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Pharmacological Management of First-Episode Schizophrenia and Related Nonaffective Psychoses

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Abstract

Schizophrenia is a severe mental illness characterised by abnormalities of thought and perception that affects 1–2% of the population. Patients who experience a first episode of schizophrenia should be treated early and optimally with antipsychotic agents to lessen the morbidity of the initial episode and possibly improve the course of the illness. Positive psychotic symptoms remit in the majority of patients who are treated with adequate trials of antipsychotic medications, but most relapse within 1 year. Non-adherence is strongly related to the likelihood of recurrence of symptoms. Innovative programmes that integrate early

intervention, psychosocial treatments and atypical antipsychotic pharmacotherapy show promise in improving outcomes.

The available research supports the use of antipsychotic medications early in the first-episode of schizophrenia and for at least 1 year after remission of positive symptoms. Antidepressants, benzodiazepines and mood stabilisers have roles in the acute and maintenance phases of treatment for some patients. Atypical antipsychotics represent a great advance in the treatment of first-episode schizophrenia with strong evidence for greater tolerability with equal or better therapeutic efficacy. Future research will further define their roles in treatment and hopefully identify targets for prevention of first-episode schizophrenia.

Schizophrenia is a severe mental illness characterised by abnormalities of thought and perception that affects 1–2% of the population worldwide over the course of a lifetime.[1-6] A first episode of psychosis is a frightening and sometimes dangerous experience for patients and families. The risk for short-term morbidity and mortality is high during this period. While acute treatment often focuses on safety and rapid stabilisation, evidence is mounting that it is also a critical period for intervention to improve the long-term course of the illness and, thereby, lessen the cumulative morbidity.

Psychosis can be a symptom of numerous psychiatric, neurological and medical illnesses, as well as states of substance intoxication or withdrawal. Demographic characteristics and medical history provide some guidance regarding the likelihood of secondary psychotic states, but generally psychosis should be viewed as a medical emergency requiring prompt evaluation and treatment of underlying causes. Current standards of care for a work-up of a first psychotic episode include a physical exam involving a thorough neurological evaluation, a full a panel of laboratory studies, toxicology screening, and brain imaging if the clinical picture provides any suggestion of a brain lesion or atypical presentation.

For many patients, unfortunately, a direct and reversible cause of psychosis cannot be identified and a schizophrenia spectrum disorder is diagnosed. Within this group of diagnoses, which includes major depression with psychotic features, bipolar disorder with psychotic features, brief psychotic disorder, schizophreniform disorder, schizoaffective disorder and schizophrenia, the profile of symptoms, their severity, treatment and the overall prognosis can vary considerably.[7] This review focuses on management strategies and relevant research data on first-episode nonaffective psychosis.

Articles for this review were identified through a Medline search limited to English language publications using various combinations of the following key phrases: first episode, psychosis, schizophrenia and antipsychotic. Articles to be reviewed were selected according to their relevance to the current clinical management of first-episode nonaffective psychosis, with preference given to randomised, controlled trials. Additional articles were found by searching the references sections of the identified studies.

1. Acute Treatment of First-Episode Schizophrenia

The small number of clinical trials on first-episode schizophrenia leaves a considerable gap between evidence-based and clinical practice management of first-episode schizophrenia. There are currently eight published studies that utilise controlled or standardised acute treatment of patients with first-

episode schizophrenia (summarised in table I).[8-14] The data from these studies, as well as that from some uncontrolled studies and secondary analyses, provide the basis for several principles underlying the guidance for treating patients with a first episode of schizophrenia and also for future research to improve on the standard of care for this critical clinical condition. With such limited data regarding the management of first-episode schizophrenia, practice is guided by a hybrid of clinical trials evidence, real life studies and clinical experience.

1.1 Treatment to Remission of Positive Symptoms

The available data indicate that in first-episode patients, positive symptoms, including hallucinations and delusions, most often will remit with antipsychotic treatment. Estimates of the proportion of first-episode patients responding to acute antipsychotic treatment vary from 29–96%.[11,16] The variance in response rates in these studies is related to a number of factors, but most importantly the duration of the antipsychotic trial, the definition of response and the drug used. For example, in an open-label study, approximately half of the patients with first-episode schizophrenia met remission criteria after 12 weeks of treatment with typical antipsychotics, while most (87%) patients met remission criteria after 1 year of treatment.[10,15] This study used a relatively stringent definition of remission and required remission to be sustained for 8 weeks, suggesting that positive symptom remission is exceedingly common in first-episode patients.[10,15] The median time to response of 12 weeks in this study underscores the importance of trials of adequate duration and may also explain the lower response rates found in antipsychotic trials of relatively short durations.[8,9,14]

An earlier study provides additional confirmation for this rationale, reporting that 96% of first-episode patients treated with trifluoperazine had responded (as measured by their ability to be discharged from the hospital) to treatment after 12 months.[11] Thus, clinicians should expect a remission of positive symptoms in first-episode patients. A series of adequate trials of available agents should be employed with this goal in mind.

1.2 Refractoriness of Negative and Cognitive Symptoms

While positive symptoms tend to improve at fairly high rates, negative and cognitive symptoms of schizophrenia have generally shown less improvement in patients with first-episode schizophrenia. Studies assessing the use of antipsychotic medications in treating negative and cognitive symptoms have found either no improvement[14] or suboptimal improvement.[9,12] This indicates that negative and cognitive symptoms may have a different time course for response than positive symptoms and/or that the relative refractoriness of negative and cognitive symptoms may contribute to the less than optimal functional recovery that is often observed in patients.

Multiple studies find little change in the severity of cognitive symptoms at least with typical antipsychotic treatment.[19-24] Improving treatments for negative and cognitive symptoms in the first episode of schizophrenia is an area of major importance in future research and drug developments efforts, especially since these symptoms are likely to affect the functional abilities of these patients.

1.3 Dosage of Antipsychotic Medication

First-episode patients may be more sensitive to adverse effects of antipsychotic agents (particularly extrapyramidal symptoms), than patients in other stages of the illness. In a sample of 70 treatment-naïve patients who received fluphenazine 20–40 mg/day for the first 10 weeks of treatment, 34% developed parkinsonism, 18% developed akathisia, and 36% developed dystonia.[25] Lower doses of

Table I. Response rates during initial treatment with antipsychotic medication in patients with acute first-episode schizophrenia

Studies	Population	Inclusion criteria	Design/Protocol	Response criteria	Response rates
May et al.[11]	228 patients selected from consecutive admissions to a state psychiatric hospital between 1959 and 1962	Patients who were hospitalised with a diagnosis of schizophrenia and no significant prior treatment. Patients had not been hospitalised for schizophrenia prior to this study. Those who were judged unlikely to be discharged and those who remitted fairly quickly (within 18d) were excluded	Randomisation to either (i) individual psychotherapy only, (ii) trifluoperazine only, (iii) psychotherapy in combination with trifluoperazine, (iv) ECT only, or (v) milieu therapy only	Release from the hospital after a 'fair trial' (6–12mo) of the assigned treatment	Individual psychotherapy (65%), trifluoperazine (96%), psychotherapy in combination with trifluoperazine (95%), ECT (79%), and milieu therapy (58%)
The Scottish Schizophrenia Research Group[14]	46 patients with first-episode schizophrenia admitted to the hospital	Patients with a diagnosis of first-episode criteria on the clinician's International Classification of Diseases, 9th Revision	5wk, double-blind, randomised trial of flupenthixol versus pimozide. Adjunctive medications allowed	Responders: patients who were able to enter maintenance treatment on their assigned drug therapy. Nonresponders: those who received further treatment, either ECT or another antipsychotic. Noncompleters: those who did not proceed to maintenance therapy but were not clearly non-responders	Overall, 63% of patients were responders. Positive symptoms improved significantly ($p = < 0.01$) for both flupenthixol and pimozide groups during the study period, but negative symptoms did not change
Lieberman et al.;[10] Robinson et al.[15]	118 RDC-diagnosed patients with schizophrenia (n = 83) and schizoaffective disorder (n = 35)	Patients aged 16–40y with no prior psychotic episodes, and no history of neurological or general medical illness that could influence diagnosis or the biological variables being studied	Open, prospective study using a standardised antipsychotic (including fluphenazine, haloperidol, molindone, and clozapine) protocol of sequential trials until response criteria were met	Responders were operationally defined as those with CGI ratings of 'much' or 'very much' improved and ratings of mild or less on specified SADS-C+PDI items with responses sustained for at least 8wks	87% of patients remitted by 1y with a median time to remission of 9wks
Szymanski et al.[13]	10 patients in the Lieberman et al.[10]	Patients who had failed treatment with a standardised protocol of three typical antipsychotics in the Lieberman et al.[10]	After a 2wk wash out period, patients were treated for 12wks with clozapine	Responders were patients with a ≥20% reduction in BPRS scores and a score of ≤3 on the CGI severity of illness scale	30% of all patients were responders
Kopala et al.[9]	22 antipsychotic-naive patients consecutively admitted for the first time	Patients (mean age 25y) with a DSM-IV diagnosis of a first episode of schizophrenia	Open trial of risperidone monotherapy for a mean duration of 7.1 (SD = 3.2, range 1.8–14.1) wks. Benzatropine for EPS and lorazepam or clonazepam for insomnia were the only adjunctives allowed	Responders were patients with a ≥20% reduction in the total PANSS scores	59% of patients were responders; negative symptoms improved to a lesser extent than positive symptoms

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Table I. Contd

Studies	Population	Inclusion criteria	Design/Protocol	Response criteria	Response rates
Sanger et al.[12]	83 first-episode patients out of 1996 patients who were enrolled in a multicenter trial of olanzapine versus haloperidol	Patients with a first episode of psychosis meeting the DSM-II-R criteria for schizophrenia, schizophreniform or schizoaffective disorder, and aged ≤45y at their episode onset; duration of episode of <5y; minimum BPRS score of 18 or intolerant to current antipsychotic therapy	6wk, double-blind, randomised trial of olanzapine (n = 59) or haloperidol (n = 24) at mean modal doses of 11.6 (SD = 5.9) and 10.8 (SD = 4.8) mg/d, respectively	Responders were patients with a ≥40% reduction in total BPRS scores from baseline (defined *a priori*); responders with a ≥20% reductions in total BPRS scores from baseline were also calculated	Responders with a ≥40% BPRS reduction in total BPRS: 67.2% of olanzapine recipients and 29.2% of haloperidol recipients (Fisher's exact test p = 0.003). Responders with a ≥20% BPRS reduction: 82.8% olanzapine recipients and 58.3% of haloperidol recipients (Fisher's exact test p = 0.03)
Emsley et al.[8]	183 patients recruited in multiple international sites	Patients aged 15–40y with a DSM-III-R diagnosis of provisional schizophreniform disorder or schizophrenia, no prior treatment beyond 3d of emergency antipsychotics and no clinically relevant medical abnormalities	6wk, double-blind study of risperidone versus haloperidol 2–16 mg/d. Antiparkinsonian drugs or benzodiazepines administered only if essential	Responders were patients with a ≥50% reduction in total PANSS scores (defined *a priori*)	63% of risperidone recipients and 56% of haloperidol recipients were responders
Yap et al.[16]	24 patients recruited from Woodbridge Hospital and Geylang Psychiatric Outpatient Clinic	Previously untreated male and female patients aged 18–65y with a DSM-IV diagnosis of schizophreniform disorder or schizophrenia for no longer than 12mo	Open-label 8wk study of risperidone	Responders were patients with a ≥20% reduction in total PANSS scores; responders with a ≥50% reduction in total PANSS scores was also calculated	87.5% of patients had a ≥20% reduction in the total PANSS scores and 54.2% had a ≥50% reduction in total PANSS scores
Lieberman et al.[17]	160 patients with first-episode schizophrenia recruited from Beijing Hui Long Guan Hospital	Patients were aged 16–40y with a diagnosis of schizophrenia or schizophreniform disorder, duration of symptoms not longer than 60mo, less than 14d of prior treatment with antipsychotic medication and at least one moderate severity active psychotic on symptom BPRS	Randomised, double-blind, 52wk trial, comparing CPZ and CLZ. The median doses (mg/d) at 12wk and at the end of 1y follow-up were 400 and 300, respectively, for CLZ, and 600 and 400, respectively, for CPZ	Responders had ≥50% reduction in total BPRS score from baseline with no score greater than mild on the 5 BPRS psychosis items and a CGI-severity item of mild or less	80% achieved remission within 1y (79% CPZ, 81% CLZ). The Kaplan-Meier estimated median time to first remission was 8wks for CLZ vs 12wks for CPZ (x^2 = 5.56, p = 0.02). CLZ was superior on many rating scale measures at 12wks

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Table I. Contd

Studies	Population	Inclusion criteria	Design/Protocol	Response criteria	Response rates
Lieberman et al.[18]	263 patients with first-episode schizophrenia	Patients were aged 16–40y, had an onset of psychotic symptoms before age 35y, met the DSM-IV diagnostic criteria for schizophrenia, schizophreniform disorder or schizoaffective disorder, experienced psychotic symptoms for at least 1mo but not more than 60mo, scored 4 on at least two PANSS psychosis items or scored 5 on one psychosis item, had a CGI severity score 4 and required treatment with antipsychotic drugs on a clinical basis	12wk, randomised, controlled trial of olanzapine versus haloperidol acute-phase mean modal doses were 9.1 mg/d of olanzapine and 4.4 mg/d of haloperidol	Patients who had no rating of >3 (mild) on items P1, P2, P3, P5 and P6 of the PANSS, had a ≥30% reduction from baseline in the PANSS total score and had a CGI severity score 4 (moderately ill)	By wk 12, 55% of those assigned to olanzapine treatment compared with 46% for those receiving haloperidol (χ^2 = 1.76, df = 1, p = 0.19) achieved response criteria. The median time to response was 7.9wks for olanzapine-treated patients and 8.4wks for haloperidol-treated patients (difference not significant)

BPRS = Brief Psychiatric Rating Scale; **CGI** = Clinical Global Impressions scale; **CLZ** = clozapine; **CPZ** = chlorpromazine; **d** = day; **DSM-II-R** = Diagnostic and Statistical Manual of Mental Disorders 2nd edition Revised; **DSM-III-R** = DSM 3rd edition Revised; **DSM-IV** = DSM 4th edition; **ECT** = electroconvulsive therapy; **EPS** = extrapyramidal symptoms; **mo** = month; **n** = number of patients; **PANSS** = Positive and Negative Syndrome Scale; **RDC** = Research Diagnostic Criteria; **SADS-C+PD** = Schedule for Affective Disorders and Schizophrenia-Change version with psychotic and disorganisation items; **wk(s)** = week(s); **y** = year.

antipsychotics may be adequate to achieve positive symptom remission but less likely to cause adverse effects.[26,27] For example, in a posthoc analysis, low-dose risperidone (≤6 mg/day) was more effective and better tolerated than high-dose risperidone (>6 mg/day).[8] Another recent study in 49 acutely psychotic, neuroleptic-naïve patients with schizophrenia, schizophreniform disorder, or schizoaffective disorder, showed that two doses of risperidone (2 or 4 mg/day) were comparable in efficacy with an advantage for the lower dose in fine motor functioning.[28]

The greater sensitivity to adverse effects of first-episode patients compared with patients with chronic disease was dramatically demonstrated by McEvoy et al.[29] These researchers compared the two groups of patients in terms of their antipsychotic thresholds for extrapyramidal symptoms. In the context of a gradual dose titration paradigm, first-episode patients exhibited lower thresholds to develop signs of extrapyramidal symptoms than previously-treated patients with chronic illness.

Since the first episode is a time when patients form their attitudes about treatment, efforts to minimise unpleasant adverse effects may influence patient's willingness to take medications for a longer period. In a study of first-episode patients, the only variable that predicted whether patients would attend a follow-up assessment was the antipsychotic dose, with those on higher doses less likely to comply.[30] Consistent with this studies, the Schizophrenia Patient Outcomes Research Team[31] recommended that patients in a first psychotic episode should be treated with relatively lower doses (chlorpromazine equivalent 300–500 mg/day) of antipsychotics than for patients with schizophrenia in general (chlorpromazine equivalent 300–1000 mg/day). Clinical experience and available research findings suggest that lower doses of antipsychotics are as effective as higher doses in patients experiencing a

first episode of schizophrenia with superior tolerability.[8,26,27]

1.4 Choice of Antipsychotic Medication

In recent reviews and editorials,[32-35] several investigators have argued that atypical antipsychotics should be preferentially used as first-line treatment in patients with first-episode schizophrenia. Four[8,9,12,13] of the seven published controlled trials of patients with first-episode schizophrenia included an atypical antipsychotic and three provided a comparison with typical antipsychotic agents. These studies found that the atypical antipsychotics had equal[8] or better efficacy[12] but considerably fewer adverse effects than haloperidol in first-episode patients. Three major consultant panels[36-38] have recently endorsed the use of atypical antipsychotics as first-line treatment in first-episode schizophrenia.

While the available data suggest that atypical antipsychotics should be first-line treatment in first-episode schizophrenia, further studies are needed to more clearly define their role. Results of recent studies assessing the use of clozapine,[17] risperidone[8] or olanzapine[18] in first-episode schizophrenia support the conclusion that atypical antipsychotics offer equal or enhanced efficacy, with improved tolerability, compared with typical antipsychotics.

1.5 Adjunctive Treatments and Comorbid Syndromes

Adjunctive treatments have two different roles in the management of first-episode schizophrenia: (i) targeting refractory psychotic symptoms; and (ii) treating comorbid syndromes. Pharmacological management of treatment refractory schizophrenia has been reviewed elsewhere.[39-41] Available data that specifically addresses the issue of treatment resistance in first episodes of schizophrenia are limited to a small study,[13] in which three out of ten first-episode patients (who had failed to respond to a previous standardised treatment algorithm including at least two trials of typical antipsychotics) responded to clozapine. A clinical approach[42] to treatment refractory first-episode schizophrenia, as described in a recent manual on first-episode schizophrenia, should include the strategies that promote medication adherence, attention to substance abuse, sequential trials of antipsychotic agents or dose adjustment if clinical improvement is not seen by 6–12 weeks of treatment, and consideration of clozapine even early in the course of treatment.

While not yet systematically studied in first-episode patients, data from studies in patients with chronic psychotic disorders suggest that cognitive therapy may also benefit residual symptoms. In a meta-analysis of studies assessing cognitive therapy, performed mainly in patients with chronic psychotic disorders, benefits included reduced duration of hospitalisation, symptomatic improvement and improved insight, although the magnitude of such improvements was relatively small.[43] Even given the lack of specific trials in first-episode patients, it is likely that cognitive behavioural therapy may have a role in the treatment of a first episode of schizophrenia, especially helping patients to comply with treatment and transition to outpatient care. More studies are needed to determine the role of individual psychotherapeutic treatment in first-episode schizophrenia.

Adjunctive pharmacological treatments that have been studied in the treatment of schizophrenia include benzodiazepines, anticonvulsants and antidepressants. Although benzodiazepines are often used as adjuncts to antipsychotic agents in acute schizophrenia, there have been no controlled studies of benzodiazepines in patients with first-episode schizophrenia. Overall, the literature in mixed populations of patients with schizophrenia suggest that benzodiazepines have a role in treating agitation, anxiety and aggression in patients with acute psychosis,[44-47] and in preventing an impending psychotic relapse.[48]

Mood stabilisers, including anticonvulsants and lithium, are widely used in patients with schizophrenia,[49] and there is some evidence that they may also have a role in reducing aggression and agitation.[50-54] Given the lack of study in first-episode patients, mood stabilisers should not be used to treat first psychotic episodes, but should be reserved for patients who develop recurrent psychotic episodes despite antipsychotic maintenance or who have residual or recurrent mood symptoms.

Depressive syndromes are common in first-episode patients. Patients who ultimately manifest symptoms of schizophrenia often report a previous depressive episode[55] and/or suicide attempt in their prodromal period.[56] On presentation with an acute psychotic episode, first-episode patients often have more mood symptoms than patients with chronic psychotic disorders during a relapse.[57] Depressive symptoms will often resolve as psychotic symptoms remit[58] and some have even observed that antidepressants can worsen acute psychosis.[59,60] Clinicians often prescribe antidepressants in addition to antipsychotics during acute psychosis in an attempt to treat negative symptoms but there is no evidence supporting this strategy.[61] For these reasons, antidepressants should be used cautiously in acute first-episode schizophrenia and their use possibly even be delayed until positive psychotic symptoms have been addressed. Antidepressants have a greater role in the maintenance phase of treatment where the risks for postpsychotic depressive episodes[62-64] and suicide[62] are high. In addition, residual negative symptoms that persist after the stabilisation of the acute episode may improve with antidepressant treatment.[65-68]

Suicidal behaviour is common among patients presenting with a first episode of schizophrenia.[69] While depression in the presenting psychotic episode or in the postpsychotic period is an important risk factor for suicide,[70] first-episode patients with schizophrenia may attempt suicide in the absence of prominent depressive symptoms as a result of hallucinations, paranoia, disorganisation or other symptoms considered more primary to psychosis. The control of psychotic symptoms through optimal antipsychotic treatment is critical to the prevention of suicide in first-episode patients. Mounting literature supports the use of clozapine[71-74] in patients with high suicidal behaviours. Although its use in first-episode schizophrenia has been studied recently,[17] clozapine is not considered at this time a first-line drug for first-episode schizophrenia. It should be considered early in the course of treatment, however, in a patient who does not respond to one of the other agents and who has demonstrated significant suicidal behaviour.

Another important comorbid syndrome in the treatment of first-episode schizophrenia is substance abuse with possible roles in lowering initial vulnerability to psychosis,[75,76] increasing likelihood of relapse,[77,78] and affecting specific symptom domains.[79,80] Estimates of the lifetime prevalence of substance abuse disorders in US patients with schizophrenia vary from 27.5% in the Epidemiological Catchment Area Study[81] to 44.8% in the National Comorbidity Survey.[82] Thorough evaluations of substance abuse habits in patients presenting with first episodes of schizophrenia is critical to providing appropriate clinical attention to this issue throughout treatment.

2. Continuation Treatment of Remission of First-Episode Schizophrenia

2.1 Long-Term Outcomes

While patients typically recover from a first episode of schizophrenia, the long-term course for most patients is still characterised by chronic illness, disability and relapse. Studies report that a minority of patients, about 15–20%, will maintain good symptomatic and functional recovery from a first episode. For example, in a study of 349 patients followed for

up to 15 years after their first onset of schizophrenia, 17% had no disability at follow-up, while 24% still suffered from severe disability and the remaining 69% had varying degrees of disability.[83,84] The long-term prognosis of patients in the pre-antipsychotic era is similar, with about 20% of patients having good symptomatic and functional recovery.[85] However, in a recent study of 1633 patients with psychotic disorders from diverse cultures more optimistic rates of favourable outcome were found, with nearly half of the patients with schizophrenia considered to be recovered.[86] The study also found that outcomes in schizophrenia were most closely correlated with the amount of time spent with active psychosis in the first 2 years after onset.

These studies identified three groups of patients: (i) those who will recover and have a good disease course regardless of treatment; (ii) those likely to have a poor disease course even with the administration of current treatments; and (iii) those who will have a moderate-to-severe disease course with varying amounts of disability. Improving the outcome of the initially treatment-resistant group will probably require significant advances in the types and delivery of treatment available. Improving the outcome of the third group, which represents the majority of patients with schizophrenia, may be possible through optimisation in the delivery of currently available treatments.

2.2 Benefits of Pharmacological Maintenance Treatment

After remission is achieved in the majority of patients with a first episode of schizophrenia, patients, families and clinicians are faced with the dilemma of how to proceed with future treatment. Ideally, this decision would be informed by data from prospective, controlled studies answering the following questions: (i) how likely is relapse with and without antipsychotic medication?; (ii) is it possible to predict who will relapse after remission of a first episode?; and (iii) will antipsychotic therapy improve the course and long-term outcome of the illness or merely suppress symptoms in the short-to-medium term? The available research specific to first-episode patients and relevant to these first two questions is sparse, and research is only beginning to be developed with regard to the third question. Table II summarises the six controlled studies of maintenance antipsychotic treatment of patients with remitted first-episode schizophrenia. Of the six studies, four[87-90] are controlled trials comparing maintenance antipsychotic treatment to placebo, one[91] is a trial of open drug discontinuation, and one[92] provides data on relapse rates of remitted first-episode patients most of whom did not continue to take antipsychotic medication. Below are principles that were derived from the evaluation of these studies and selected other studies as they relate to these clinical questions.

2.3 Risk of Relapse

In a meta-analysis of 66 studies in patients with varying stages of schizophrenia, Gilbert et al.[93] found a relapse rate of 53% in patients withdrawn from antipsychotic therapy compared with 16% for those who were maintained on antipsychotic agents over a mean follow-up period of 9.7 months. The studies specific to remitted first-episode patients in table II report relapse rates varying from 0 to 96%. This wide variation in reported relapse rates can be partially explained by differences in the criteria used to define relapse, the populations studied and the lengths of follow-up. For example, the studies by Kane et al.[88], Crow et al.[87] and McCreadie et al.[89] employed relapse criteria that were not operationally defined and required marked impairment usually resulting in hospitalisation. The more sensitive and operationally defined criteria (re-occurrence of delusional ideation or hallucinations) used in the study by Gitlin et al.[91] yielded much higher relapse rates (78% at 1 year and 96% at 2 years for patients on

Table II. Relapse rates during maintenance treatment with antipsychotic medication in patients with first-episode schizophrenia

Study	Population	Inclusion criteria	Design/Protocol	Relapse criteria	Relapse rates
Kane et al.[88]	28 patients referred for aftercare with a diagnosis of a single episode of schizophrenia. 19 of the 28 patients met RDC criteria for schizophrenia	Patients had at least 4wks of remission, 1y or less since hospitalisation, no treatment prior to 3mo before hospitalisation, no evidence of drug abuse, alcoholism, or important medical illness	Double-blind, 1y duration; random assignment to fluphenazine (5–20 mg/d), fluphenazine (12.5–50 mg/2wks) or placebo. Only patients thought to have possible compliance problems were randomised to fluphenazine; procyclidine was given to all patients, with substitution of placebo in 2nd mo for the placebo patients	Substantial clinical deterioration with a potential for marked social impairment; patients were considered dropouts only if they showed no clinical deterioration at the time they withdrew from the study	Overall, relapses were noted in 0% (0 out of 11) of fluphenazine recipients and 41% (7 out of 17) of placebo recipients. Of those with RDC schizophrenia, relapses were noted in 0% (0 out of 6) of fluphenazine recipients and 46% (6 out of 13) of placebo recipients. Follow-up with 26 patients (mean interval of 3.5y) showed that 69% had a 2nd relapse and 54% had 3rd relapse
Crow et al.[87]	120 patients diagnosed with a first episode of schizophrenia recruited from both psychiatric and district general practices in Harrow, England	Patients aged 15–70y had a clinical diagnosis of first-episode schizophrenia which was 'not unequivocally affective' with an absence of organic disease of probable aetiological significance. Patients had also been admitted to an inpatient psychiatric unit for at least 1wk	Patients initially received one of the following: flupenthixol (40 mg/mo IM), chlorpromazine (200 mg/d PO), haloperidol (3 mg/d PO), pimozide (4 mg/d), or trifluoperazine (5 mg/d) chosen by clinicians, then were randomised to either drug or placebo 1mo after the remission of their initial episode; adjunctive medications allowed	Psychiatric readmission for any reason; readmission deemed necessary by treating clinician but not possible; or active antipsychotic medication considered to be essential because of features of imminent relapse; relapse determinations made by treating clinicians	Actuarial relapse rates at 6, 12, 18 and 24mo were 43%, 63%, 67% and 70%, respectively, with placebo and 21%, 38%, 46% and 58%, respectively, with active medication
The Scottish Schizophrenia Research Group[89]	15 patients who had suffered a first episode of schizophrenia	Patients had to respond to acute treatment and then be relapse free for an additional year of treatment while taking either once-weekly pimozide or intramuscular flupenthixol	Double-blind trial of active medication (either once-weekly pimozide or IM flupenthixol) or placebo for 1y	Deterioration in schizophrenia symptoms or behaviour sufficient to warrant the patient's withdrawal from the study	0% (0 of 8) of patients who received active drug, but 57% (4 of 7) who received placebo were readmitted in year 2 of the study treatment

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Table II. Contd

Study	Population	Inclusion criteria	Design/Protocol	Relapse criteria	Relapse rates
Neuchterlein et al.[90]	106 patients from four public hospitals and an outpatient clinic of an academic medical centre; 66% had never taken antipsychotic medication and the remainder had a mean duration of treatment of 2.7mo (SD = 3.1)	Patients aged 18–45y with recent onset psychotic symptoms lasting at least 2wks and not more than 2y, and an RDC diagnosis of schizophrenia or schizoaffective disorder (mainly schizophrenia). Patients with a known neurological disorder, recent significant substance abuse, or who were of African-American decent[a] were excluded	Phase I: stabilised patients were treated with 12.5mg of fluphenazine every 2wks for 12mo. Phase II: those who remitted in phase I were recruited into phase II during which they were treated for 12wks with either placebo or fluphenazine, followed by crossover to the opposite treatment	Operationally defined as a 2 point worsening on any 3 BPRS psychotic items, excluding changes where the scores remained at nonpsychotic levels. A score of 6 or 7 was obtained on any 3 items; or clinical deterioration warranting a change in treatment as judged by treating psychiatrist	Phase I: 11 patients needed to have their dose lowered due to adverse effects and 6 were prescribed antidepressants. Phase II: 6% (3 of 53 patients) relapsed while on active medication and 13% (7 out of 53) relapsed on placebo
Robinson et al.[92]	104 patients who responded to treatment of their index episode of schizophrenia and were at risk for relapse	Patients had an RDC diagnosis of schizophrenia or schizoaffective disorder, total lifetime exposure to antipsychotic medications of ≤12wks, a rating of ≥4 (moderate) on at least 1 psychotic symptom item on the SADS-C+PD, no medical contraindications to treatment with antipsychotic medications, and no neurologic or endocrine disorder or neuromedical illness that could affect diagnosis or the biological variables in the study	Patients were treated openly according to a standard algorithm, progressing from one phase of the algorithm to the next until they met response criteria. The sequence was initial treatment with fluphenazine, then haloperidol, then lithium augmentation, then molindone or loxapine, then clozapine	At least 'moderately ill' on the CGI Severity of Illness Scale, 'much worse' or 'very much worse' on the CGI Improvement Scale, and at least 'moderate' on 1 or more of the SADS-C+PD psychosis items; these criteria had to be sustained for a minimum of 1wk	5-y overall relapse rate was 81.9%; the second relapse rate was 78.0%. By 4y after recovery from a second relapse, the cumulative third relapse rate was 86.2%. Discontinuing antipsychotic drug therapy increased the risk of relapse by almost 5 times
Gitlin et al.[91]	53 patients with RDC schizophrenia or schizoaffective disorder who had been stabilised for 1y on fluphenazine	Patients who completed phase II of the Neuchterlein et al.[90] study and did not relapse	Open label discontinuation of drugs	2-point worsening on any 3 BPRS psychotic items, excluding changes where the scores remained at nonpsychotic levels, a score of 6 or 7 was obtained on any 3 items, or the treating psychiatrist deemed that there was a clinical deterioration warranting a change in treatment	78% relapsed by 1y and 96% by 2y with a low threshold for relapse. Only 13% required hospitalisation

a Excluded because of differences in electrodermal conductivity from other groups since this was a biological variable being studied.

BPRS = Brief Psychiatric Rating Scale; **CGI** = Clinical Global Impressions scale; **d** = day; **IM** = intramuscularly; **mo** = month; **PO** = orally; **RDC** = Research Diagnostic Criteria; **SADS-C+PD** = Schedule for Affective Disorders and Schizophrenia-Change version with psychotic and disorganisation items; **wk(s)** = week(s); **y** = year.

open drug discontinuation after up to 74 weeks of initial treatment). However, only 13% of the patients required hospitalisation as a result of the early identification and treatment of recurrent symptoms.

Despite the wide variations in their methodologies and resultant reported relapse rates, some general conclusions can be reached. The risk of relapse increases over time, and can be estimated at about 40–50% in the first year after treatment discontinuation, and almost all remitted first-episode patients will experience some re-occurrence of symptoms within 5 years after the cessation of treatment. Maintenance antipsychotics reduce the risk of relapse, although the magnitude of the protective effect is not precisely defined.

2.4 Predictors of Relapse

The high probability of relapse in patients with a remitted first episode of schizophrenia and the relatively higher relapse rates for patients not on antipsychotics provides valuable evidence supporting maintenance therapy; however, all of the studies identified a small minority of patients who did not relapse even after discontinuing antipsychotics for as long as they were followed. Obviously, knowing which patients would not relapse would be tremendously valuable information and could potentially save this subgroup from the consequences of prolonged treatment. However, no clinically useful predictors of long-term relapse risk have been identified. Poor premorbid function and long duration of untreated psychosis are predictors of relapse risk, but the magnitude of effect is limited and thus not useful clinically.[87,88,92] No other variables have been found to have significant predictive value (including sex, diagnosis, obstetric complications, duration of psychotic illness before treatment, baseline symptoms, neuroendocrine measures, pharmacologic challenge tests, neuropsychological and magnetic resonance imaging measures, time to response of the initial episode, adverse effects during treatment, and the presence of residual symptoms after the initial episode).

2.5 Summary of Benefits of Pharmacological Treatment and Treatment Guidelines

The risk of eventual relapse after recovery from a first psychotic episode is very high and is greatly diminished by maintenance with antipsychotic treatment. However, even with strong evidence of the risk of relapse without antipsychotic medication, there is still no clear consensus on the recommended duration of treatment for patients who have recovered from a first episode of schizophrenia. Clinicians may have a difficult time convincing patients who have recovered from one episode of schizophrenia that indefinite and possibly life-long antipsychotic treatment is indicated because of the diagnostic uncertainty and instability associated with a first psychotic episode,[94] limited patient understanding and awareness of the illness,[95] and risks of long-term antipsychotic therapy.

The most recent American Psychiatric Association Practice Guideline for the Treatment of Patients With Schizophrenia,[96] published in 1997, recommends that patients who have had only one episode of positive psychotic symptoms and have been symptom-free during the subsequent year of maintenance therapy can be considered for a trial period without medication, provided that dose reductions are made gradually over several months with frequent visits. Similarly, the Schizophrenia Patient Outcomes Research Team[31] recommended in their 1998 report that patients should continue treatment for at least one year after remission of acute symptoms with continual reassessment of the maintenance dose for possible reduction.

The draft consensus statement of 26 international consultants,[36] previously mentioned in section 1.4, recommends taking into consideration the severity of the first episode when deciding how long to continue maintenance treatment. These consultants

suggest that patients who achieve full remission should be offered gradual withdrawal of medication after 12 months of maintenance treatment, but patients experiencing more severe and slow to respond episodes should be maintained for 24 months. This panel further suggests that patients who respond incompletely to medication, but clearly benefit from treatment, be maintained for 2–5 years.

3. The Case for Early Intervention

The treatment of a first episode of schizophrenia enables most patients to achieve symptom remission. Management of the acute symptoms will hopefully stabilise the patient, decrease the risk of imminent harm, decrease the period of deterioration in social and occupational functioning, and lessen the overall morbidity of the presenting episode. Long-term antipsychotic treatment exposes patients to potential risks including extrapyramidal symptoms, tardive dyskinesia, neuroleptic malignant syndrome, weight gain, lipid and glucose abnormalities, and possible cardiac toxicity. The justification for promptly identifying and treating first-episode schizophrenia would be bolstered by evidence showing that antipsychotic medication affects the long-term course and outcome of the illness, in addition to reducing short-term morbidity. The idea that the treatment of first-episode schizophrenia is an effective strategy for secondary prevention is supported by research demonstrating that poorer outcomes are correlated with longer lengths of time between initial symptom onset and the initiation of treatment (duration of untreated psychosis).

Lieberman et al.[97] recently reviewed 25 studies that examined the relationship between the duration of untreated psychosis and outcome. Of these 25 studies, 18 showed at least some indication that a longer duration of untreated psychosis was associated with a poorer outcome. Despite using retrospective determinations of duration of untreated psychosis and having other individual methodological limitations, these studies still provide substantial support that early intervention after the onset of psychosis may improve the long-term course of schizophrenia.

There is wide consensus in psychiatry that prompt pharmacological treatment of schizophrenia after the onset of overt psychosis is appropriate clinical care and justified by the available evidence base. What is considerably more controversial is whether primary prevention of schizophrenia is possible through interventions aimed at those thought to be at risk for developing psychotic illnesses or those who have developed symptoms considered prodromal for schizophrenia. This important discussion has been covered elsewhere[98-103] and is beyond the scope of this paper.

4. Model Programmes

An episode of schizophrenia is almost certain to be disruptive to a patient's life in terms of social and occupational functioning, and family relationships. This disruption can be even more intense for patients in young adulthood or adolescence – the most typical age of onset – who are in the midst of working through important developmental tasks. Individuals may be forced to change their sense of identity and to re-examine their goals. Psychosocial therapies are important throughout the course of schizophrenia to help patients resume their developmental tasks, reduce secondary morbidities such as depression and anxiety, and reinforce medication adherence. Patient and family education is critical in helping first-episode patients to develop insight and make informed decisions. Reviewed below are two model programmes for first-episode schizophrenia, which integrate psychosocial and pharmacological treatments. These two model programmes were chosen as examples of the types of existing integrated first-episode schizophrenia treatment programmes because of the availability of published outcome data for them.

4.1 Prevention and Early Intervention Programme for Psychoses

Malla et al.[104] studied the progress of 85 patients enrolled into their Prevention and Early Intervention Program for Psychoses. This programme stresses the importance of treatment with low doses of mostly atypical antipsychotics and various psychosocial interventions targeted specifically to patients experiencing a first psychotic episode. Among the psychosocial treatments available were group therapies, cognitive skills training, family education workshops, individual supportive psychotherapy and intensive case management.

Complete data (completed baseline and 1-year assessments) were available for 53 of the original 85 patients, showing a complete remission rate of 70% and a hospital readmission rate of 20%.[104] The group showed highly significant improvements in total scores on the Scale for the Assessment of Positive Symptoms,[105] and in total scores as well as reality distortion, disorganisation and psychomotor poverty syndrome scores on the Scale for the Assessment of Negative Symptoms.[106] Patients who did not achieve remission had a mean duration of untreated psychosis that was twice as long as those who did remit (10.5 vs 5.6 months) but the difference was not statistically significant. This study showed high rates of remission for patients in a representative community sample of patients who had experienced a first episode of nonaffective psychosis. An impressive 89% of patients remained in treatment at 1 year.

4.2 Early Psychosis Prevention and Intervention Centre

Researchers at the Early Psychosis Prevention and Intervention Centre at the University of Melbourne in Australia developed a Cognitively Oriented Psychotherapy for Early Psychosis (COPE), which aims to help first-episode patients adjust to their illness, resume developmental tasks, and prevent the development of secondary morbidity such as anxiety and depression. The four phases of the treatment, with the last two considered key elements of cognitive behavioural therapy, are: (i) assessment, which focuses on understanding symptoms and their impact on a person's sense of self; (ii) engagement, which focuses on building a working alliance with the patient; (iii) adaptation, which focuses on the effect of psychosis on a person's psychology and helps the individual develop coping strategies to resume everyday living; and (iv) a final phase which focuses on treating secondary morbidity such as social anxiety and depression.

An initial trial[107] evaluated the COPE therapy in three groups totalling 80 patients: (i) those who were offered and accepted COPE therapy; (ii) those who refused COPE therapy; and (iii) those who were offered neither the COPE therapy nor any other continuing treatment from the service (control patients). Patients who received COPE did significantly better ($p < 0.05$) than the control group on four of the seven measures[1] but only significantly out-performed the refusal group on one of the seven measures ($p < 0.05$). The COPE group performed significantly worse on the Beck Depression Inventory than the refusal group ($p < 0.05$).

A follow-up study[30] aimed to evaluate the durability of the treatment gains in the absence of COPE. Fifty-one of the original 80 patients consented to follow-up 1 year after completing COPE. The paper did not report on whether patients were taking medication at follow-up. Patients were evaluated using the Explanatory Model Scale,[108] the Integration/Sealing Over (I/SO) measure[109-112] and the General Symptoms Index of the Symptom Checklist-90.[113,114] The only significant difference found

1 Integration/Sealing Over, Explanatory Model, Scale for the Assessment of Negative Symptoms, Brief Psychiatric Rating Scale, Quality of Life Scale, Symptom Checklist-90-R and Beck Depression Inventory measures.

between the three groups was the I/SO measure, with the COPE group showing significantly better integration than the refusal group. Analyses of changes in status between end-of-treatment and follow-up showed statistically significant deterioration on the Brief Psychiatric Rating Scale measure ($p = 0.03$) and trends towards significant worsening for the refusal group on the Explanatory Model ($p = 0.09$) and the Quality of Life Scale ($p = 0.06$). The authors considered this lack of positive effect of COPE to be discouraging, but also pointed out limitations on statistical analyses, such as the low follow-up rates in the refusal and control groups. The researchers at the Early Psychosis Prevention and Intervention Centre at the University of Melbourne in Australia have now completed a randomised, controlled trial of COPE with stricter adherence to their intervention manual.

5. Conclusion

Patients who experience a first episode of schizophrenia respond very favourably to antipsychotics in the acute phase of treatment with regard to positive symptoms. Unfortunately, cognitive and negative symptoms are often slower to improve or are refractory to treatment, leaving many of these individuals with significant functional and social disabilities. Sequential trials of adequate dose and duration of antipsychotics and adjunctive treatments should be employed to help patients achieve their optimal response. Psychosocial therapies such as cognitive behavioural therapy and psycho-education groups may be helpful in addressing residual symptoms and helping patients to adhere to their medication regimens. In addition to lessening the morbidity of the presenting episode, early intervention in first-episode schizophrenia may improve the long-term course of the disorder, as evidenced by studies showing inverse correlations between the duration of untreated psychosis and outcome. Effective treatment of the symptoms of first-episode schizophrenia will also reduce the personal suffering of patients and families in ways that may not be reflected in rating scale scores or compliance rates.

The prevention of schizophrenia through presymptomatic treatment is an exciting possibility but future research is needed to develop the methodology by which to reliably identify those at risk before this strategy can become part of routine clinical practice. Once remission from the first episode is reached, maintenance antipsychotic treatment is indicated for at least 1 year. The overwhelming majority of individuals who do not remain on antipsychotic therapy eventually experience a relapse. This raises the question of what is the optimal length of continuation and maintenance treatment for patients who have recovered from a first episode of schizophrenia or related psychoses. Clinically useful predictors of the small minority who maintain remission without pharmacotherapy have not yet been identified.

Atypical antipsychotics represent a great advance in the treatment of first-episode schizophrenia with strong evidence for greater tolerability with equal or better therapeutic efficacy. While future research will help to characterise their efficacy relative to one another and define the effect of their use on long-term outcomes of schizophrenia, available evidence and consensus expert opinion support their use as first-line treatment in first-episode schizophrenia. Still, many patients optimally treated with atypical antipsychotics are not able to return to their premorbid functioning and experience significant persistent morbidity. Basic neuroscience research will hopefully lead to a better understanding of the pathophysiology of schizophrenia, and the development of compounds with even greater therapeutic efficacy and tolerability.

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