

Clozapine: A Comparison With Other Novel Antipsychotics

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Clinical studies with clozapine have clearly demonstrated its superior efficacy over that of conventional antipsychotics in treatment-resistant schizophrenic patients. In comparative trials with these drugs, considerably more patients respond to treatment with clozapine than to conventional antipsychotic medication. Recently, new antipsychotics, such as olanzapine, quetiapine, risperidone, sertindole, and zotepine, have been introduced, but extensive data on their effects in treatment-resistant patients are not yet available. Published studies have drawn criticism in terms of inappropriate titration schedules, nonequivalent dosing between treatment groups, short treatment duration, and inadequate sample sizes. Further research will be needed to determine whether novel antipsychotics may substitute for clozapine in the future or whether clozapine will retain its unique role in the management of patients suffering from difficult-to-treat schizophrenic disorders.

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Following the introduction of chlorpromazine in the early 1950s, specific pharmacologic treatment became available for patients with schizophrenia. Treatment was far more effective than existing therapies against the positive symptoms of the condition, and the associated sedative effects were welcomed. Forty years later, the demands made on current antipsychotic medication include superior efficacy against the positive, negative, and affective symptoms of the disease; fewer extrapyramidal side effects (EPS); improvement in cognitive function; improved quality of life; reduction in suicidality; pharmacoeconomic advantages; and improved psychosocial reintegration. These demands have been at least partially fulfilled by the development of clozapine, a so-called atypical antipsychotic.¹⁻¹¹ While clozapine is associated with a much reduced propensity of inducing EPS,^{12,13} reports of other adverse effects, particularly neutropenia and agranulocytosis, are cause for concern.^{14,15} Regulatory restrictions limit the practical use of the drug to patients who fail to respond to conventional antipsychotic therapy and those with intolerable side effects. Usually, these are the most severely ill patients. In a landmark clinical study of treatment-resistant schizophrenia, the superior efficacy of

clozapine was clearly demonstrated over chlorpromazine, a conventional antipsychotic.¹⁶

The pharmaceutical industry has recently conducted a considerable amount of research in this area with the objective of developing other novel antipsychotics that share the efficacy of clozapine without inducing hematologic side effects. Over the past 6 to 7 years, several new antipsychotics have entered clinical trials including risperidone, olanzapine, quetiapine, sertindole, zotepine, and ziprasidone.¹⁷ However, only a limited number of studies have been conducted to compare these newer antipsychotics with clozapine. This review summarizes the results to date.

COMPARATIVE STUDIES OF CLOZAPINE VERSUS OTHER NOVEL ANTIPSYCHOTICS

A search of the MEDLINE database was conducted to identify any double-blind, crossover, naturalistic prospective or retrospective trials comparing treatment with clozapine and other novel antipsychotics (Table 1).

Randomized, Double-Blind Studies

In a recent randomized, double-blind study, the efficacy and safety of clozapine and risperidone were evaluated in 86 hospitalized patients with treatment-resistant schizophrenia over an 8-week period.¹⁸ Patients suffered from chronic, severe schizophrenia but did not fulfill the treatment resistance criteria used by Kane et al.¹⁶ They had previously failed to respond to, or were intolerant of, at least 2 different classes of antipsychotics given at appropriate doses for a minimum of 4 weeks.

Following a washout period of 7 days, which could be reduced to 3 days if psychotic symptoms were evident,

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Table 1. Comparative Trials of Clozapine Versus Other Novel Antipsychotics^a

Reference	Trial Design	Treatment	No. of Patients	Results
Bondolfi et al, 1998 ¹⁸	Randomized, double-blind	Clozapine vs risperidone for 8 weeks	86 patients with severe, chronic schizophrenia	Comparable improvements in total, positive, negative, and GPS subscale scores of PANSS. No significant difference in ESRS scores at endpoint. Statistically significant increase in asthenia/lassitude/increased fatigability in the clozapine group
Beuzen et al, 1998 ¹⁹	Randomized, double-blind	Clozapine vs olanzapine for 18 weeks	180 resistant schizophrenic patients	Significant improvements in PANSS total score in both treatment groups with no significant difference between the treatments
Meyer-Lindenberg et al, 1997 ²⁰	Randomized, double-blind	Clozapine vs zotepine for 6 weeks	50 patients with treatment-resistant schizophrenia	Focused on neurocognitive effects. Similar highly significant improvements in BPRS and SANS scores in both treatment groups. Significant improvements in maze tests in both treatment groups
Heinrich et al, 1994 ²¹	Randomized, double-blind	Clozapine vs risperidone, 4 mg, or risperidone, 8 mg, for 28 days	59 patients with acute schizophrenia	Similar improvements in BPRS scores and in the percentage of patients very much or much improved (CGI assessment) in all 3 treatment groups. Significantly higher incidence of hypersalivation in the clozapine group
Klieser et al, 1994 ²²	Randomized, double-blind	Clozapine vs remoxipride or haloperidol for 28 days	54 patients with acute schizophrenia without previous neuroleptic treatment	Similar improvements in BPRS score in all 3 treatment groups. Clozapine treatment resulted in significantly fewer EPS than remoxipride or haloperidol treatment (Simpson-Angus scores)
Flynn et al, 1998 ²³	Open	Clozapine vs risperidone for at least 4 weeks	86 patients with treatment-resistant schizophrenia	Significantly more improvement in GAF, CGI, PANSS total and positive subscale scores in the clozapine group than in the risperidone group. Significantly more patients in the risperidone group received sedative/hypnotics or antiparkinsonian agents than in the clozapine group
Miller et al, 1998 ²⁴	Single-blind (observer)	Clozapine vs risperidone or a conventional antipsychotic for at least 3 months	106 patients	Significantly lower total score on the Simpson-Angus scale for EPS for the clozapine group compared with the conventional antipsychotic group with no significant difference between the risperidone and conventional antipsychotic group. Significantly higher incidence of hypersalivation with clozapine than with risperidone or conventional antipsychotics
Fogelson et al, 1997 ²⁵	Open, crossover	Clozapine followed by sertindole or risperidone	7 patients with chronic psychosis	No significant differences in treatment efficacy between clozapine, sertindole, and risperidone. EPS ratings lower for clozapine and sertindole compared with risperidone
Daniel et al, 1996 ²⁶	Open	Clozapine vs risperidone for 6 weeks	20 patients with chronic schizophrenia or schizoaffective disorder	Clozapine and risperidone were equally effective. Patients required more bupropion for motor effects and complained of more insomnia in the risperidone group while those in the clozapine group complained of more sedation and had a significantly higher body weight at the end of the trial
Still et al, 1996 ²⁷	Open	Clozapine-treated patients switched to 12 weeks of risperidone	10 patients with treatment-resistant schizophrenia	None of the patients improved after switching to risperidone and 5 withdrew due to exacerbation of psychotic symptoms or intolerable side effects

^aAbbreviations: BPRS = Brief Psychiatric Rating Scale, CGI = Clinical Global Impression, EPS = extrapyramidal side effects, ESRS = Extrapyramidal Symptom Rating Scale, GAF = Global Assessment of Function, GPS = General Psychopathology Subscale, PANSS = Positive and Negative Syndrome Scale, SANS = Scale for the Assessment of Negative Symptoms.

patients were administered either clozapine or risperidone titrated to doses of 300 mg/day or 6 mg/day, respectively, during the first 7 days of treatment. Further dose adjustments, up to 600 mg/day of clozapine or 12 mg/day of risperidone, were made on days 14, 28, and 42. The mean maintenance clozapine dose remained below 300 mg/day over the course of the study, which is consistent with current European practice.²⁸ Consequently, only 25% of

the responders had plasma clozapine levels in excess of 350 ng/mL, the minimum level suggested in the United States to produce optimal clinical benefit,²⁹ although this recommendation is still under debate.^{30,31}

Results indicated comparable improvements in the Positive and Negative Syndrome Scale (PANSS) total score and positive, negative, and general psychopathology subscale scores in both treatment groups. Responder rates

(defined as a 20% decrease in PANSS total score) were approximately 65% in both groups, i.e., markedly higher than the rates observed by Kane et al.¹⁶

Although EPS incidence rates were not reported in this study, no significant differences were evident in mean total Extrapyramidal Symptom Rating Scale scores or the various cluster scores. Only 3 patients from each group required antiparkinsonian medication. The only statistically significant difference between the treatment groups in non-EPS-related side effects was an increased incidence of asthenia/lassitude/increased fatigability in the clozapine group ($p < .05$).

This trial has been criticized on various grounds: (1) the authors themselves acknowledge that the sample size was small; (2) the rapid titration of clozapine was felt to compromise the benefit-risk ratio of the drug; (3) the use of a lower dose of clozapine, which is also extensively discussed in the article; (4) there was a failure to differentiate between treatment nonresponders and patients intolerant to previous treatment (one would clearly expect the latter group to do better when receiving either clozapine or risperidone; future studies will need to analyze these 2 groups separately); (5) the patients did not fulfill the strict nonresponse criteria defined by Kane et al.¹⁶ This final point further emphasizes that the results obtained by Bondolfi et al.¹⁸ cannot easily be compared with those generated by Kane et al.¹⁶ However, the definition used by the Swiss group reflects common treatment practice and as such has value in contributing information about the usefulness of the 2 drugs in these specific circumstances. Leaving aside the question of the relative efficacy of these 2 compounds, it is encouraging to find such high response rates in a chronic, difficult-to-treat group of patients.

The results of a randomized, double-blind study comparing treatment with clozapine and olanzapine were recently reported.¹⁹ One hundred eighty treatment-resistant schizophrenic patients were enrolled in this trial with the aim of establishing the "noninferiority" of olanzapine. Again, the criteria for defining treatment resistance were not as stringent as those proposed earlier by Kane et al.¹⁶

Both treatments were reported to have similar efficacy with no significant differences evident between the treatment groups in the mean change in PANSS total score using a last-observation-carried-forward (LOCF) approach. As approximately 40% of the patients from both treatment groups withdrew from the study, the suitability of adopting an intent-to-treat analysis with LOCF must be discussed. From the limited details of the study currently available, other potential advantages or disadvantages of the trial design cannot be determined at this point in time.

Meyer-Lindenberg et al.²⁰ conducted a double-blind, randomized trial primarily to assess the effect of clozapine and zotepine on cognitive function. Fifty patients with schizophrenia were assigned to 6 weeks' treatment with

clozapine or zotepine; however, only 26 patients who were matched at baseline for age, Brief Psychiatric Rating Scale (BPRS) scores, and Scale for the Assessment of Negative Symptoms (SANS) scores were analyzed. Both treatments significantly improved BPRS and SANS scores and performance in maze tests with no significant intergroup differences. The failure to identify a significant difference between the 2 treatment groups may be the result of the trial having insufficient power to show a difference because of the small number of patients. Furthermore, the trial was designed to compare cognition (assessed using experimental methodology) and not efficacy.

The double-blind, randomized study of Heinrich et al.²¹ compared 28 days' treatment with 4 mg of risperidone ($N = 20$), 8 mg of risperidone ($N = 19$), or 400 mg of clozapine ($N = 20$) daily in 59 patients with acute schizophrenia. Comparable improvements in BPRS scores were evident in all 3 treatment groups, and approximately half of the patients were very much or much improved on the Clinical Global Impression (CGI) scale (again, in all 3 groups). No significant differences were observed in EPS ratings when using the Simpson-Angus rating scale scores except for a higher incidence of hypersalivation in clozapine-treated patients. In terms of a general perception of tolerance, using a global rating scale, 4 mg of risperidone was tolerated better than 8 mg of risperidone, which had the same tolerance level as 400 mg of clozapine. No significant difference was found in the incidence of adverse events.

A number of flaws are apparent in the study design: (1) the sample size was small, (2) the titration period was only 1 week, (3) the titration schedule was not adjusted in line with the observed clinical response or evident toxicity, and (4) the duration of treatment with the maintenance dose was only 3 weeks. Not surprisingly, a large proportion of the patients withdrew from this trial: 45%, 68%, and 30% of the patients from the risperidone, 4 mg; risperidone, 8 mg; and clozapine, 400 mg, treatment groups, respectively. The conclusions of this trial should therefore be interpreted with due caution.

Clozapine treatment has also been compared with another novel antipsychotic treatment, remoxipride, in a double-blind study of 54 patients with schizophrenia.²² Remoxipride has since been withdrawn as it induced aplastic anemia.³² Clozapine, 350 mg/day, was compared with remoxipride, 375 mg/day, and haloperidol, 16 mg/day, in this short trial of only 28 days' duration (which also included a titration period). An improvement of approximately 30% in BPRS scores occurred in all 3 groups, and a significantly lower incidence of EPS was found with clozapine treatment compared with either remoxipride or haloperidol treatment ($p < .05$). These significant differences were evident despite the small sample size. Many of the criticisms leveled at the other trial from this group²¹ also apply to this study.

Open Studies

A limited number of open studies have also compared clozapine with other novel antipsychotics.

In a recent trial comparing clozapine (mean dose = 420 mg/day) with risperidone (mean dose = 7.75 mg/day), Flynn et al.²³ administered clozapine (N = 57) or risperidone (N = 29) to treatment-resistant patients for at least 4 weeks, with a mean treatment duration of 12 weeks. PANSS total and positive subscale scores were significantly improved in the clozapine group compared with the risperidone group ($p < .05$), and 33% of the patients receiving clozapine were assessed as being very much or much improved on CGI scores in comparison with 14% of the risperidone group. In addition, significantly fewer patients in the clozapine treatment group received either sedatives/hypnotics ($p = .0004$) or antiparkinsonian drugs ($p = .003$). These results suggest better efficacy for clozapine than risperidone in this population; however, the study was of open design and the sample size was small, which limits the conclusions that can be drawn from the trial.

Miller et al.²⁴ also compared clozapine (N = 41) with risperidone (N = 23), as well as with conventional antipsychotic therapy (N = 42). This study was designed to compare the propensity of the trial medication to induce EPS in real-life treatment conditions. Patients who had received stable treatment for at least 3 months with clozapine, risperidone, or conventional antipsychotics were treated with the same antipsychotic at a stable oral dose for a further 3 months after which the point prevalence of EPS was determined (by an observer who was blind to the patients' treatment). The total score on the Simpson-Angus scale at endpoint was significantly lower for the clozapine group than for those taking conventional antipsychotics ($p < .05$).

Interestingly, although rates of EPS were smaller with risperidone than with conventional antipsychotics, patients who developed EPS while receiving risperidone had significantly higher rating scale scores than those developing EPS with traditional antipsychotics. The only item with a higher incidence in the clozapine treatment group was hypersalivation; this was reported significantly more frequently with clozapine than with risperidone or conventional antipsychotics ($p < .05$). Despite the similar incidence of EPS with risperidone and conventional antipsychotics on the Simpson-Angus scale, on the subjective EPS scale there was a statistically significant difference in the total score in favor of conventional antipsychotics over risperidone ($p < .05$). Clozapine had a statistically significantly lower score compared with risperidone ($p < .05$).

In a small, crossover pilot study comparing the side effect profiles of clozapine and risperidone, Daniel et al.²⁶ found that clozapine (mean dose = 375 mg/day) and risperidone (mean dose = 6.1 mg/day) were equally effective after a 6-week stable dose period. However, 7 patients required benztropine for treatment of EPS while receiving

risperidone treatment, whereas no patients receiving clozapine did, and significantly more patients complained of insomnia while receiving risperidone ($p < .05$). While receiving clozapine treatment, patients showed significantly more sedation ($p < .05$) and a higher body weight at the end of treatment ($p < .005$). Nevertheless, these results require careful interpretation as only 17 patients completed the trial and the crossover design introduces possible time and carryover effects.

In pilot studies conducted by Fogelson et al.²⁵ and Still et al.,²⁷ patients were switched from clozapine to sertindole or risperidone²⁵ or to risperidone.²⁷ Fogelson et al.²⁵ found no significant difference in efficacy between the 3 treatments in 7 patients. Still et al.²⁷ found that none of 10 patients with a suboptimal response to clozapine or intolerance to clozapine-induced side effects improved after switching to risperidone and 5 of the patients withdrew due to exacerbation of psychotic symptoms or intolerable side effects. The results of both of these studies are difficult to evaluate because of the very small number of patients involved and the crossover design. However, Lacey et al.³³ also reported that 4 of 5 patients relapsed when switched from clozapine to risperidone.

CONCLUSIONS

Although a number of studies have compared the efficacy and tolerability of clozapine with those of newer novel antipsychotics in treatment-resistant schizophrenic patients, most have problems associated with design or sample size. Patient numbers are generally too small to have sufficient power to identify treatment differences. Frequently, the titration procedure and period and the final doses are not those recommended for the drugs in question, and patients with varying treatment responsiveness have been included, making intertrial comparisons difficult.

Conducting double-blind trials with clozapine will always pose logistical difficulties. However, the mandatory requirement for weekly white blood cell counts and the subsequent blinded evaluation, although problematic, can be resolved.

While results from a single trial may be used to claim that any one drug is efficacious in treatment-resistant schizophrenia, confirmatory results from additional studies are awaited for all of the newer antipsychotics. To date, clozapine alone has demonstrated efficacy in independent trials in this population.

For olanzapine, contradictory results have recently been reported.^{19,34} While Beuzen et al.¹⁹ found equal and good efficacy for olanzapine and clozapine, Conley et al.,³⁴ adopting essentially the same entry criteria as used in the landmark study of Kane et al.,¹⁶ found no difference in efficacy between olanzapine and chlorpromazine in the treatment of psychotic symptoms in patients with treatment-resistant schizophrenia. Both drugs led to only marginal

improvement. Indeed, 11 (52%) of 21 patients who failed to respond to olanzapine therapy have subsequently shown at least a 20% improvement following clozapine administration.³⁴

In conclusion, further large, long-term, randomized, double-blind, controlled comparative trials in clearly defined homogeneous patient populations are required before other novel antipsychotics can be recommended instead of clozapine for the treatment-resistant patient. Until proven otherwise, clozapine remains the treatment of first-choice for patients suffering from treatment-resistant schizophrenia.

Drug names: benzotropine (Cogentin and others), chlorpromazine (Thorazine and others), clozapine (Clozaril, Leponex), haloperidol (Haldol and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal).

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