and treatment responsiveness across agents, the medication regimen should be determined on an individual basis to ensure an optimal effect in its long-term use. This review also highlights that the recent practice guidelines and standards have recommended that a combination of treatment modalities be adopted to meet the complex health needs of people with schizophrenia spectrum disorders. In view of the heterogeneity of the risk factors and the illness progression of individual patients, the use of multifaceted illness management programs consisting of different combinations of physical, psychological, and social interventions might be efficient and effective in improving recovery.

Keywords: schizophrenia, schizophrenia spectrum disorders, treatment, psychosocial intervention, pharmacology, antipsychotics

Introduction

Schizophrenia and its spectrum disorders (all falling under the term “schizophrenia” in this article) are chronic remitting and disruptive disorders associated with significant abnormalities and the progressive deterioration of a wide variety of cognitive, psychosocial, vocational, and behavioral functioning. 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 problems.¹ The onset of symptoms typically occurs in adolescence and young adulthood, with a worldwide

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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} A recent systematic review indicated that patients diagnosed with this disorder have a shorter lifespan than the average general population and are particularly at risk for suicide, increased physical risk (eg, limited exercise, poor diet, and obesity), and reduced access to medical treatment and healthcare services.⁴ In addition, 5%–8% of healthy people indicate an attenuated form of schizoid personality and schizophrenia-like symptoms, such as paranoid delusional thinking and auditory hallucination.⁵

Because of the complex health problems and wide range of abnormalities and impairments concerning schizophrenia, comprehensive and multimodal treatment approaches are considered and tested in different combinations, with the goal of reducing patients' illness episodes and symptoms, as well as improving their functioning and quality of life in the longer term. Antipsychotic medications have been recommended consistently and continuously as the main-stream and standard treatment for nearly all patients with schizophrenia, to provide them with a safe and therapeutic environment and effective symptom control since the introduction of chlorpromazine (the first antipsychotic) in the 1960s. In the last three to four decades, physical treatments such as electroconvulsive therapy (ECT; in the 1930s) and different approaches to psychosocial interventions such as psychoanalysis (in the 1950s), family therapy (in the 1960s), psychoeducation (in the 1980s), cognitive-behavioral therapy (in the 1990s), and cognitive remediation (in the 2000s) have been introduced successively,^{7–14} and their comparative or combined efficacies for schizophrenia treatment have been increasingly evaluated in various clinical trials.^{8,10,12,13} Recent systematic reviews and practice guidelines have recommended that as an adjunct to psychopharmacological treatment, psychosocial interventions designed to support both people with schizophrenia and their families should also be used to improve their rehabilitation, reintegration into the community, and recovery from the illness.^{6,15} Different modalities and combinations of psychosocial programs are recommended to address the complex individualized needs of these patients for multimodal care, particularly regarding relapse prevention, management of negative symptoms and cognitive dysfunction, and medication adherence.^{14,16} Despite increased recognition and demands for an individualized treatment plan and the integration of different intervention approaches to optimize patient outcomes, current psychiatric treatments and services still involve practicing the same set of treatment approaches for each patient group in the

course of illness. More clinical trials are recommended to examine the active ingredients of unimodal or integrated psychosocial interventions for schizophrenia that can be effective in enhancing recovery and other patient outcomes. There has also been increasing attention and demand for cost-effectiveness analyses of these interventions.

To gain a more in-depth and focused understanding of the effects and benefits of recent approaches to treatments for schizophrenia, we performed a comparative review, summarized here, of the efficacy, safety, and tolerability of the current pharmacological and other medical treatments for these patients. In another article, we also performed a comparative review of the efficacy of approaches to psychosocial interventions for schizophrenia and a critical discussion about patient-focused perspectives of acceptance, benefits, and satisfaction in psychiatric care. Recommendations for best practices for continuity of schizophrenia care are also made. This article also provides an overview of the approaches to treatments across different stages of schizophrenia and the future direction of treatments for this illness.

Review of current approaches to medical treatments for schizophrenia

During the last two decades, the mainstream of medical treatment for schizophrenia has remained the use of antipsychotics and/or other psychotropic medications. With increasing initiatives and evidence of the effectiveness of psychosocial interventions for schizophrenia, the highly structured or manualized (eg, cognitive-behavioral and psychoeducation programs) and a few integrated programs (eg, the Schizophrenia Patient Outcomes Research Team Programs and the Recovery After an Initial Schizophrenia Episode Early Treatment Program in the United States),^{17,18} used as an adjunct to antipsychotics, have indicated positive patient outcomes. On the basis of several large-scale randomized controlled trials, single and multiple types of antipsychotics, or polypharmacy in combination with other psychotropic drugs, are considered useful in schizophrenia treatment. The introduction of second-generation antipsychotics has further improved the desired effects of these medications for schizophrenia care and, more important, reduced their undesirable effects such as extrapyramidal adverse effects, mortality, and metabolic disorder. Before exploring the recent changes or improvements needed in schizophrenia treatment and rehabilitation, it is important to review and understand the current knowledge about pharmacological and other medical treatments for schizophrenia sufferers.

Pharmacological treatment First- and second-generation antipsychotics

More than 70 antipsychotics have been introduced. They are mainly categorized into first- and second-generation agents and share a similar pharmacological mechanism in blocking the dopamine D-2 receptors.¹⁹ Their blocking mechanisms or actions are linked to their efficacy against positive and disorganization symptoms of schizophrenia.^{11–13}

The first-generation antipsychotics (FGAs), or typical antipsychotics (eg, chlorpromazine, fluphenazine, and haloperidol, included in the World Health Organization's list of Essential Medications in 2009),²⁰ were first introduced for the treatment of schizophrenia in the 1950s. The second-generation (atypical) antipsychotics (eg, clozapine, olanzapine, and risperidone) introduced in the last three decades were believed to be more efficacious and tolerable than the FGAs, and a few have progressively replaced the older FGAs to become the first-line prescription or the standard of care. To capture the research evidence or drug trials on antipsychotics, full-text articles published in English between 1966 and 2010 were searched for in CINAHL, MEDLINE, EMBASE, The Cochrane Library, Cochrane Schizophrenia Group's Register, Biological Abstracts, Sociological Abstracts, Sociofile, and PsycLIT. Participants included people with schizophrenia, schizophrenia-like psychoses such as schizophreniform and schizoaffective disorders, and psychotic disorders such as delusional disorder, nonaffective psychosis, or dual diagnosis. The main outcomes identified from the reviewed articles mainly involved mental state, global functioning, and adverse events.

Thirteen systematic reviews on the efficacy of FGAs using a randomized controlled trial design were found (Table 1). With similar intended outcomes, several outcome measurement tools were commonly used, including the Clinical Global Impression, Global Assessment Scale, and Global Assessment of Functioning scale for patients' global functioning; the Brief Psychiatric Rating Scale, Positive and Negative Syndrome Scale, Scale for the Assessment of Negative Symptoms, and Scale for the Assessment of Positive Symptoms for their mental state or symptom severity; and the Involuntary Movement Scale, Extrapyramidal Symptom Rating Scale, Extrapyramidal Rating Scale, and Simpson and Angus Scale for the adverse effects of medication used. Most of the clinical trials (>70%) evaluated the medication effects over a short period of time (eg, up to 12 weeks), whereas a few (<10%) involved a long-term follow-up (eg, >1 year).

The first FGA invented – chlorpromazine, has become the well-established and benchmark treatment for people with schizophrenia to facilitate their deinstitutionalization²¹ and has been used for more than 40 years. Nevertheless, the reviewed literature showed that the incidence and average dose of chlorpromazine prescribed to people with schizophrenia has been decreasing.²² Other commonly used FGAs such as trifluoperazine, thioridazine, sulpiride, pimozide, perphenazine, and fluphenazine were tested and confirmed to have similar and satisfactory efficacy in symptom reduction – mainly for positive symptoms (eg, delusions and hallucinations).^{23–28} However, there was limited evidence to support their efficacy at lower doses or in short-term treatment.^{28–31} Major adverse events induced by FGAs generally include sedation, movement disorders, endocrine disturbance, and metabolic and electrocardiogram changes.^{24,25,28,32}

Most of all, FGAs are a relatively low-cost treatment and commonly used medication; however, there is little evidence to support their efficacy in reducing negative symptoms (eg, anhedonia, loss of volition, and social withdrawal) and cognitive functioning, which may contribute much to the functional disability of people with schizophrenia.^{26,29,33} It is generally concluded that there is similar satisfactory clinical efficacy in terms of mental state and global functioning across the FGAs and second-generation antipsychotics.^{34–37} However, a few trials indicate the superiority of individual second-generation agents over the FGAs in specific illness condition or patient outcomes.^{29,33,37,38} In two meta-analyses of placebo-controlled trials,^{39,40} haloperidol was reported to be less effective in reducing symptoms and/or relapse than certain second-generation agents (eg, clozapine and olanzapine).

Second-generation (or atypical) antipsychotics were believed to have good antipsychotic properties and minimal adverse effects compared with those noted with the use of FGAs. Some of them have been shown to be more efficacious and less problematic in terms of sedative and neurological effects than FGAs.^{41,42} Using the same databases and a similar procedure as the literature search on FGAs presented earlier, 12 systematic reviews (between 1966 and 2010) have been conducted to compare the effects among second-generation antipsychotics and the effects between these second-generation agents and FGAs or a placebo (Table 2). In addition to the main patient outcomes used (ie, mental state, global functioning, and relapse), several other psychosocial outcomes were usually compared across studies, including level of depression, acceptability of treatment (eg, dropout

Table 1 Summary of reviews on first-generation antipsychotics for schizophrenia

| Authors | Clinical trials reviewed, N | Interventions | Sample size and study setting | Length of study or follow-up ^a | Summary of main findings | Conclusion |
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| Adams et al ²¹ | 50 | Chlorpromazine (oral or by injection) vs placebo | N = 1,395; mainly hospital-based; a few conducted in the community | 24 hours to 5 years; follow-up in only 22 short-term studies, 20 medium-term studies, and eight long-term studies | <ul style="list-style-type: none"> Six of 50 controlled trials found that chlorpromazine could reduce relapse in a short- to medium-term follow-up; three were in a long-term follow-up (6 months to 2 years); and two in a much longer-term follow-up (2–5 years). Twenty-four of the trials found that antipsychotics could induce global improvements in positive symptoms and functioning in a short- to medium-term (up to 6 months) follow-up. Not surprisingly, a range of adverse effects such as extrapyramidal symptoms, sedation, dizziness, and weight gain was found. | <ul style="list-style-type: none"> FGAs such as chlorpromazine can be the benchmark of treatment for schizophrenia. It is well-established but imperfect treatment. Most evidence on their significant effects has been found in hospitals, and relatively little was applicable to patients in community care. |
| Fenton et al ²⁴ | 42 | Thioridazine vs FGAs, second-generation antipsychotics, and/or placebo | N = 3,498; mainly hospital-based; three trials conducted in outpatient settings | Follow-up: 30 short-term, ten medium-term, and two long-term trials | <ul style="list-style-type: none"> As compared with the placebo controls, three RCTs favored thioridazine in terms of global functioning after longer-term follow-up (ie, up to 6 months), and another three RCTs found it sedating, but it was not generally found to cause movement disorders. Compared with FGAs, 11 small and three medium RCTs found no difference in global functioning; 19 small RCTs found no difference in early attrition or defaults; and seven RCTs found thioridazine to have fewer extrapyramidal adverse events, but three RCTs reported it was associated with cardiac adverse effects. | <ul style="list-style-type: none"> Thioridazine indicated no significant difference in clinical efficacy when compared with other commonly used antipsychotics in terms of global functioning. The researchers suggested considering other alternatives when patients did not respond well to thioridazine. |
| Hartung et al ²⁶ | 25 | Perphenazine vs placebo and other antipsychotics | N = 2,478 (2,285 randomized); all conducted in hospitals or outpatient settings | Two short-term, two medium-term trials | <ul style="list-style-type: none"> Twenty RCTs found perphenazine as effective as other antipsychotics in terms of safety, illness behavior, and tolerability. Poor data reporting and the use of various comparators limited the validity of the review. | <ul style="list-style-type: none"> It was not possible to draw clear conclusions; perphenazine indicated similar desirable and adverse events to other drugs. However, it is relatively low-cost, and thus more frequently used. |
| Irving et al ³¹ | 21 | Haloperidol (oral) vs placebo | N = 1,519; all conducted in hospital or outpatient settings; usually multicenter design | Eleven short-term and ten medium-term trials | <ul style="list-style-type: none"> Three RCTs found that haloperidol produced improvement in global functioning during the first 6 weeks of follow-up; eight RCTs favored the drug at 6–24 weeks. | <ul style="list-style-type: none"> It was suggested that prescribing alternative drugs and haloperidol should not be an option for a randomized controlled trial. It is, however, still surprisingly widely used. |

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| | | | <ul style="list-style-type: none"> About half failed to complete the short-term follow-up (0–6 weeks), and eleven studies found that the outcome difference only marginally favored haloperidol. Haloperidol is a potent cause of movement disorders in the short-term; a significant number of people suffered from sleepiness, and a few adverse effects such as parkinsonism, akathisia and acute dystonia were found in eleven RCTs. | | | | <ul style="list-style-type: none"> Two RCTs did not report the findings of global or mental state outcomes, but an increased risk of experiencing extrapyramidal adverse effects was found. Compared with FGAs, seven RCTs showed that zuclopenthixol decreased the risk of no change or a worsening of the illness; nine RCTs showed no difference in terms of adverse effects. As compared with second-generation antipsychotics, two RCTs showed no difference in terms of global state and weight gain with risperidone, but one found that more anti-Parkinsonian medications were prescribed in people taking zuclopenthixol. | |
| Kumar and Strech ³⁰ | 18 | Zuclopenthixol dihydrochloride vs placebo, FGAs, and/or second-generation antipsychotics | N = 1,578; mainly conducted in inpatient or outpatient settings; a few settings were not able to be identified | 18 short-term studies | | | <ul style="list-style-type: none"> Some clinical advantages of zuclopenthixol dihydrochloride in the short-term, such as significant improvements in global state. More movement disorders were found than with the newer generation of drugs. There is no clear and adequate information about service use, functional and behavioral outcomes, and relapse prevention. | |
| Leucht et al ³² | 14 | Haloperidol vs chlorpromazine (oral and intramuscular route) | N = 794; ten studies conducted in inpatient settings and four in nonidentified settings | Follow-up: 48 hours to 3 years, mostly short-term | | | <ul style="list-style-type: none"> Nine RCTs favored haloperidol, even though the difference was not statistically significant. Six RCTs reported that movement disorders with haloperidol were more frequent, and five found that hypotension was associated with chlorpromazine. No difference was found between intramuscular and oral administration. | <ul style="list-style-type: none"> Fewer than 800 people were randomized, and reporting on the main results was incomplete. Haloperidol indicated statistically nonsignificant efficacy in terms of various patient outcomes, thus making it difficult to draw conclusions. |
| Leucht and Hartung ²⁸ | Six | Perazine vs other FGAs and/or placebo | N = 288; five conducted in inpatient settings and one in a nonidentified setting | Six short-term trials | | | <ul style="list-style-type: none"> One RCT with a 5-week follow-up found that perazine was superior to the placebo on improvement in global functioning but made no significant difference to mental state. Similar adverse effects were found among the medications used and compared; most participants received at least one dose of anti-Parkinsonian medication. Five RCTs provided insufficient information of outcomes to draw conclusion, and three RCTs showed the drug indicated similar risks of extrapyramidal adverse effects to other drugs. | <ul style="list-style-type: none"> There was no statistically significant difference in most clinical outcomes, and limited evidence to draw conclusions. |

(Continued)

Table 1 (Continued)

| Authors | Clinical trials reviewed, N | Interventions | Sample size and study setting | Length of study or follow-up | Summary of main findings | Conclusion |
|--|--|---|---|---|---|---|
| Liu and De Haan ²² | Four | Chlorpromazine vs placebo | N = 1,012; mainly conducted in hospital settings | Four short-term trials | <ul style="list-style-type: none"> Two RCTs found fewer extrapyramidal adverse effects in a low-dose group of chlorpromazine, facilitating a better quality of life. One RCT favored the high-dose group with much better functioning, even though they indicated more adverse effects. <p>Both groups experienced akathisia.</p> | <ul style="list-style-type: none"> The dose of chlorpromazine given declined across time, thus contributing to favorable outcomes and less adverse effects. It is extensively used in developing countries. |
| Marques et al ²³ | 50 | Trifluoperazine vs placebo, other FGAs, and/or second-generation antipsychotics | N = 2,583; 44 studies conducted in hospital settings | 28 short-term, six medium-term, and one long-term trial | <ul style="list-style-type: none"> When compared with the placebo, three small-scale short-term RCTs favored trifluoperazine in terms of global improvements, four found that more people allocated to trifluoperazine used anti-Parkinsonian drugs, and seven reported 12% attritions in both groups at follow-ups. When compared with the FGAs, 22 RCTs found no difference in terms of global improvement between groups, 14 found that similar number of participants reported at least one adverse effect, and three found trifluoperazine most likely caused extrapyramidal adverse effects. One small-scale RCT found no difference between trifluoperazine and second-generation antipsychotics on patient outcomes. | <ul style="list-style-type: none"> Similar efficacy and adverse events are found between trifluoperazine and the other commonly used antipsychotics. Trifluoperazine is a potent FGA, inexpensive and widely accessible, but its superiority is inconclusive when compared with second-generation antipsychotics. |
| Matar, Almerie and Sampson ²⁷ | Seven | Fluphenazine (oral) vs placebo | N = 439; mainly in hospital or community settings | Most short-term (6) | <ul style="list-style-type: none"> Two RCTs found no difference on global states between fluphenazine and placebo group in the short-term. Four reported fluphenazine group trial indicated a higher risk of developing adverse effects in the short-term. | <ul style="list-style-type: none"> Fluphenazine is an effective but imperfect treatment; it is inexpensive and accessible. The researchers prefer to use other alternatives with fewer adverse effects. |
| Rathbone and McMonag ²⁵ | 35 (27 randomized; eight double-blind) | Pimozide vs placebo | N = 1,348; mainly conducted in inpatient or outpatient settings | Follow-up: from 28 days (short-term) to 3 years (long-term) | <ul style="list-style-type: none"> Two RCTs suggested pimozide could better prevent relapse when compared with placebo. Six found the drug had similar efficacy and did not have a higher mortality rate than other FGAs, but more likely caused limb tremor in the short-term. However, five indicated the drug was less likely to cause sedation in medium-term. Four indicated anti-Parkinsonian medication should be needed. | <ul style="list-style-type: none"> Most studies cannot be useful to comment on efficacy of pimozide for people with delusional disorders. It shows similar efficacy to other FGAs. |

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| Soares et al ²⁹ | 18 | Sulpiride vs placebo, FGAs, and/or second-generation antipsychotics | N > 900; 14 studies conducted in hospital settings and one in the community; three in nonidentified settings | Most follow-up over 8 weeks (short-term). | <ul style="list-style-type: none"> • Sulpiride indicated fewer adverse effects, and little difference was found between the drug and other antipsychotics. • No findings of negative symptoms were shown. • There were limited results on negative symptoms. • Efficacy and adverse effect profiles are similar among FGAs, no matter whether by oral or depot route. • Penfluridol is an option for chronic illness with residual psychotic symptoms and is considered a low-cost intervention. |
| Soares and Silva de Lima ³³ | 27 (eleven studies randomized) | Penfluridol vs FGAs, depot injections, and/or placebo | N = 1,024; mainly conducted in hospital or outpatient settings; four with nonidentified settings | Five short-term and 22 medium-term trials | <ul style="list-style-type: none"> • Four medium-term RCTs found penfluridol superior to placebo in terms of global functioning, whereas another five RCTs showed that a combination of antipsychotics was considered necessary. • Ten showed no difference between penfluridol and other FGAs in terms of global state over 3–6 months. • Five found that the drug was superior in keeping patients in treatment. |

Notes: Duration of study or follow-up, with trials ranging from short-term, up to 12 weeks, to medium-term, 13–24 weeks, to long-term, more than 24 weeks.

Abbreviations: FGAs, first-generation antipsychotics; RCTs, randomized controlled trials; vs, versus.

rate and patient dissatisfaction), inability to work, family burden, and social and cognitive functioning. Therefore, there are a wider variety of outcome measurements than used in previous studies, such as depression (eg, the Calgary Depression Scale, the Hamilton Rating Scale for Depression, or the Montgomery Asberg Depression Rating Scale), quality of life (eg, the Quality of Life Scale, the Schizophrenia Quality of Life Scale, the Subjective Well-being on Neuroleptics [Antipsychotics] Scale, or the Personal and Social Performance Scale), and patient satisfaction (eg, the Nurses Observational Scale Inpatients Evaluation) measures. Similar to those receiving FGAs, most of the clinical trials evaluated the short-term effects (up to 12 weeks) of the second-generation antipsychotics, even though a few long-term evaluations appear promising.^{39,40}

A few systematic reviews also indicated that the controlled trials of second-generation antipsychotics have mainly tested only a few kinds, including risperidone, olanzapine, quetiapine, loxapine, sertindole, aripiprazole, and amisulpride, and mostly compared them with placebo controls.^{43–50} The reviews concluded that second-generation antipsychotics had similar effects to FGAs in terms of reduction of positive symptoms. The treatment efficacy of both FGAs and second-generation antipsychotics varies in terms of stages of the illness, with first-episode schizophrenia responding faster and better than at later illness stages.^{35,41,51} Nevertheless, most of the second-generation antipsychotics had comparatively fewer and lower levels of adverse effects such as movement disorders and cardiac and sedative problems than FGAs. Clozapine, the first second-generation antipsychotic, has been found to be particularly effective in treating refractory patients and reducing suicidality.^{36,41} A recent meta-analysis comparing nine second-generation antipsychotics with the FGAs (eg, chlorpromazine, fluphenazine and haloperidol) for overall efficacy concluded that four second-generation antipsychotics (namely, amisulpride, clozapine, olanzapine, and risperidone) were better than the FGAs, with small to medium effect sizes (ie, 0.13–0.52).³⁷ The four second-generation antipsychotics have been shown to induce fewer extrapyramidal adverse effects than the low-potency FGAs. Although olanzapine can induce more weight gain and production of prolactin, it is shown to exert a persistent treatment effect over other second-generation antipsychotics in chronic schizophrenia.^{37,52}

A recent Cochrane's systematic review was published on nine randomized, placebo-controlled trials of aripiprazole, which is one of the newer second-generation antipsychotics. Its main results indicated that aripiprazole can significantly

Table 2 Summary of reviews on second-generation antipsychotics for schizophrenia

| Authors | Clinical trials reviewed, N | Interventions | Sample size and study setting | Length of study or follow-up ^a | Summary of main findings | Conclusion |
|--------------------------------------|---|--|--|---|---|--|
| Alprekin et al ³⁴ | One RCT and a few with nonrandomized comparison groups design | Olanzapine, risperidone or haloperidol vs ziprasidone | N = 287; multicenter trials in a hospital or outpatient setting | Follow-up: up to 12 weeks (short-term) | <ul style="list-style-type: none"> Ziprasidone showed significant effects on improvement in mental state and cognitive functioning. It has a comparatively neutral metabolic profile and is clinically valuable when taken with food. | <ul style="list-style-type: none"> The findings confirm the effectiveness of ziprasidone as an appropriate choice for switching of drugs whenever needed. |
| Belgamwar and El-Sayeh ⁴⁶ | Nine | Aripiprazole vs placebo | N = 2,585; mainly conducted in a hospital or outpatient setting | Eight short-term and two medium-term trials | <ul style="list-style-type: none"> One RCT with less than 3 months follow-up found that aripiprazole significantly reduced relapse. Eight RCTs showed better medication compliance, and two showed lower risks of raised prolactin and prolongation of the corrected QT interval of ECG (represents the depolarization and repolarization of the left and right ventricles or ventricular arrhythmias). Most were unable to extract any usable data on mortality, service utilization and satisfaction, and cognitive functioning. | <ul style="list-style-type: none"> Aripiprazole can be effective in the short- to medium-term of treatment. There was high attrition in all studies (>30%). |
| Chakrabarti et al ⁴⁷ | 41 | Loxapine vs placebo, second-generation antipsychotics, and/or FGAs | N = 2,381; all conducted in hospitals | Follow-up: from 72 hours (short-term) to 6 months (long-term) | <ul style="list-style-type: none"> Thirteen short-term RCTs found loxapine as effective as other FGAs, whereas six longer-term RCTs reported it was as effective as second-generation antipsychotics in terms of relapse and a few patient outcomes. Four found the drug had similar adverse effects to other FGAs and that they were more severe than those of second-generation antipsychotics. | <ul style="list-style-type: none"> Loxapine can be effective from short- to long-term treatment in schizophrenia, but with similar efficacy to a few other FGAs and second-generation antipsychotics. It may cause more extrapyramidal adverse effects when compared with other second-generation antipsychotics. |
| Citrome ³⁵ | 32 | Lurasidone vs placebo | N = 8,071; most settings not specified | Follow-up: from 7 days (short-term) to 18 months (long-term) | <ul style="list-style-type: none"> Lurasidone was shown to be efficacious and tolerable with food and had a highly favorable metabolic profile. Akathisia or Parkinsonism was reported in most RCTs. | <ul style="list-style-type: none"> Additional data were necessary to support its long-term efficacy as a maintenance treatment. |
| Duggan et al ⁴⁶ | 56 | Olanzapine vs FGAs, second-generation antipsychotics, and/or placebo | N > 10,000; mainly conducted in the hospital or outpatient setting; eleven conducted in nonidentified settings | 31 short-term, 23 medium-term, and two long-term trials | <ul style="list-style-type: none"> Sixteen RCTs showed high attrition by 6 weeks in both olanzapine and placebo/FGAs; four found the drug as effective as FGAs. Four found olanzapine to cause fewer movement disorders but more weight gain from 3 to 12 months of treatment. Eleven recorded that 23% of people in trials of olanzapine and other second-generation antipsychotics left by 8 weeks, and 48% by 3 to 12 months. | <ul style="list-style-type: none"> Most studies reported very high attrition in both olanzapine and placebo/FGA/other second-generation antipsychotic groups, ranging from >30% by 6 weeks to 50% by 12 months. There was similar efficacy to other second-generation antipsychotics in relapse prevention and reduction of positive symptoms, but no notable benefit in negative symptoms. |

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| <p>El-Sayeh and Morganti⁴⁹</p> | <p>15</p> | <p>Aripiprazole vs FGAs, second-generation antipsychotics, and/or placebo</p> | <p>N = 7,110; eight conducted in hospital setting and two in outpatient setting; five with nonidentified settings</p> | <p>Ten short-term, three medium-term, and two long-term trials</p> | <ul style="list-style-type: none"> • One RCT showed that aripiprazole could significantly decrease relapse in short- and medium-term follow-up. • Eight RCTs found that the drug produced better compliance; seven reported that it produced a lower risk of akathisia when compared with FGAs and less risk of metabolic and cardiac events when compared with other second generation antipsychotics. • It was not possible to extract any usable data on mortality, service use and satisfaction, and general and cognitive functioning. | <ul style="list-style-type: none"> • Most RCTs reported high attrition rates (30%–50%). • Aripiprazole can be effective in medium-term treatment, with similar efficacy to other second-generation antipsychotics and most FGAs in relapse prevention and reduction of positive symptoms. • Its prescription as routine or usual practice cannot be confirmed. |
| <p>Karaya et al⁵⁴</p> | <p>An open-label, flexible-dose trial</p> | <p>Switching from quetiapine to ziprasidone</p> | <p>N = 241; conducted in an outpatient setting</p> | <p>All participants were followed-up over 3 months (medium-term)</p> | <ul style="list-style-type: none"> • The RCT showed that switching to ziprasidone could produce a significant decrease in weight and improvements in mental state and cognitive functioning, with a neutral metabolic profile. • It was recommended to be taken with food. | <ul style="list-style-type: none"> • Ziprasidone shows significant benefits in overall mental state and functioning in the medium-term. • Patients taking this drug showed satisfactory tolerability and safety; therefore, it is a good choice for the switching of second-generation antipsychotics. |
| <p>Lewis et al⁶⁹</p> | <p>Three</p> | <p>Sertindole vs placebo or haloperidol</p> | <p>N = 1,104; mainly conducted in the hospital or outpatient setting</p> | <p>One short-term, one medium-term, and one long-term trial</p> | <ul style="list-style-type: none"> • When compared with the placebo, no significant difference was found with a dose of more than 12 mg daily, but a marginally significant difference was found when taking 20 mg daily. • There was no significant difference between low and high doses of sertindole in terms of most adverse events; cardiovascular adverse effects showed significant difference between groups at all doses by 8 weeks, whereas weight gain was significantly higher with a high dose of sertindole. • When compared with haloperidol, sertindole induced more cardiac problems, rhinitis, and weight gain, but fewer movement disorders and less sexual dysfunction and sedation than haloperidol. | <ul style="list-style-type: none"> • Sertindole appears to have similar efficacy but to be more tolerable than haloperidol. • Sertindole 16 mg/day is suggested to be the most optimal dose. |
| <p>Nussbaum and Stroup⁶⁵</p> | <p>Eight</p> | <p>Paliperidone (oral and intramuscular) vs placebo or second-generation antipsychotics</p> | <p>N = 2,562; mainly conducted in a hospital or outpatient setting; a few not specified</p> | <p>All followed up in short-term</p> | <ul style="list-style-type: none"> • When compared with placebo, seven RCTs indicated that fewer people randomly assigned to the paliperidone group left the studies and that less relapse was reported; four found that the drug produced significant improvement in global functioning, but most RCTs indicated that this drug caused adverse events such as tachycardia and extrapyramidal syndrome. | <ul style="list-style-type: none"> • Paliperidone appears to be effective in relapse prevention, although no firm conclusions were drawn as to its long-term effects. • There are similar levels of adverse effects when it is compared with other second-generation antipsychotics. |

(Continued)

Table 2 (Continued)

| Authors | Clinical trials reviewed, N | Interventions | Sample size and study setting | Length of study or follow-up ^a | Summary of main findings | Conclusion |
|---|-----------------------------|---|--|---|--|--|
| Ratthalli Jayaram and Smith ⁴³ | Ten | Risperidone vs placebo | N = 24–303; mainly conducted in a hospital or outpatient setting; four studies with nonidentified settings | All followed-up in short-term | <ul style="list-style-type: none"> When compared with other second-generation antipsychotics, three RCTs indicated no difference in efficacy between paliperidone and olanzapine in the short term; another three favored the drug in terms of relapse prevention and weight change, and all results favored the drug for causing fewer movement disorders. No data were found on service use, quality of life, behavior changes, satisfaction with treatment received, cognitive functioning, and cost-benefit. Ten RCTs showed high attrition (60%) in placebo groups by 6 weeks. Three RCTs found no difference between risperidone and a placebo in terms of global functioning, whereas seven showed that risperidone produced significant improvements in mental state. Five trials reported a few adverse effects in the medium-term, mainly in terms of metabolic and cardiac profiles. | <ul style="list-style-type: none"> Because of high attrition rates, risperidone is suggested to have moderate biases in the interpretation of the findings, thus drawing no firm conclusions about its efficacy and adverse events. There were marginal benefits in terms of a few patient outcomes by the first few weeks, such as improvements in mental state and global functioning. |
| Silveira da Mota et al ⁵⁰ | 19 | Amisulpride vs placebo, FGAs, and/or second-generation antipsychotics | N = 2,443; mainly conducted in a hospital or outpatient setting; four studies with nonidentified settings | Most followed-up in short-term (17); two in medium-term | <ul style="list-style-type: none"> When compared with a placebo, four RCTs favored a low dose of amisulpride in terms of global functioning and negative symptoms; two showed that amisulpride caused more adverse effects. When compared with FGAs, 14 RCTs confirmed the drug as being more effective in terms of global functioning, mental state, and negative symptoms. One RCT compared the efficacy of the drug with that of risperidone and found no difference in most patient outcomes. Data on service use, family burden, and quality of life were not thoroughly evaluated. | <ul style="list-style-type: none"> More patient benefits were found in those with low doses of amisulpride when compared with FGAs. Similar efficacy with other second-generation antipsychotics was noted. Amisulpride can be an effective alternative to other second-generation antipsychotics. |

| | | | | | | |
|----------------------------------|----|--|---|--|--|---|
| Srisurapanont et al ⁴ | 12 | Quetiapine vs placebo, FGAs, and/or second-generation antipsychotics | N = 3,443; most study settings not reported | Ten short-term, two medium-term trials | <ul style="list-style-type: none"> • Four RCTs reported that the quetiapine groups indicated higher attrition (>50% in short-term follow-ups) than the placebo; one RCT reported two deaths in the group with higher doses of quetiapine. • When compared with FGAs, six RCTs found that the quetiapine groups indicated 36% dropouts in the short-term; five indicated that quetiapine produced moderate changes in global functioning and mental state in the short-term; and severe adverse effects were found in five RCTs, whereas four reported that it produced fewer movement disorders. • When compared with risperidone, 30% of people left the study in one RCT, and another reported that four people died during the study. • One RCT found fewer people receiving quetiapine presenting with extrapyramidal adverse effects; four studies found that the drug produced a lower risk for movement disorders but higher risks for dizziness, dry mouth, and sleepiness. • Limited data were found on service use, economic outcomes, social function, and quality of life. | <ul style="list-style-type: none"> • Although potential biases may occur because of higher attrition rates among the studies, quetiapine can be equally effective in improving patients' mental state and global functioning as the FGAs and other typical agents, but with fewer extrapyramidal adverse effects and movement disorders. • However, more research evidence of the longer-term efficacy of this drug with low attrition rates is needed. |
|----------------------------------|----|--|---|--|--|---|

Note: ¹Duration of study or follow-up, with trials ranging from short-term, up to 12 weeks, to medium-term, 13–24 weeks, to long-term, more than 24 weeks.

Abbreviations: FGAs, first-generation antipsychotics; RCTs, randomized controlled trials.

decrease relapse in both the short-term (<3 months; $n = 310$; risk ratio, 0.59 [95% confidence interval, 0.45–0.77]) and medium-term (3–6 months; $n = 310$; risk ratio, 0.66 [95% confidence interval, 0.53–0.81]) when compared with placebo controls.⁴⁸ Aripiprazole can also produce less attrition and better compliance with study protocol ($n = 2,275$; risk ratio, 0.74 [95% confidence interval, 0.59–0.93]), and lower risk for raised prolactin level than that expected from the placebo ($n = 305$; risk ratio, 0.21 [95% confidence interval, 0.11–0.37]).

Apart from oral medication, inhaled loxapine is considered a well-tolerated and rapid acute treatment for agitation but needs further longer-term controlled trials to verify its efficacy.⁵³ Studies on relatively new second-generation antipsychotics such as ziprasidone have shown that their efficacy on positive symptoms is much better than that of other second-generation antipsychotics, whereas ziprasidone and lurasidone are clinically valuable and suggested to be taken with food.^{34,54}

Most of the reviews appear not only to be concerned with their clinical efficacy and tolerability but also to pay more attention to psychosocial functioning and cognitive performance in activities of daily living. Among few systematic reviews/meta-analyses of the effect of FGAs on cognition in schizophrenia, one meta-analysis by Mishara and Goldberg⁵⁵ included 34 randomized, placebo-controlled trials and suggested that most FGAs can provide modest to moderate benefits (ie, effect sizes ranged from 0.13 to 0.29) in multiple cognitive domains, whereas motor function was affected negatively. Although most of the newest second-generation antipsychotics have shown similar treatment efficacy in improving mental state and general functioning, they have not yet shown significant differences or consistent effects on reducing negative symptoms or cognitive dysfunction.^{36,56–60} Although one review reported that social functioning was better for people with schizophrenia taking the newer second-generation antipsychotics,³⁶ most of the controlled trials only evaluated their efficacy over 3–6 months, and very high attrition rates and limited long-term effects on cognitive functioning, quality of life, service use and satisfaction, and other psychosocial functioning and behaviors were noted.^{36,57–62} Therefore, it is difficult to draw conclusions with regard to these second-generation antipsychotics, both on most patient outcomes, particularly in the longer-term, or on their cost benefits.^{46,49,63} Nevertheless, it is noteworthy that a recent population-based cohort study in Finland with 11 years of follow-up indicated decreased rates of mortality with perphenazine when compared with

the other FGAs and a few second-generation antipsychotics and that only the use of clozapine was associated with lower rates of overall mortality.⁶⁴

In conclusion, FGAs and second-generation antipsychotics are found to be similar and robust in treatment efficacy among acute and sometimes chronic schizophrenia, particularly against positive and disorganization symptoms.⁶⁵ Their efficacy varies according to the course or stage of the illness; people with first-episode schizophrenia can respond faster and better to antipsychotics than those at later stages of the illness. In contrast, neither is effective in reducing negative symptoms, and they can even worsen the negative symptoms associated with extrapyramidal adverse effects (eg, antipsychotic-induced dysphoria).⁶⁶ The efficacy of FGAs and second-generation antipsychotics on cognitive and social functioning, as well as other longer-term effects such as mortality and quality of life, are inconsistent. However, individual antipsychotics have shown significant differential efficacy in particular illness conditions and related problems, as well as different adverse effects. All of them reveal their onset of action within a few days and achieve optimal antipsychotic effect over the course of several weeks. Although antipsychotics substantially decrease patients' relapse from schizophrenia, it is not possible to ensure medication or other treatment compliance; thus, long-term injectable antipsychotics (eg, oil-based fluphenazine decanoate) may be considered. In view of the significantly varied pharmacokinetics of and treatment responses to antipsychotics among people with schizophrenia, it is recommended not only to examine the overall efficacy within and across patient groups but also to consider the efficacy of each antipsychotic medication for each individual patient when it is prescribed.^{67,68}

Safety and tolerability of antipsychotics

Antipsychotics, particularly FGAs, can have a wide range of undesirable and adverse effects on patients, mainly including neurological, metabolic, cardiovascular, hematological, endocrine, and genitourinary disturbances. In addition, they differ from one to another in the levels and nature of these adverse effects. Although a few had less-extreme adverse effects (eg, perphenazine and sulpiride),^{26,29} all of the reviews indicated that the profile of adverse events concerning these adverse effects found in most FGAs (eg, acute extrapyramidal symptoms and tardive dyskinesia) is substantial and of major concern, thus reducing patients' medication compliance and treatment efficacy.^{23,24,26–30,33}

Nevertheless, most second-generation antipsychotics have comparatively fewer and lower levels of adverse effects such as movement disorder, increased prolactin, and cardiac and sedative problems, than FGAs. In contrast, there may be higher risks for dizziness, sedation, weight gain, substantial increases in serum prolactin, and tachycardia for individual second-generation antipsychotics.^{44-48,69} However, there has not been any systematic work or classification to categorize or distinguish the risks of these adverse effects between antipsychotics, particularly the second-generation antipsychotics. As these adverse effects may affect aspects of patients' lives and treatment adherence and satisfaction, more work on such classification of antipsychotics in terms of their types or levels of adverse effects should be considered.

Clozapine, the first second-generation antipsychotic, does not show any extrapyramidal effects or tardive dyskinesia, but other serious adverse effects such as agranulocytosis and metabolic syndrome have limited its utility. In contrast, Tiihonen et al⁶⁴ reported that clozapine was associated with a significantly lower mortality rate than other antipsychotics and also concluded that a lower mortality rate could be associated with a longer-term use of antipsychotics. Although clozapine is expected to have higher risks of a few adverse effects, inducing increased mortality, the researchers explained it has been shown to demonstrate very positive effects on symptom reduction and treatment compliance. Studies on relatively new second-generation antipsychotics such as ziprasidone have shown that they had fewer adverse effects in terms of metabolic profile (eg, metabolic disturbance and weight gain) and cognitive functioning and that their effects on positive symptoms are much better than those of other second-generation antipsychotics.^{34,44} Lurasidone has also indicated a highly favorable metabolic profile but is still not free from adverse events such as akathisia and Parkinson's syndrome.³⁵

A large, 25-year cohort study measuring the mortality of 370 people with schizophrenia in Southampton, United Kingdom, reported that the cohort had an all-cause standardized mortality ratio of 289 (95% confidential interval, 247–337), indicating small and nonsignificant changes between 1981 and 2006 but falling sharply from 376 (1981–1986) to 264 (1986–1991) in the first 10 years.⁷⁰ This considerable reduction of mortality rate in the 1980s was mainly a result of a significant fall in unnatural deaths over the period (ie, the mortality ratio of suicide decreased from 6,110 in 1981–1986 to 0 in 1986–1991). In addition, the findings of the study support previous findings that people with schizophrenia have a mortality between two and three

times that of the general populations,⁷⁴ as well as raise concern about the cardiovascular mortality of schizophrenia, which has significantly increased during the past 25 years.⁸⁰ Nevertheless, the effects of clozapine and other second-generation antipsychotics on mortality and treatment compliance among patients with schizophrenia reveal the difficulties in linking medium- or long-term patient outcomes with short-term drug effects; that is, whether symptom reduction can be mainly explained by the efficacy of antipsychotic use. It is therefore recommended that more longitudinal research be conducted with longer-term follow-up on predictors or mediators of patient outcomes in schizophrenia in relation to antipsychotic use.

Patterns in medication use: mono- and polypharmacy

Treatment of people with schizophrenia who are resistant to treatment and have persistent cognitive and negative symptoms remains a challenge to most clinicians. Many controlled trials of antipsychotics and their combined use with other psychotropic drugs (eg, acetylcholinesterase inhibitors, glutamatergic agents, antidepressants, benzodiazepines, and anticonvulsants) have been carried out in people with treatment-resistant and chronic schizophrenia, particularly on the means for improvement of negative symptoms, quality of life, and social function. However, very limited and weak evidence has been shown to confirm whether a particular antipsychotic medication or any of the combination strategies used could be efficacious in main patient outcomes and/or superior to the others in the treatment of schizophrenia,⁷¹⁻⁷⁶ and none can be considered a robust treatment or prevention prescription for schizophrenia care.⁷⁷⁻⁸⁴ Nevertheless, psychosocial interventions, together with pharmacological treatment, are recommended to be the most effective strategies in the treatment and rehabilitation of people with schizophrenia.⁸⁵

Despite such inconclusive and weak evidence on pharmacological agents to control negative symptoms or treatment-resistant cases, some combinations of medication use have indicated modest to satisfactory benefits in targeting specific psychotic symptoms.^{71,86-88} For instance, anticonvulsants such as valproic acid and carbamazepine are found to be useful as adjuncts to antipsychotics in treating aggression and impulsivity in schizophrenia,^{75,76} and adjunctive antidepressants can be useful in treating depression and anxiety symptoms and in reducing craving in comorbid substance use.^{83,84,89} Interestingly, a double-blinded, multi-center randomized placebo-controlled trial on the effects

of a Warm-Supplementing Kidney Yang capsule containing 13 traditional Chinese herbs indicated that the capsule had demonstrated significant improvements in quality of life and social function, as well as in depression symptoms, in 200 patients with schizophrenia at a 4-week follow-up.⁹⁰

Depot injections have also been used extensively for controlling treatment noncompliance and long-term maintenance therapy, thus reducing the risk of relapse.^{91–93} Reviews on second-generation antipsychotic or FGA depots (eg, bromperidol decanoate, haloperidol depot, risperidone depot, and fluphenazine decanoate) versus oral antipsychotic drugs and placebo indicated that patients with FGA depots had few relapses and fewer oral medications, even though the difference did not reach statistical significance.^{94–96} Together with similar levels of adverse effects found in depot medications, it was also difficult to conclude that a particular depot was no better than any other depot or oral medication.⁹⁶ Despite showing similar clinical efficacy between oral and depot medications, depot injections can avoid frequent regular administration of and nonadherence to oral medication, rendering them more desirable for maintenance or compliance therapy.

Pharmacological treatment used in different developmental stages of life

During the last decade, there have been an increasing number of randomized controlled trials of the efficacy and safety of the FGAs and secondary-generation antipsychotics in children and adolescents with schizophrenia, involving double-blind, placebo-controlled, or open-labeled design and short- to medium-term follow-up (ie, 4–8 weeks).^{97–103} Those aged 12–17 years were usually included in the controlled trials, and a wide variety of second-generation antipsychotics such as quetiapine,⁹⁷ risperidone,⁹⁸ paliperidone,⁹⁹ and olanzapine¹⁰⁰ were tested. A few main patient outcomes were commonly used, including global functioning, symptom severity, and quality-of-life assessment; however, few of the studies involved any long-term follow-up (ie, >8 weeks).^{97–103} In addition, a few types of treatment-emergent adverse events specifically for the second-generation antipsychotic used were observed (eg, metabolic and endocrine abnormalities for olanzapine and somnolence, agitation and electrocardiogram (ECG) and ophthalmic abnormalities for quetiapine). Similar to other age groups, most of the antipsychotics have had positive benefits for adolescents on reducing psychotic symptoms and global functioning, and the treatment was well-tolerated with acceptable levels of adverse events in low

and medium dosages. None of the FGAs or second-generation antipsychotics has shown its superiority over the others, and the benefits of polypharmacy to any psychotic symptoms and comorbidities such as mood disorders for adolescents are also inconclusive.^{102,103} Nonetheless, it is suggested that antipsychotics are generally better tolerated and more effective in early psychosis.

Interestingly, a case study on a 17-year-old patient with intractable catatonic schizophrenia showed moderate effects in the resumption of spontaneous movement as a result of ECT as an adjunct to clozapine treatment.¹⁰⁴ The researchers suggested that appropriate combinations of antipsychotic medication and other treatment modalities could also be considered in young patients, although it would be unusual.

It is estimated globally that about 23% of hospitalized patients with schizophrenia are older than 40 years and that more than 0.1% of elderly people have a diagnosis of late-onset schizophrenia.¹⁰⁵ Very few studies have been done on those aged more than 65 years, and thus there are inadequate data and evidence to support any guidelines for treatment of late-onset schizophrenia or to serve these older patients' quality of life, functioning, and service use.^{105,106}

ECT and other treatments

ECT, in which clonic seizure is electrically induced in anesthetized patients for therapeutic effects such as improved mood and volition, was commonly used in the 1930s–1970s. One of the major patient groups for this treatment comprised those with schizophrenia or schizoaffective disorder. Although recent research findings are limited, ECT is considered an alternative treatment for those with unfavorable responses to antipsychotics alone after receiving different courses of medical or psychological treatment, and/or those with very strong suicidality and catatonic features.^{107,108} It is an effective adjunct to clozapine in treating refractory schizophrenia.¹⁰⁴ There is certainly no strong or conclusive evidence to suggest that ECT alone or as an adjunct to antipsychotics is superior to antipsychotics alone or to any combination of different treatment modalities for schizophrenia. In addition, ECT may cause short-term, or occasionally long-term, memory impairment and leaves many unanswered questions about its role and mechanisms in the treatment of schizophrenia.¹⁰⁸ Similarly, transcranial magnetic stimulation (a procedure that uses magnetic fields to stimulate the depolarization or hyperpolarization of the neuron cells in the cortical regions of the brain) has shown preliminary positive evidence in treating refractory negative symptoms and auditory hallucinations.^{109,110}

It is also believed that Chinese herbal medicine produces progressive positive changes in physiological and mental state and fewer adverse effects when compared with Western medicine. The adverse effects of antipsychotics-induced psycho- and physiopathological changes (eg, dysfunctions of the body organs and sleep–wake cycle) in the body can be treated with such herbal medicine, which is considered to promote the Yin–Yang balance and maintain a homeostatic environment of the internal bodily condition.¹¹¹ Electroacupuncture for schizophrenia sufferers with auditory hallucination who were partially or fully nonresponsive to risperidone monotherapy was studied with a small-sized sample. The results showed that there was no significance difference between the two treatment modalities in terms of adverse effects, whereas electroacupuncture could induce a satisfactory improvement in auditory hallucination and a few other positive symptoms.¹¹² Nevertheless, no conclusions were drawn on the potential efficacy of traditional Chinese medicine in treating schizophrenia, because of the very limited empirical evidence on this topic.

Approaches to treatment for schizophrenia from prodromal to later stages of illness

Various pharmacological treatments and psychosocial interventions for people with schizophrenia have been developed and evaluated over the last four decades. Although these innovative treatments and interventions have aroused much attention and accelerated deinstitutionalization, moderately low improvements in recovery, community-based rehabilitation, and quality of life among people with schizophrenia have been the result. The modest nature of these improvements may be because of the limited accessibility and availability of different alternatives or combined treatments and/or very advanced pathological and severe symptoms of patients when they present to and seek treatments from the mental healthcare system.⁶⁶ More important, current treatments demonstrate that fairly positive patient outcomes in schizophrenia can be explained by the fact that most treatment plans do not vary across the course of the illness, even though different psychopathological processes are closely linked with different stages of schizophrenia. The three main stages of schizophrenia can include the premorbid and prodromal stage, the first onset or episode of acute illness, and the later stages of ongoing management, rehabilitation, and recovery.

To better understand the common treatment modalities, their main purposes, and their levels of effectiveness

and reproducibility, a summary of current approaches to treatments for schizophrenia specific to the three stages of schizophrenia mentioned earlier is presented in Table 3. In the summary of the current body of knowledge about phase-specific treatment approaches (Table 3), it is essential to note that the mainstay treatments and management strategies of schizophrenia seem to have evolved at a slow pace and are highly reliant on antipsychotic agents as the basic treatment for all schizophrenia sufferers. The effectiveness and/or cost-benefit analysis of most psychosocial interventions used, as well as their superiority and therapeutic components, are somewhat inconsistent and inconclusive.

Throughout the course of schizophrenia, more than 70 types of antipsychotic agents classified into first- and second-generation groups can be useful for symptom management. Nearly all antipsychotics share similar properties to block the dopamine D-2 receptor in terms of different potencies relating to their affinity for the receptor.¹⁹ They show no major differences in clinical efficacy for the overall schizophrenia group in meta-analyses of recent placebo-controlled studies.^{40,66,113} Although antipsychotics are found to significantly reduce a wide range of psychotic symptoms, and thus relapses, their effects on psychosocial functioning, cognitive and vocational skills, and longer-term community living skills in schizophrenia are vague and inadequately studied.^{114,115} It is also essential to point out that this similar overall efficacy reported in schizophrenia is not equal to and does not signify the same desirability or adverse effects, safety, tolerance, and/or other clinical responses in each individual patient.

Nevertheless, new pharmacological treatments for schizophrenia have been merging as a result of better understanding of its etiology and pathophysiology and the specific targeting of individual symptom domains.¹¹⁴ For instance, N-methyl-D-aspartate glutamate receptor agonists and glycine site agonists have been used in combination with antipsychotics, or the activating agents of the metabotropic glutamate 2/3 receptors, and can be successful in reducing negative symptoms.¹¹⁵ Alpha 7 nicotinic receptor agonists, dopamine 1 receptor agonists, and modulators of glutamatergic aminomethylphosphonic acid (AMPA) receptors have been found to be useful in reducing cognitive impairments in schizophrenia.¹¹⁶ Therefore, different pharmacological treatment plans can be designed to target different pathophysiological processes relevant to different stages of schizophrenia.

For the premorbid phase (Table 3), most people with psychotic features experience a lengthy prodromal period of nonspecific symptoms and slowly progressive functional impairments before the full emergence of the diagnostic

Table 3 Approaches to continuity of care for people with schizophrenia in three stages of illness

| Phase of illness | Approaches to care | Level of evidence | Duration | Applicability |
|------------------------------|--|---|--|--|
| Premorbid or prodromal phase | <p>Community-based approaches to care, targeted at prevention and early interventions of the illness.</p> <ol style="list-style-type: none"> 1. Population-based or selected at-risk group illness prevention programs recognize earlier the risk factors for schizophrenia and reduce the development of behavioral and cognitive pathology with target medications and treatment approaches. 2. Low dosage of prophylactic antipsychotics and/or antidepressants can exert optimal effects on symptom reduction within 1–2 weeks. 3. In the prodromal phase, cognitive therapy as an adjunct to a low dose of antipsychotics can prevent transition to psychotic disorders and reduce medication use and the severity of subclinical symptoms. 4. Assertive outreach service with evidence-based interventions adapted to the needs of individuals with subclinical or prodromal symptoms, including low-dose antipsychotics, cognitive therapy, family counseling, and vocational training. | <p>*</p> <p>**</p> <p>*</p> <p>*</p> | <p>*</p> <p>**</p> <p>**</p> <p>*</p> | <p>*</p> <p>**</p> <p>**</p> <p>*</p> |
| Acute phase or first-episode | <p>Effective treatment and care are provided in the acute phase of the illness for active and efficient interventions to control severe symptoms and prepare for longer-term illness management.</p> <p>Antipsychotics produce significant positive effects on the short-term clinical outcomes of acute schizophrenia; for example, symptom reduction and relapse and suicide prevention.</p> <ol style="list-style-type: none"> 1. Psychotropic drugs are prescribed for efficient control of acute psychiatric symptoms: <ul style="list-style-type: none"> • Antipsychotics (both the first and second generation) are the most effective for positive symptoms and attention (but have limited effects for cognitive and negative symptoms). • Clozapine is relatively more effective than other antipsychotics in refractory schizophrenia and suicidality. • Antidepressants are effective in treating depressive and anxiety symptoms in some patients with less-prominent positive symptoms. • Anticonvulsants such as carbamazepine and valproic acid, as adjuncts to antipsychotics, can treat aggression and impulsivity. 2. Electroconvulsive therapy can be effective in treating very severe psychotic and catatonic symptoms. This therapy, together with clozapine, can also be used for treating refractory schizophrenia. 3. Transcranial magnetic stimulation demonstrates effects in treating negative symptoms and auditory hallucinations. 4. Family psychoeducation (6–9 months) consisting of education about the illness and its treatment, problem-solving skills, and crisis intervention can reduce relapse rates, family burden, and treatment adherence. <p>Wide varieties of approaches to treatment and care are aimed at enhancing the continuity and quality of ongoing illness management, psychosocial rehabilitation, and relapse prevention.</p> | <p>***</p> <p>**</p> <p>**</p> <p>*</p> <p>**</p> <p>**</p> <p>**</p> | <p>***</p> <p>*</p> <p>*</p> <p>*</p> <p>**</p> <p>**</p> <p>*</p> | <p>***</p> <p>**</p> <p>**</p> <p>*</p> <p>**</p> <p>**</p> <p>*</p> |
| Later stages of illness | <p>Wide varieties of approaches to treatment and care are aimed at enhancing the continuity and quality of ongoing illness management, psychosocial rehabilitation, and relapse prevention.</p> <ol style="list-style-type: none"> 1. Antipsychotic agents are effective in the persistent control and reduction of psychotic symptoms in various illness conditions: <ul style="list-style-type: none"> • A few second-generation antipsychotics such as olanzapine indicate persistent treatment effects in symptom reduction, as well as fewer extrapyramidal adverse effects and anticholinergic activity. • Long-acting injection of antipsychotics as a treatment regimen indicates some advantages over oral medication in community care and reducing nonadherence and relapse. • However, people with later stages of schizophrenia have been shown to be less responsive to antipsychotic agents. | <p>**</p> <p>**</p> <p>**</p> <p>**</p> | <p>*</p> <p>**</p> <p>**</p> <p>*</p> | <p>*</p> <p>**</p> <p>**</p> <p>*</p> |

2. Psychosocial interventions are used in combination with antipsychotics to help in reducing symptoms and improving treatment adherence, social and cognitive functions, and quality of life.
 - Patient and family psychoeducation programs are effective in providing illness-related information and psychosocial support, as well as effective coping strategies and problem-solving skills. ***
 - Cognitive-behavioral therapy demonstrates significant effects in reducing positive symptoms and disorganized thoughts in those with persistent and residual psychotic symptoms. **
 - Cognitive remediation is effective in treating impaired cognition (eg. attention, working memory, executive function, and social cognition) and is associated with improvements in psychosocial functioning. *
 - Social skills training can improve performance-based social and community functioning but has little effect on symptom control and relapse prevention. **
 - Supportive employment with work skills training is tailored to those who need job placement or vocational training and is effective in helping patients obtain and maintain open competitive employment. However, there is limited evidence on longer-term employment outcomes such as job retention and economic independence. *
3. Peer-led patient and family support group programs provide flexible and nonhierarchical psychosocial support to patients and/or their family members and have an effect on reducing patient relapse, improving family and social support, enhancing medication adherence, and improving coping skills. *
4. Assertive community treatment offers a multidisciplinary approach to intensive patient care, support and contacts in the community, or in a homeless situation is effective in reducing hospitalizations and improving social integration for those who are treatment-resistant and prone to high readmission rates. *
5. Multifaceted illness management programs, including social skills training, medication adherence therapy, problem-solving and communication skills training, supported employment, and even family behavioral and case management, can improve patients' recovery, treatment compliance, and social reintegration. *

Notes: "Level of evidence" denotes the three levels of evidence on the approaches to caring for schizophrenia in terms of the amount and consistency of the research evidence. ***, very much consistent and conclusive, positive findings; **, satisfactory consistency and replicability with a few nonsignificant or negative findings; and *, few or inconsistent findings. "Duration" indicates the duration of the research evidence on the approaches to care identified in the literature, including ***, evidence noted for more than 20 years; **, evidence noted for 10–20 years; and *, evidence noted for not more than 10 years. "Applicability" denotes the levels of feasibility and applicability for the intervention to be applied to mental health care practice. ***, very flexible and applicable to field practice; **, satisfactory applicability to practice; and *, not easily or commonly applied to practice.

psychotic symptoms. The development of higher levels of dysfunction and disability during the prodromal period creates major inhibitory factors influencing recovery, thus providing very strong rationale for premorbid assessment and interventions. To promote accurate and valid assessment of high-risk individuals or groups, specific scales are being developed, such as the Bonn Scale for the Assessment of Basic Symptoms and the Comprehensive Assessment of At-Risk Mental State, as well as the Scale of Prodromal Symptoms.^{117,118} Without any of the strategies currently used, specific population-based prevention and assessment efforts should be made, targeting high-risk groups with mild early psychotic symptoms. Most important, identification of risk factors and symptomatic indicators is critical for accurately selecting at-risk persons and matching them to the most appropriate preventive treatment. As suggested by Birchwood, Todd, and Jackson's hypothesis of critical periods of onset and early intervention of psychosis,¹¹⁹ therapeutic interventions such as cognitive-behavioral therapy and assertive outreach services are most effective if they are offered at the earliest possible moment during the most vulnerable periods of illness onset.^{120,121} Research evidence suggesting that these cognitive and behavioral interventions can help people in the prodromal stage of schizophrenia is emerging, but is as yet inconclusive.¹²²

In acute-episode or first-onset schizophrenia, the use of different antipsychotic agents is found to be crucial and effective in symptom reduction, especially for positive symptoms and attention. Second-generation (atypical) antipsychotics showing less risk for extrapyramidal adverse effects and tardive dyskinesia can be considered as the first-line treatment for acute psychosis. The second-generation antipsychotic clozapine is more effective in treating refractory schizophrenia and suicidality.¹²³ Other psychotropic drugs such as antidepressants and anticonvulsants can be used as an adjunct to antipsychotics to control specific psychiatric symptoms such as depression, anxiety, aggression, and impulsivity. Physical treatments, especially ECT, are found effective in controlling a few treatment-resistant symptoms such as catatonic state, strongly depressive and suicidal ideation, and some negative symptoms.¹⁰⁷ Repetitive transcranial magnetic stimulation studies have demonstrated some promise in the treatment of schizophrenia, particularly for those with treatment-resistant auditory hallucinations and severe mood problems.¹²⁴ Family psychoeducation (6–9 months) can reduce relapse rates, family burden, and treatment adherence.⁷

For ongoing management and later-stage schizophrenia, a variety of psychosocial interventions are found

useful in reducing patients' relapses and rehospitalizations, enhancing their functioning and medication adherence, and facilitating their rehabilitation and recovery. As indicated in Table 3, the more conclusive and consistent therapeutic interventions with moderate to large effect sizes in symptom control, relapse prevention, and levels of psychosocial functioning included patient and/or family psychoeducation programs,¹²⁵ cognitive-behavioral therapy,¹²⁶ and an integrated program with antipsychotics and different approaches to psychosocial care.^{127,128} Although small effect sizes to relapse prevention were found, a few commonly used approaches to psychosocial intervention for schizophrenia show increasingly consistent effects on specific patient outcomes, such as patients' social and community functioning being improved by social and vocational skills and short-term competitive employment being enhanced by supported employment with work skills training.^{65,129}

Similar to Amsterdam's first-aid service in the 1970s, crisis intervention models for people with schizophrenia and other serious mental illnesses have at times emerged, aimed at treating psychiatric crises in the community and reducing relapses and/or the number of hospitalizations.¹²⁹ Multidisciplinary, around-the-clock crisis intervention services advocate prompt detection of symptom exacerbation and immediate intensive treatments as needed (eg, psychotropic agents, individual and family counseling, psychological therapies, and practical assistance in activities of daily living) in both community and home settings. Programs in Australia and the United States, such as mobile crisis teams, crisis units in hospitals, crisis day treatment centers, and crisis residential programs, have been integrated into routine mental healthcare services.^{64,130} Nevertheless, recent clinical trials suggested that about half of the crisis intervention groups indicated nonsignificant effects on improvements in mental state or reducing hospitalization during the treatment period, as well as lacking evidence of their long-term benefits in terms of patient outcomes.¹³¹ In addition, recent research has also evaluated the effectiveness of multifaceted illness management programs consisting of a wide variety of biological/physical, psychological, and social interventions and suggested these programs might efficiently and effectively improve patient recovery and social reintegration.^{65,127,131}

Conclusion

Antipsychotics (first- and/or second-generation antipsychotics) are shown to be effective in reducing overall psychotic symptoms and relapse in patients with schizophrenia. It is therefore recommended in most of the literature as first-line

treatment for people with schizophrenia, at least in the short-term or at the acute stage of illness. However, the use of antipsychotics alone as the main treatment modality may be limited not only by their inability to tackle the frequently occurring negative symptoms and cognitive impairments but also by producing a wide variety of adverse effects in the internal body or organ functioning. The FGAs and second-generation antipsychotics are two distinct classes of antipsychotics with quite different potency and adverse effects, but these two classes do not have any definitive categorization between them in terms of efficacy, safety, and tolerability or in their clinical outcomes. However, because of the varied pharmacokinetics and patients' treatment responsiveness across different agents, the medication regimen should be determined on an individual basis to ensure optimal effect in their long-term use. Other medical and psychological treatments should be considered as an adjunct to antipsychotic agents. However, many of these alternative treatments are not strongly evidenced or conclusive in producing specific therapeutic effects in treating schizophrenia. More controlled trials are recommended to enhance understanding about their efficacy as a monotherapy or in combined use with antipsychotics, other medication, and/or psychosocial interventions.

Many patients with schizophrenia often have unresolved life events and psychological distress, as well as illness-related or drug-induced problems, which significantly affect their normalcy of daily life. In the last few decades, various models of psychosocial intervention have been developed and implemented as an adjunct to the pharmacological or other medical treatments at different stages of schizophrenia. The main purpose of these approaches to treatment is to provide these patients (and their family members) with adequate knowledge of and skills in this illness and its treatment and care, emotional support, problem-solving and coping skills, and/or enhancing cognitive and functional recovery. The current models commonly used for schizophrenia care include cognitive-behavioral therapy, psychoeducation, family intervention, social skills training, and cognitive remediation therapy. These psychosocial interventions and their comparative efficacy in treating people with schizophrenia will be discussed in another article. Recent systematic reviews on psychosocial interventions for schizophrenia have indicated significant positive medium-term (up to 18 months) effects of a few approaches (eg, psychoeducation and cognitive-behavioral therapy) integrated or embedded into routine care (and medication use) in people with acute or chronic schizophrenia. To overcome the shortcomings

of antipsychotics in the treatment of schizophrenia, clinical guidelines and standards of practice have recommended that a combination of treatment methods or modalities be adopted to meet the complex psychiatric and other health needs of people with schizophrenia. We are assured of and also highly recommend more research in the clinical efficacy of different existing and new models of psychosocial interventions, together with antipsychotics or other psychotropic drugs, to ascertain a treatment approach for people with schizophrenia with the highest possible levels of efficacy, safety, and acceptability.

Disclosure

The authors report no conflicts of interest in this work.

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