PSYCHOPHARMACOTHERAPY

4.1 Relapse prevention in schizophrenia: evidence from long-term, randomized, double-blind clinical trials

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Summary

Fourteen long-term (duration at least 26 months) double-blind, randomized studies comparing second-generation antipsychotics (SGAs) with placebo, conventional antipsychotics, or two or more SGAs, published after 2002 have been reviewed and are summarized in this chapter. Methodological problems and factors influencing results such as patient populations involved, outcome criteria, and dosages of evaluated drugs are discussed.

4.1. Introduction

Schizophrenia is one of the most serious mental disorders. Although the lifetime prevalence of schizophrenia is about 1% in the general population, its long duration and consequent disability place it among the top 10 causes of disability-adjusted life-years in the world (Mathers et al., 2002). The disorder is characterized by a broad spectrum of symptoms that can be classified into several syndromes. Positive syndrome consists of the main psychotic features

— hallucinations, delusions, and bizarre behaviours. Negative and cognitive symptoms are clinically less salient but may be even more influential for the long-term outcome of the disorder because of their impact on social relationships and working ability (Norman et al., 1999).

The course of disease varies and ranges from a simple episode without residual symptoms to a chronic and deteriorating course with severe impairment. A periodic course is frequent, and some residual symptoms may be seen even after the first acute episode is resolved.

Relapse prevention is considered to be among the most important issues in the management of schizophrenia. Although different social, rehabilitation, and psychotherapeutic measures are helpful, long-term pharmacological treatment with antipsychotic medication is the mainstay treatment approach. Antipsychotic treatment may reduce the frequency of relapses to one-third during one year (Bosveld-van Haandel et al., 2001). Placebo-controlled studies with discontinuation of previous antipsychotic treatment have confirmed the high relapse rate in patients who stop the treatment (Beasley et al., 2003; Gitlin et al., 2001).

One of the problems in assessing the efficacy of relapse prevention is the uncertainty about the natural course of schizophrenia. This problem is further complicated by the fact that the natural course of schizophrenia is now almost impossible to observe because treatment with antipsychotics usually starts as soon as the diagnosis is made. Relevant sources for the estimation of the natural course of schizophrenia are therefore older studies; for example, the long-term follow-up of 208 patients from the district of Zurich who were recruited during hospitalisation at Burghölzli Hospital in 1942 and 1943. Patients were diagnosed by Eugen Bleuler and Manfred Bleuler. Most of the patients were followed up for 25 years. Bleulers divided the course of illness into the types defined by the onset (acute or insidious), by a simple or episodic course, and by a good or poor outcome. The simple course without remission was identified in 38% of patients; 22% of patients had an undulating course with one or several episodes of schizophrenia ending with full remissions; and 27% had an undulating course that ended with moderate/mild impairment and 9% with severe impairment. The remaining patients had an atypical course. The value of these results for recent psychiatric practice was heightened by a study in which the original diagnoses were confirmed using the criteria of several recent diagnostic systems (Modestin et al., 2003).

In the long-term International Study of Schizophrenia (ISoS) coordinated by WHO, patients were evaluated for 15 or 25 years of follow-up. They were divided into two groups. An "incidence" group (1171 subjects) consisted of patients who were involved in the study at the first contact with the health system for psychosis or at the first admission to hospital care. A "prevalence" group consisted of 462 subjects who were identified using a screening method and included new patients as well as some with previous episodes. The total sample consisted of cohorts from different countries. Authors (Harrison et al., 2001) used Bleuler's course typology, and the results revealed that 60.9% of patients from the "incidence" group had some form of episodic course with good or poor outcome, 5.3% of patients had an acute simple course with a good outcome, and 9.1% had an acute simple course with a bad outcome. The data for the "prevalence" group were similar. The study demonstrated that the course of schizophrenia in undeveloped countries is milder than in developed countries and identified various factors influencing outcome.

The results from other studies vary considerably. For example, the range for the course of schizophrenia characterized by acute onset, undulating course, and recovery or mild impairment at the end state is between 7% to 40% in five long-term follow-up studies summarized by Häfner (Häfner and Heiden, 2003). According to these findings, it is questionable whether it is meaningful to expect relapse in all patients with schizophrenia, or only in that portion of patients who exhibit an undulating course. We can expect that a substantial proportion of patients perhaps never will relapse or have remission because their course of illness is simple with a poor outcome. In another way, the general definition of relapse as "the return of a disease after partial recovery" (Lader, 1995) could be applicable for only a portion of patients with schizophrenia.

In a definition of the course of schizophrenia and the phases of therapy, we are far away from the state-of-the-art achieved in the field of depression, where definitions are much clearer and the response, remission, recovery, relapse, and recurrence are defined operationally. The "Kupfer curve" (Kupfer, 1991) is an integral part of general psychiatric knowledge, and criteria based on standardized assessment scales are proposed and used (O'Donovan, 2004).

A consensus statement about the remission criteria for schizophrenia was only recently proposed (Andreasen et al., 2005), and the definition of relapse varies substantially across different studies. It can be viewed, for example, as a change in the scores of assessment scales, the change in the psychotic items

of the scales, clinically meaningful worsening of clinical status, a need for a change of therapy, or a need for hospitalisation of the patient.

Although the problem with the definition of relapse exists, the consequences of relapse are serious and complex. Relapses usually occur during the 5–7 years after the first episode, which is a vulnerable period when one is expected to complete education, start to work, and create close relationships with a partner and social network. Patients with more relapses have worse functioning and overall quality of life. The cost of treatment for patients who experience relapses is much higher, mainly because of higher inpatient-treatment costs. Many of the risk factors for relapse have been identified, among them male gender and young age at onset of psychosis, long duration of untreated psychosis, comorbidity with personality disorders, substance abuse, or expressed emotions in families. Poor adherence to treatment appears to be among the main factors, which increases the probability for relapse (Almond et al., 2004; Bosveld-van Haandel, 2001; Harris et al., 2005).

Because relapse prevention is one of the most essential goals of antipsychotic treatment, the high expectations in this field have been directed at a group of novel antipsychotics, the second-generation antipsychotics, or SGAs. Most studies show that SGAs have a better efficacy profile with a broader spectrum of symptoms targeted by the treatment and a better safety profile mainly because of a significant reduction in extrapyramidal adverse effects. These advantages should result in better efficacy and tolerability in long-term treatment with better patient adherence to medication and a subsequent reduction in relapses and a better quality of life. Long-term studies to show this, however, suffer from many methodological problems. The diagnostic system, sample selection, type of measurements, reliability and validity of assessment, length of follow-up, and criteria for course and outcome are among the methodological shortcomings of different studies (Furukawa, 2004; Gaebel and Frommann, 2000). Confirmation of expectations directed towards SGAs has not been unambiguous, and discussions about the profit of SGA in contrast with the substantially higher cost of treatment are ongoing (e.g. Tandon and Fleischhacker, 2005).

The metaanalysis published by Leucht et al. (Leucht et al., 2003) is considered to be one of the most influential studies evaluating the efficacy of SGAs in the long-term treatment of schizophrenia. Randomized, controlled trials comparing SGA with placebo or conventional antipsychotics that lasted at least 6 months and reported the relapse rate were identified for inclusion in

this metaanalysis. The last search for studies in electronic databases was done in July 2002. Authors also scrutinized other sources (review articles, requests sent to pharmaceutical companies) for relevant published trials. Metaanalysis of six studies with 983 total subjects (range, 62 to 326 subjects in particular studies) comparing amisulpride (one study), olanzapine (three studies), ziprasidone (one study), and zotepine (one study) with placebo revealed the risk of difference for a raw relapse rate of –0.21 and the risk of difference calculated by survival analysis of –0.33 in favour of SGAs. Analysis of 11 studies with 1170 patients comparing SGAs (two studies with amisulpride, three with olanzapine, three with clozapine, two with risperidone, and one study with sertindole) with first-generation antipsychotics (FGAs) (haloperidol in 10 studies and different FGAs in one study) revealed a risk difference for relapse of –0.08 for raw data and –0.11 when survival curve estimates were used for calculation. The authors commented that several other head-to-head studies with SGAs were ongoing, with no sufficient data for inclusion at that time. They stressed the problem with the very different methodologies of particular studies and suggested that findings would be changed after new studies were published.

In the following part of this chapter the long-term (lasting at least 26 weeks), randomized, double-blind studies with SGAs allowing the assessment of relapse rate will be described (Table 1). Studies were identified by searching the Medline database for references from relevant, recently published articles and from a Web search. The search was performed from July 2002 (the time of the last search for available studies in the Leucht et al. metaanalysis (Leucht et al., 2003) to the end of October 2005.

Table 4.1. Summary of studies considered in the overview

Study	Drugs studied	Daily dose	No. of patients	Diagnosis	Duration of study
Sechter et al., 2002	amisulpride	mean dose of the longest exposure = 683 mg	152	schizophrenia (chronic)	6 months
	risperidone	mean dose of the longest exposure = 6.9 mg	158		
Pigott et al., 2003	aripiprazole	15 mg	155	schizophrenia (chronic course)	26 weeks
	placebo	NA	155		

Study	Drugs studied	Daily dose	No. of patients	Diagnosis	Duration of study
Kasper et al., 2003	aripiprazole	30 mg	861	schizophrenia (acute relapse, pooled from two double blind studies)	52 weeks
	haloperidol	10 mg	433		
Clinical Study Report CN138003, 2005	aripiprazole	15 to 30 mg	355	schizophrenia (responders from 6-week, acute phase)	52 weeks
	olanzapine	10 to 20 mg	348		
Rosenheck et al., 2003	olanzapine	mean dose in last 6 months = 15.8 mg	159	schizophrenia, schizoaffective disorder	1 year
	haloperidol	mean dose in last 6 months = 14.3 mg	150		
Gureje et al., 2003	olanzapine	mean modal dose = 17.2 mg	32	schizophrenia, schizophreniform disorder, schizoaffective disorder,	30 weeks
	risperidone	mean modal dose = 6.6 mg	33		
Lieberman et al., 2003	clozapine	median dose at the end of study = 400 mg	80	schizophrenia, schizophreniform disorder (first episode)	52 weeks
	chlorpormazine	median dose at the end of study = 300 mg	80		
Marder et al., 2003	risperidone	mean dose at 2 years = 5.7 mg	30	schizophrenia, (stabilized, 2 months pretreatment period)	2 years
	haloperidol	mean dose at 2 years = 4.5 mg	33		
Mortimer et al., 2004	amisulpride	mean dose = 504 mg	189	schizophrenia, schizophreniform disorder	6 months
	olanzapine	mean dose = 13 mg	188		
Schooler et al., 2005	risperidone	mean modal dose = 3.3 mg	278	schizophrenia, schizophreniform disorder, schizoaffective disorder (first episode)	median treatment length 206 days
	haloperidol	mean modal dose = 2.9 mg	277		
Breier et al., 2005	ziprasidone	mean modal dose = 115.9 mg	271	schizophrenia	28 weeks
	olanzapine	mean modal dose = 15.2 mg	277		
Naber et al., 2005	olanzapine	mean dose = 16.2 mg	57	schizophrenia	26 weeks
	clozapine	mean dose = 209 mg	57		
Simpson et al., 2005	ziprasidone	mean dose at 6 months = 135.2 mg	55	schizophrenia, schizoaffective disorder (responders from 6-week acute phase)	6 months with possible extension; mean treatment duration 195 days
	olanzapine	mean dose at 6 months = 12.6 mg	71		

Study	Drugs studied	Daily dose	No. of patients	Diagnosis	Duration of study
CATIE study; Lieberman et al. 2005	olanzapine	mean modal dose = 20.1 mg	336	schizophrenia	18 months
	quetiapine	mean modal dose = 543.4 mg	337		
	risperidone	mean modal dose = 3.9 mg	341		
	ziprasidone	mean modal dose = 112.8 mg	185		
	perphenazine	8 to 32 mg	261		

4.2. An overview of long-term randomized double-blind controlled studies with SGAs published between 2002 and 2005

The primary goal of the 6-month, double-blind, randomized study comparing amisulpride and risperidone published by Sechter et al. (Sechter et al., 2002) with a non-inferiority approach was the assessment of efficacy and safety of the treatments and assessment of the functional effects of two drugs used. Patients with chronic schizophrenia and predominantly positive symptoms were involved. The study started with a 6-day placebo washout period; patients who responded to placebo in this period were not eligible for the next phase of the study. The dose range scheduled for amisulpride was from 400 to 1000 mg/day, and the dose range of risperidone was 4–10 mg/day. The mean dose of the longest exposure was 683 mg/day for amisulpride and 6.92 mg/day for risperidone. A total of 60% of 310 patients who were randomized completed the study (64% in the amisulpride group and 56% in the risperidone group). Premature withdrawal because of a lack of efficacy was found in 7% of patients treated with amisulpride and 11% of patients treated with risperidone. Authors provided the data about the "maintenance of effect" for a subpopulation of patients with improvement defined by a decrease in total PANSS score ≥ 40% from baseline to the second month of the study. Lack of maintenance of effect was defined as discontinuation for any reason and for treatment failure (lack of maintenance of improvement). A total of 65% of responders in the amisulpride group and 57% of responders in the risperidone group maintained efficacy, which was a non-significant difference.

Pigott et al. (Pigott et al., 2003) compared aripiprazole with placebo in a 26-week randomized, double-blind study. The clinical status of patients with a

chronic course of schizophrenia was stable, defined by no significant improvement or worsening of symptoms within the past 3 months, but still had significant symptomatology with a mean baseline PANSS score of 81.8. A three-day washout period was included before randomization to the fixed dose of 15 mg of aripiprazole or placebo. The primary efficacy criterion was the time to relapse following randomization. The relapse was defined as "impending decompensation" based on one or more of the following: a CGI-I score ≥ 5 (minimally worse); PANSS score of ≥ 5 (moderately severe) on the items of hostility or uncooperativeness on 2 successive days; or a ≥ 20% increase in PANSS total score. A total of 310 patients were assigned to the aripiprazole and placebo groups (n=155 in each group); efficacy was evaluated for 297 patients. In the placebo group, patients relapsed sooner and with higher frequency than in the aripiprazole group. The estimated Kaplan-Meier survival rates at week 26 were 62.6% in the aripiprazole group and 39.4% in the placebo group ($p<0.001$). The relative risk of relapse with aripiprazole treatment compared to placebo was 0.50 (95% CI = 0.35 to 0.71). A total of 54.2% of patients from the aripiprazole group and 71% of patients from the placebo group dropped out of the study prematurely. The main reasons for discontinuation were lack of efficacy (or relapse): 27.1% in the aripiprazole group and 49% in the placebo group. Adverse effects were the reason for discontinuations in 10.3% in the aripiprazole group and 8.4% in the placebo group.

Kasper et al. (Kasper et al., 2003) reported results of a pooled analysis from two double-blind, randomized, multicentre studies. A total of 1294 patients with acute relapse of schizophrenia were enrolled. After the placebo washout period, the patients were re-evaluated at the baseline visit and, if still eligible for the further study (among inclusion criteria was a total score ≥ 60 on PANSS with a score ≥ 4 on any two of the four PANSS psychotic items), they were randomly assigned in a 2:1 ratio to the treatment with aripiprazole (30 mg/day) and haloperidol (10 mg/day) groups. The double-blind treatment period was planned for 52 weeks. The primary efficacy outcome was "the time to failure to maintain response" in a subgroup of responders. The criteria for response were defined as ≥ 20% decrease in total PANSS score at any single time point after the baseline plus a CGI-I score of 6 or 7 with a condition that the adverse event "worsening of schizophrenia" or a score of ≥ 5 in at least one of the four PANSS psychotic subscale items was not concurrently present. The response rate was 72% in the aripiprazole group and 69% in the haloperidol group ($p=0.362$). When an additionally set criterion of ≥ 30% reduction of PANSS total score was used as the definition of response, the response rate was 52% for aripiprazole and 44% for haloperidol. There was

no significant difference between treatments in the time to failure to maintain response for a subgroup with a ≥ 20% decrease in PANSS score at any single point in the study (77% in the aripiprazole group vs. 73% in the haloperidol group; p=0.427). A statistical difference between groups was found for maintaining the response, defined as a ≤ 30% reduction in the PANSS total score for 28 days and one additional visit (85% vs. 79%, p=0.098). A total of 43% of patients in the aripiprazole arm and 30% in the haloperidol arm completed the study.

A synopsis of results from a long-term, double-blind, randomized trial comparing aripiprazole and olanzapine was published on the website (www.clinicalstudyresults.org/documents/company-study_509_5.pdf). Besides efficacy and tolerability measures, the response and discontinuation rates were among the secondary objectives. Patients involved in the study underwent a 2–7 day washout phase before randomization for the 6-week acute treatment phase with a starting aripiprazole dose of 15 mg and 10 mg of olanzapine. The doses could be increased up to 30 mg for aripiprazole and up to 20 mg of olanzapine. At the end of the acute phase, patients with a score of 1–3 on CGI-I or with at least a 20% reduction in the PANSS total score continued to the extended period up to 140 weeks of treatment. Results were published for 52 weeks of study duration. A total of 703 patients were randomized. The discontinuation rate before week 52 was 53% (183 patients) for the olanzapine group and 61% (218 patients) for the aripiprazole group. For 19.2% of patients treated with aripiprazole and for 14.9% of patients treated with olanzapine, adverse events were considered as the reason for discontinuation. Although the responders were defined by the specified improvement of the scores of CGI-I and PANSS, no information about maintenance of response or discontinuation for worsening of symptoms is provided in the synopsis.

The primary outcomes of a double-blind, randomized, 1-year study published by Rosenheck et al. (Rosenheck et al., 2003) comparing olanzapine and haloperidol were severity of symptoms of schizophrenia, quality of life, and an estimation of the costs of the treatments. The inclusion criteria were as follows: Patients had currently been hospitalised for no more than one year, had a score of ≥ 36 on the BPRS scale, and had serious social dysfunction during the previous 2 years. Criteria were later expanded, and patients with a diagnosis of schizoaffective disorder and participants from outpatient settings could be involved. A total of 4386 patients from 17 departments of veteran affairs were assessed for eligibility, and 309 were randomized (159 to the olanzapine group with a dose range of 5–20 mg/day and 150 to haloperidol with a dose

range of 5–20 mg/day and prophylactic benztropine 1–4 mg/day). The mean dose for the last 6 months of the trial was 15.8 mg/day for olanzapine and 14.3 mg/day for haloperidol. A nonsignificant difference was found for the discontinuation rate from the study (54.1% in the olanzapine group and 60.7% in the haloperidol group, p=0.24). The difference of the rate of discontinuation from the study because of lack of efficacy or worsening of symptoms was not statistically significant; it was the reason for discontinuation in 12.7% of patients on olanzapine and 17.6% of patients on haloperidol.

Gureje et al. (Gureje et al., 2003) published results from their double-blind, randomized study with 65 patients with a diagnosis of schizophrenia, schizoaffective disorder, or schizophreniform disorder. The study was designed with a 30-week, double-blind phase and an optional 48-week extension phase, but because of the high rate of drop-outs, it was terminated after 30 weeks and only data for this phase were analyzed. Two arms with treatment with olanzapine (mean modal dose 17.2 mg/day; n=32) and risperidone (mean modal dose 6.6 mg/day; n=33) were compared. The primary objective was the assessment of efficacy defined by change in the total PANSS score, the BPRS score, and the change in the CGI-severity scale. A total of 53.1% of patients from the olanzapine group and 36.4% from the risperidone group completed the study. Information about relapses is not explicitly described and thus only secondary deduction is possible. "Lack of efficacy" was the reason for study discontinuation in 6 patients (18.8 %) from the olanzapine group and 11 patients (33.3 %) from the risperidone group. During 30 weeks of treatment, more patients treated with olanzapine were hospitalised, although exact data about hospitalisations are not presented.

Lieberman et al. (Lieberman et al., 2003) compared treatment with clozapine and with chlorpromazine in a randomized, double-blind study conducted in China. Patients involved were aged 16 to 40 years with a first episode of schizophrenia or schizophreniform disorder, duration of symptoms no longer than 60 months, total lifetime usage of antipsychotics less than 14 days, and moderate or greater severity according to the five psychotic items score of BPRS. A total of 164 patients were randomized to treatment with clozapine or with chlorpromazine plus 2 mg of benztropine. The treatment started during hospitalisation for the first 12 weeks. The primary measure of efficacy was the time to the first remission (defined as an improvement ≥ 50% in the BPRS score, a score ≤ 3 on five BPRS psychotic items, and a score of CGI-S ≤ 3) and proportion of time in remaining remission. Eighty patients in each group were available for analysis. The median dose at the end of study was 300 mg/day for

chlorpromazine and 400 mg/day for clozapine. In 79% of patients on chlorpromazine and in 81% of patients on clozapine, the criteria for remission was fulfilled (non-significant difference). The proportion of time in remission was longer for patients on clozapine (odds ratio 1.73; p=0.003) even after controlling for the differences for several variables. A total of 22.5% patients from the chlorpromazine group and 15% of patients from the clozapine group discontinued from the study up to the 52nd week. Eleven patients had to be rehospitalised (total 14 rehospitalisations) during weeks 13–52 of the study.

Marder et al. (Marder et al., 2003) compared treatments with risperidone and haloperidol in a randomized double-blind study projected for 2 years. A total of 63 patients from 110 who underwent a 2-month pretreatment stabilisation period were randomized to risperidone (n=30) or haloperidol (n=33) at entering the double-blind phase. The mean daily dose of haloperidol was in the range of 5.2 mg at the start to 4.5 mg at 2 years; the mean daily dose of risperidone ranged from 6.1 to 5.7 mg for the same time span. A psychosocial treatment program was also provided for all patients. At the 26th week, 46 patients were still in the study, 37 at the 52nd week, 33 at the 78th week, and 27 at the 104th week of the study. No significant difference was found for the number of patients remaining in the study between the groups when all reasons for dropouts were included (40% of patients receiving haloperidol and 58% of patients receiving risperidone remained in the study; p=0.19). No significant difference was found for the time until psychotic exacerbation, which was defined as a numerically specified worsening of the scores for thought disturbance and hostile-suspiciousness items from the BPRS. A total of 88% of patients treated with risperidone and 73% of patients treated with haloperidol remained on therapy without psychotic exacerbation (p=0.27).

Mortimer et al. (Mortimer et al., 2004) published results of a double-blind, randomized study with a non-inferiority approach comparing olanzapine and amisulpride. The primary objective was the assessment of efficacy of the drugs in the treatment of patients with a diagnosis of schizophrenia or schizophreniform psychosis with prominent positive symptomatology. The study started with 3–6 days of the placebo washout period; thereafter, the patients were randomized to a double-blind, active treatment phase with a daily dosage range of 200 to 800 mg of amisulpride or 5–20 mg of olanzapine for the 6 months of the study. A total of 372 patients were available for analysis because they had at least one post-randomization assessment. Of these, 117 (64%) patients from the olanzapine and 125 (66%) of patients from the amisulpride group completed the study. There were no relapse criteria stated in the study,

only the number of patients "who did not discontinue because of lack of efficacy", and the authors were using a reduction of baseline BPRS score of at least 20% between 2 and 6 months. A total of 110 (82%) of patients from the olanzapine group and 121 (89%) patients from the amisulpride group satisfied these criteria. No statistical computation was published for this difference.

Schooler et al. (Schooler et al., 2005) compared in a double-blind, randomized study the low dose of risperidone and haloperidol (mean modal dose 3.3 mg of risperidone and 2.9 mg of haloperidol) in the treatment of first-episode patients aged 16 to 45 years with schizophrenia, schizoaffective disorder, or schizophreniform disorder. It is the longest double-blind study with SGA as the earliest patients involved could be evaluated for 6 years. The relapse rate assessed in a subpopulation of patients who reached a given level of improvement was among the primary outcome measures. The criteria for relapse were the same as those in the study of Csernansky et al. (2002): a 25% increase in PANSS total score (or 10-point increase in patients with a total score at baseline of 40 or less); a CGI change to much worse or very much worse; reported self injury; clinically significant suicidal or homicidal ideation; or completed suicide and violent behaviour. A total of 278 patients on risperidone and 277 patients on haloperidol were included in the analysis for safety. Of these, 197 patients in the risperidone group and 203 patients in the haloperidol group met the criteria for response and were available for relapse analysis. Fewer relapses were found in the risperidone group (42.1% vs. 54.7%) with a significant difference for the time to relapse (median 466 days for risperidone and 205 days for haloperidol). A significant difference between groups emerged by 145 days. The total discontinuation rate in the study was 39.3% (42.1% in the risperidone group and 36.5% in the haloperidol group).

In a double-blind, randomized study comparing olanzapine with ziprasidone published by Breier et al. (Breier et al., 2005), 548 patients (277 in the olanzapine group and 271 in the ziprasidone group) were assigned to the active treatment after the single-blinded placebo washout period. The study was designed for 28 weeks. The mean modal dose reached was 15.27 mg/day for olanzapine and 115.96 mg/day for ziprasidone. The primary outcome measure was a reduction in the PANSS score. A response was defined as a reduction of 30% or more on the PANSS total score. The PANSS score together with the CGI severity of illness scale were used to measure symptom exacerbation and time to exacerbation. A total of 59.6% of patients from the olanzapine group and 42.4% of patients from the ziprasidone group completed the study

($p<0.001$; Fisher's exact test). Among the reasons for premature discontinuation, statistical differences were found for "aggravation of psychosis" (1.4% in the olanzapine group vs. 4.4% in the ziprasidone group; $p=0.05$) and for "lack of efficacy" (7.2% in the olanzapine group vs. 13.7% in the ziprasidone group; $p=0.02$). No statistical difference was found between the groups for exacerbation of symptoms, defined as the worsening of 20% or more on the PANSS total score and a worsening in the CGI severity of illness score of 1 point after 8 weeks of study (14.6% in the olanzapine group, and 25.3% in the ziprasidone group; $p=0.06$).

The primary aim of the double-blind, randomized study published by Naber et al. (Naber et al., 2005) was to compare the effects of olanzapine and clozapine on subjective well-being and to demonstrate non-inferiority between the treatments. Patients included in the study had a documented failure to respond to antipsychotic treatment with a drug other than clozapine or olanzapine, or they had previously experienced intolerable side-effects. The duration of study was planned for 26 weeks of double-blind treatment, and the washout period and taper period were included. A total of 114 patients were randomized to the treatment of 5–25 mg of olanzapine (mean dose 16.2 mg/day) and to 100–400 mg of clozapine (mean dose 209 mg/day). Twenty-one patients from the olanzapine group and 22 patients from the clozapine group completed the study. No definition of relapse or analysis of relapses (except two discontinuations for relapse mentioned in a flowchart) were provided in the publication. There were 65% of patients on clozapine and 67% on olanzapine who discontinued from the study prematurely. Mean duration of treatment was 109 days in the olanzapine and 101 days in the clozapine group.

Simpson et al. (Simpson et al., 2005) published in a brief report results from a double-blind study comparing the efficacy and tolerability of the treatments with ziprasidone and olanzapine. Patients with a diagnosis of schizophrenia and schizoaffective disorder who were treated in an outpatient setting and were considered as responders (CGI improvement score ≤ 2 or a $\geq 20\%$ improvement in the PANSS total score) in the 6-week acute study entered a continuation phase (lasting 6 months from the acute phase baseline). After 6 months of treatment, the optional extension phase started with up to 2 years duration. Flexible dosing was used with 40, 60, or 80 mg of ziprasidone and 5, 10, or 15 mg of olanzapine. The continuation phase entered 126 patients. Similar proportions of patients discontinued the study during all three phases (69.1% on ziprasidone and 70.4% on olanzapine) with a median time of remaining in the study of 195 days for both treatment groups. The response was defined as an

improvement of ≥ 20% of the total score on PANSS. The rate of patients who maintained response was not significantly different at 6 months: 85.5% (n= 47) for the ziprasidone group and 84.5% (n=60) for the olanzapine group. No significant differences were found for the time to "significant symptom exacerbation" defined by a ≥ 20% worsening of the PANSS total score and a CGI score ≥ 3 using the Kaplan-Meier survival curves for comparison.

The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE), initiated by the National Institute of Mental Health in U.S.A, is an exceptional study involving comparison of five SGAs and one FGA for the treatment of schizophrenia under double-blind randomized conditions (Lieberman et al., 2005). The primary outcome of the study was to assess the effectiveness of the different treatments. Effectiveness was conceptualized as a combination of efficacy and tolerability. As the measure of effectiveness, the discontinuation of the treatments for any reason was selected because it can reflect the integration of the patient's and clinician's approach to evaluation of treatment. The main secondary outcome was the specific reason for discontinuation. The study duration was planned for 18 months in the first phase with a double-blind condition of treatment. After discontinuation from the first phase, patients could be assigned for other treatments in phases 2 and 3. A total of 1493 patients with schizophrenia were randomly assigned to treatment with olanzapine (n=336, dose range 7.5 to 30 mg/day), perphenazine (n=261, dose range 8 to 32 mg/day), quetiapine (n=337, dose range 200 to 800 mg/day), risperidone (n=341, dose range 1.5 to 6.0 mg/day), or ziprasidone (n=185, dose range 40 to 160 mg/day). The presence of tardive dyskinesia was an exclusion criterion for the assignment to the treatment with perphenazine. A ziprasidone arm was added to the study later, and all comparisons with ziprasidone were limited to the patient population randomized after the opening of the ziprasidone arm. All 33 patients from one centre were excluded from analysis, and 28 of the randomized patients did not take the medication. The number of patients available for analysis was 330, 257, 329, 333, and 183 in the olanzapine, perphenazine, quetiapine, risperidone, and ziprasidone groups, respectively. The trial had a statistical power of 85% to identify an absolute difference of 12% in the rates of discontinuation between two atypical agents used. Because of limitations in randomization given for perphenazine and ziprasidone, the study had a statistical power of 76% for comparisons involving perphenazine and of 58% for comparisons involving ziprasidone. The authors used a conservative statistical approach for comparisons, and Kaplan-Meier survival curves were used for estimation of the time to discontinuation.

The discontinuation rates for any reason in patients involved in the analysis were 64% in the olanzapine group, 75% in the perphenazine group, 82% in the quetiapine group, 74% in the risperidone group, and 79% in the ziprasidone group. The time for discontinuation from the treatment was longer for the-olanzapine group in comparison to the quetiapine group ($p<0.001$), the risperidone group ($p=0.002$), and the perphenazine group ($p=0.021$). Patients treated with olanzapine also had a longer time to discontinuation in comparison with patients treated with ziprasidone when analysis was done for a subpopulation of 889 patients after the ziprasidone arm was included ($p=0.028$). But the differences between the olanzapine and perphenazine groups and olanzapine and ziprasidone groups lost significance after adjustments for multiple comparisons.

An analysis of the "duration of successful treatment" is among many considerable results of the study. It was defined as the time (number of months) when the CGI score of at least 3 (mildly ill) or 4 (moderately ill) with an improvement of at least two points from baseline was achieved after the baseline and maintained thereafter. This approach could reflect the relapse caused by worsening of the symptoms. The comparisons using this parameter revealed significant differences between olanzapine vs. quetiapine ($p<0.001$), risperidone ($p=0.002$), and perphenazine ($p=0.013$), and for risperidone vs. quetiapine ($p=0.021$). In absolute number, the time of duration of successful treatment was 3 months (2–5 months) for olanzapine; in all other groups, the ranges of the time of duration of successful treatment were 0–1 or 0–2 months.

4.3. Discussion

Fourteen double-blind, randomized, controlled studies with a duration of treatment of at least 6 months comparing one or more SGAs were identified for the given period of publication and included in this review. In one study, the newest SGA, aripiprazole, was compared with placebo (Pigott et al., 2003). Four studies used haloperidol for comparison to SGAs, one study with aripiprazole (Kasper et al., 2003), one study with olanzapine (Rosenheck et al., 2003), and two studies with risperidone (Marder et al., 2003; Schooler et al., 2005). In one study, clozapine was compared to chlorpromazine (Lieberman et al., 2003). In seven studies, two SGAs were compared in a head-to-head design: aripiprazole vs. olanzapine (www.clinicalstudyresults.org/documents/company-study_509_5.pdf), olanzapine vs. ziprasidone in two studies (Breier at al., 2005; Simpson et al., 2005), olanzapine vs. risperidone (Gureje

et al., 2003), olanzapine vs. amisulpride (Mortimer et al., 2004), amisulpride vs. risperidone (Sechter et al., 2002), and clozapine vs. olanzapine (Naber et al., 2005); and in one study, four SGAs (olanzapine, quetiapine, risperidone, and ziprasidone) were compared with the FGA perphenazine (Lieberman et al., 2005).

The possibility of influence of pharmaceutical companies on study design, published results, and biased interpretations is frequently discussed (Kim, 2004). The probability of positive results can be up to 8.4 times more likely in studies with declared conflict of interests (Perlis et al., 2005). That trend is also seen in studies comparing SGAs and conventional antipsychotics (Montgomery et al., 2004). Only two studies involved in this review were primarily supported by grants from NIMH and other public institutions (Lienberman et al., 2005; Marder et al., 2003). In the publications of the other 10 studies, the sponsoring pharmaceutical company was mentioned. In one study (Mortimer et al., 2004), there is no explicit statement about support, but pharmaceutical company sponsorship is clearly identifiable from the context. Three studies with identifiable conflicts of interest were planned to test non-inferiority between compared drugs (Mortimer et al., 2004; Naber et al., 2005; Sechter et al., 2002). The results of one study (www.clinicalstudyresults.org/documents/company-study_509_5.pdf) were published on the Internet by the sponsor. This move reflects a new approach by pharmaceutical companies of disclosing all initiated clinical trials and their results for the public, regardless of outcome (e.g., www.lillytrials.com). This policy can diminish the doubts about any publishing bias of negative results.

Patient populations involved in the reviewed studies were different even at the basic level of diagnosis. In several studies, the patients with a diagnosis other than schizophrenia were also involved, including diagnosis of schizophreniform disorder (Gureje et al., 2003; Mortimer et al., 2004; Schooler et al., 2005; Lieberman et al., 2003) or schizoaffective disorder (Rosenheck et al., 2003; Simpson et al., 2005). In two studies (Lieberman et al., 2003; Schooler et al., 2005), only the younger first episode patients with schizophrenia or schizophreniform or schizoaffective disorder with minimal exposure to psychiatric treatment were included. There is evidence about different long-term outcomes in different diagnoses of schizophrenia spectrum disorders (Benazzi, 2003; Marneros et al., 1992); thus, the heterogeneity of populations in different studies may influence the results. Other inclusion and exclusion criteria used in particular studies make the differences among patient populations even more apparent. There were different requirements for patient

status at the start of studies with an outpatient condition strictly required in some studies (Gureje et al., 2003; Marder et al., 2003; Simpson et al., 2005), both outpatient or inpatient treatment possible at the start of other studies (Breier et al., 2005; Mortimer et al., 2004; Piggot et al., 2003; Rosenheck et al., 2003), "hospitalisation recommended" (Sechter et al., 2002) or "no requirement to be hospitalised" (www.clinicalstudyresults.org/documents/company-study_509_5.pdf), or patient status was not precisely specified. According to the inclusion criteria, only the responders from a previous phase of shorter treatment were eligible for continuation (www.clinicalstudyresults.org/documents/company-study_509_5.pdf; Simpson et al., 2005), patients able to take oral medication were involved (Lieberman et al., 2005), or stable patients for three months with ongoing symptomatology were eligible for involvement (Pigott et al., 2003).

The design of a long-term study may be different if the main outcome measure is relapse or maintenance of response. In relapse studies, the patients involved are stable and may be randomized to a different type of treatment. In maintenance of response studies, the patients who achieved the defined remission or improvement are evaluated in a continuation phase for improvement sustained over time (Csernansky, 2003). In the reviewed studies, the pretreatment stabilization phase was included before the long-term treatment and evaluation started (Marder et al., 2003) or placebo responders from the pretreatment period (included washout period) were excluded (Mortimer et al., 2004; Sechter et al., 2002). Patients with a documented failure of previous treatment were involved in the study comparing olanzapine and clozapine (Naber et al., 2005), and special conditions had to be fulfilled in two studies with first-episode patients (Lieberman et al., 2003; Schooler et al., 2005). In one publication, the pooled analysis from two studies involving patients with acute relapses was reported (Kasper et al., 2003).

A high attrition rate is a typical problem for long-term studies in schizophrenia. High dropout rates decrease the power of the analysis. The reasons for discontinuation can be directly related to outcome measures, and a common statistical method LOCF (Last Observation Carried Forward), which involves including missing data in the analysis, may distort results and their interpretations (Mallinckrodt et al, 2003). The rates of discontinuation in the reviewed studies were in general high. The lowest rates were found in two studies with first-episode patients: In the study comparing clozapine and chlorpromazine, the discontinuation rates were 15% vs. 22.5% (Lieberman et al., 2003), and in the second study, the rates were 42% for risperidone and 36.5% for hal-

operidol (Schooler et al., 2003). In all other studies, the attrition rates were more than 50% at least in one arm. In the CATIE (Lieberman et al., 2005) study comparing six drugs, the discontinuation rates (the primary outcome measure) even ranged from 64% (olanzapine) to 82% (quetiapine). Although double-blind, randomized controlled studies are the gold standard for clinical research, these figures may raise many questions about the value of the results per se.

The trend to better effectiveness of SGAs can be seen from comparisons of SGAs to conventional antipsychotics in the studies reviewed here. Haloperidol, chlorpromazine, and perphenazine were used for comparisons. Totals of 77% and 85% of patients on aripiprazole and 73% and 79% of patients on haloperidol "maintained response", defined as a reduction of ≥ 20% or ≤ 30% in the PANSS score (Kasper et al., 2003); relapse occurred in 42.1% in the risperidone group vs. 54.7% in the haloperidol group (Schooler et al., 2003); 12.7% of patients in the olanzapine group and 17.6% of patients on haloperidol discontinued from the study because of a lack of efficacy or worsening of symptoms (Rosenheck et al., 2003); 88% of patients on risperidone and 73% of patients on haloperidol remained on therapy "without psychotic exacerbation" (Marder et al., 2003); the "proportion of time in remission" was longer for patients on clozapine vs. chlorpromazine (odds ratio 1.73) (Lieberman et al., 2003); and in comparison to perphenazine the "duration of successful treatment" was significantly longer for olanzapine (hazard ratio 0.73; $p = 0.013$) but not for other SGAs in the CATIE study (Lieberman et al., 2005).

4.4. Conclusions

The differences in design, patient populations, primary outcome criteria, instruments used for evaluation, and dosage of study drugs make attempts to compare the results across studies difficult. It is not possible to generalize the results on relapse prevention from the studies reviewed because the relapse rate was declared as the primary outcome in only two studies (Marder et al., 2003; Schooler et al., 2005), and in most of the studies, the relapse rate (with very different definitions) could only be inferred from other outcome measures. High rates of dropouts are also a factor that lessens the value of the results. It seems to be questionable whether studies with a double-blind, randomized design, although the gold standard in evidence-based medicine, could answer questions about SGA effectiveness for the kind of complex problem that relapse prevention in schizophrenia is. Additional important

data about relapse prevention are available from the results of open-label prospective studies (e.g. Dossenbach et al., 2005; Fleischhacker et al., 2003) and may help to create a more realistic picture about the effectiveness of SGAs in long-term treatment of schizophrenia. Because "in clinical medicine we are dealing with complex, ever changing units of analysis that are people with illnesses" (Furukawa, 2004), the results from the reviewed studies should serve primarily as the navigator for clinical decisions.

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