Abstract

Clozapine (Clozaril) represents the first major advance in the pharmacological treatment of schizophrenia since the introduction of antipsychotics into clinical practice in the 1950s. Studies consistently support its efficacy for reducing positive symptoms in acutely psychotic patients and in treatment-resistant patients, for preventing positive symptom exacerbations as a maintenance treatment, and for reducing symptoms of hostility and violence. There is evidence to suggest that clozapine may improve social and occupational functioning and quality of life and may reduce affective symptoms, hospitalizations, secondary negative symptoms, and tardive dyskinesia. Its most significant side effects include agranulocytosis, seizures, weight gain, hypotension and tachycardia, sedation, and perhaps rebound psychosis (with abrupt discontinuation of medication).


Clozapine (Clozaril) represents the first major advance in the pharmacological treatment of schizophrenia since the introduction of antipsychotics into clinical practice in the 1950s. The introduction of clozapine and further research regarding its novel clinical effects have stimulated renewed interest in drug development and fostered several hypotheses regarding ways in which the efficacy or adverse effects profile of antipsychotic drugs might be improved.

First manufactured in 1959, clozapine is a dibenzodiazepine derivative with unique preclinical and clinical characteristics. In preclinical studies, clozapine, like other antipsychotic drugs, blocks conditioned avoidance behaviors, a measure that is considered predictive of antipsychotic activity (Fitton and Heel 1990). However, unlike other antipsychotic drugs, clozapine does not cause catalepsy, block apomorphine- or amphetamine-induced stereotyped behaviors, elevate serum prolactin, or cause dopamine receptor hypersensitivity in laboratory animals (Fitton and Heel 1990). Clozapine is further distinguished from other antipsychotic drugs by its relatively higher affinity for D1 than for D2 dopaminergic receptors, its higher affinity for 5-HT2a serotonergic than for D2 dopaminergic receptors, and its strong affinity for the D4 dopaminergic receptor (Baldessarini and Frankenburg 1991; Jann 1991; Meltzer 1993). Clozapine is also highly anticholinergic and has significant alpha1 and alpha2 antiadrenergic properties (Baldessarini and Frankenburg 1991; Jann 1991). In clinical studies, clozapine has been shown to have differential clinical efficacy for treatment-resistant schizophrenia patients and to be associated with a low incidence of extrapyramidal side effects (EPS) (Kane et al. 1988). The combination of these preclinical and clinical characteristics has led clozapine to be termed an "atypical antipsychotic" (Kane et al. 1988).

This review addresses the following questions:

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1. What is the efficacy (vs. placebo and/or conventional antipsychotics) of clozapine during acute symptom episodes for reduction of positive symptoms, negative/deficit symptoms (i.e., primary, enduring negative symptoms), and other outcomes?

2. What is the efficacy (vs. placebo and/or conventional antipsychotics) of clozapine during maintenance treatment for reduction of positive symptoms, negative/deficit symptoms, and other outcomes?

3. Is clozapine efficacious for schizophrenic patients who fail to respond to conventional antipsychotics?

4. What are the side effects and risks associated with clozapine?

Methods

Computerized searches of MEDLINE, MEDLARS, and PSYCLIT data bases were conducted back to 1966. In addition, the references in articles obtained from the computerized searches were checked to ensure that relevant articles not otherwise identified were included. Conference abstracts, book chapters, and unpublished data are not included in this review.

The inclusion and exclusion criteria used to select studies vary for the different review questions, reflecting the different levels of progress in the investigation of different outcome measures, and the different levels of feasibility in the conduct of methodologically rigorous studies for each outcome. The clinical efficacy of clozapine for two outcomes, positive and negative symptoms, in acutely psychotic patients and in treatment-resistant schizophrenia patients has been most extensively studied.

Therefore, the selection criteria for primary articles addressing these two outcomes in these two populations are the most rigorous: (1) the study must have been a randomized, double-blind trial; (2) the study must have used standardized, structured rating instruments to measure positive and negative symptoms; and (3) the article must be in English.

The studies examining the use of clozapine as a maintenance treatment are not as methodologically rigorous as those examining the drug’s clinical efficacy in acutely psychotic or treatment-resistant patients. This is largely owing to the difficulty in conducting long-term prospective double-blind trials of maintenance treatment. Therefore, the selection criteria studies addressing this issue were expanded to include open-labeled, retrospective, and prospective followup studies that examined clozapine’s efficacy as a maintenance treatment. And because the literature evaluating clozapine’s efficacy for other outcome measures (i.e., violent behavior and affective symptoms) is not as extensive as that in other areas, the selection criteria for those studies were expanded to include open-labeled studies and case reports that use standardized, structured rating instruments (if applicable), in addition to double-blind studies. All articles and letters that provide primary information on clozapine’s side effects and are written in English were included. The rationale for using such broad criteria is the inherent nature of side effects (i.e., they may be rare in occurrence), which means that management strategies for treating serious or life-threatening side effects often cannot be evaluated in a methodologically rigorous manner.

Findings

What Is the Efficacy (vs. Placebo and/or Conventional Antipsychotics) of Clozapine During Acute Symptom Episodes for Reduction of Positive Symptoms, Negative/Deficit Symptoms, and Other Outcomes? Nine studies of the efficacy of clozapine for acutely psychotic patients met the review criteria and are summarized in table 1. Most of these studies found clozapine to be equally or more effective than traditional neuroleptics (Ekblom and Haggstrom 1974; Gerlach et al. 1974; Singer and Law 1974; Chiu et al. 1976; Guirgis et al. 1977; Gelenberg and Doller 1979; Shopsin et al. 1979; Claghorn et al. 1987). Only the study by Fischer-Cornelissen and Ferner (1976) failed to find clozapine to be at least as effective as traditional neuroleptics. Specifically, these authors report trifluoperazine to be more effective than clozapine but note that this may have been related to methodological problems surrounding the dosage schedule for clozapine. The uniformity of these findings suggests that clozapine is at least as effective as traditional neuroleptics for the treatment of acutely ill schizophrenic patients. However, these studies are characterized by small sample sizes or by the use of low dosages of either clozapine or chlorpromazine. These methodological limitations preclude a definitive conclusion that clozapine is more effective than traditional neuroleptics for acutely ill schizophrenic patients, and leave open the highly unlikely possibility that clozapine is less effective.
<table>
<thead>
<tr>
<th>Study</th>
<th>Characteristics: design, location, duration, sample size</th>
<th>Comparison treatments</th>
<th>Outcomes results</th>
<th>Positive symptoms</th>
<th>Negative symptoms</th>
<th>Side effects</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ekblom and Haggstrom (1974)</td>
<td>Double-blind, parallel groups; inpatient; 40 days; n = 41</td>
<td>Chlorpromazine (CPZ)</td>
<td>Not significant (NS)</td>
<td>Clozapine (CLZ) &gt; CPZ on BPRS emotional withdrawal</td>
<td>No extrapyramidal side effects (EPS) in either group</td>
<td>Not assessed (NA)</td>
<td></td>
</tr>
<tr>
<td>Gerlach et al. (1974)</td>
<td>Double-blind, cross-over; inpatient; 8 weeks; n = 20</td>
<td>Haloperidol (HDL)</td>
<td>CLZ = HDL for BPRS psychotic symptoms; CLZ &gt; HDL for BPRS conceptual disorganization</td>
<td>CLZ = HDL for BPRS anergia</td>
<td>CLZ &lt; HDL for EPS</td>
<td>CLZ &gt; HDL for BPRS anxiety</td>
<td></td>
</tr>
<tr>
<td>Singer and Law (1974)</td>
<td>Double-blind, parallel groups; inpatient; 40 days; n = 38</td>
<td>CPZ</td>
<td>NS</td>
<td>NS</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Chiu et al. (1976)</td>
<td>Double-blind, parallel groups; inpatient; 6 weeks; n = 64</td>
<td>CPZ</td>
<td>NS</td>
<td>NS</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Fischer-Cornelissen and Femer (1976)</td>
<td>Double-blind, parallel groups; inpatient (multicenter); 7 weeks; n = 723</td>
<td>CPZ, HDL, trifluoperazine, clopenthixol</td>
<td>CLZ &gt; HDL</td>
<td>CLZ &gt; HDL</td>
<td>NS</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Guirguis et al. (1977)</td>
<td>Double-blind, parallel groups; inpatient; 7 weeks; n = 50</td>
<td>CPZ</td>
<td>NS</td>
<td>CLZ &gt; CPZ on BPRS anergia</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Gelenberg and Dolier (1979)</td>
<td>Double-blind, parallel groups; inpatient; 4-8 weeks; n = 15</td>
<td>CPZ</td>
<td>CLZ &gt; CPZ on BPRS thought disorder</td>
<td>CLZ &gt; CPZ on BPRS anergia</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Shopsin et al. (1979)</td>
<td>Double-blind, parallel groups; inpatient; 5 weeks; n = 31</td>
<td>CPZ, placebo</td>
<td>NS</td>
<td>NS</td>
<td>NA</td>
<td>CLZ &gt; CPZ on BPRS depression</td>
<td></td>
</tr>
<tr>
<td>Claghorn et al. (1987)</td>
<td>Double-blind, parallel groups; inpatient (multicenter); 28-56 days; n = 151</td>
<td>CPZ</td>
<td>CLZ &gt; CPZ on BPRS thought disorder</td>
<td>CLZ &gt; CPZ on BPRS anergia</td>
<td>CLZ &lt; CPZ for EPS</td>
<td>CLZ &gt; CPZ on BPRS hostility/suspiciousness</td>
<td></td>
</tr>
</tbody>
</table>

Note.—BPRS = Brief Psychiatric Rating Scale (Overall and Gorham 1962).
None of the studies used specific assessments of negative symptoms, and there was no attempt to differentiate the effect of clozapine on deficit versus secondary negative symptoms. Therefore, definitive statements about clozapine's efficacy for negative symptoms in acutely psychotic patients are not possible.

Clozapine was observed to be effective in reducing symptoms of irritability, hostility, and suspiciousness (Chiu et al. 1976; Gelenberg and Doller 1979; Claghorn et al. 1987) and of anxiety and depression (Gerlach et al. 1974; Gelenberg and Doller 1979; Shopsin et al. 1979; Claghorn et al. 1987). However, none of the studies examined how clozapine's sedative actions or its decreased likelihood of inducing EPS relate to its therapeutic effect on these outcomes. Several studies found it to have a more rapid onset of action, with differences emerging between clozapine and the comparison drug by 2 weeks (Ekblom and Haggstrom 1974; Singer and Law 1974; Claghorn et al. 1987).

What Is the Efficacy (vs. Placebo and/or Conventional Antipsychotics) of Clozapine During Maintenance Treatment for Reduction of Positive Symptoms, Negative/Deficit Symptoms, and Other Outcomes? The characteristics and findings from the 11 studies that examined clozapine as a maintenance treatment and met review criteria are shown in table 2. A number of general limitations apply to most, if not all, of these studies. Specifically, all the retrospective studies are limited by their dependence on medical records as the major source of information; their lack of objective symptom ratings, which precludes the specific evaluation of positive and negative symptom response to clozapine treatment; and their failure to use objective criteria to define treatment response. The prospective studies are characterized by small sample sizes and the lack of nonblind ratings of outcome measures. All the retrospective and prospective studies, except Leon (1979), are limited by the lack of comparison treatment groups, which makes it impossible to definitively ascribe changes in clinical status to clozapine treatment. As a result, definitive conclusions about the efficacy of clozapine as a maintenance treatment await further study.

The data from these studies thus provide the following qualified conclusions. First, most of the patients included in these studies had not experienced adequate treatment responses to traditional neuroleptics. Therefore, the results of these studies provide further support for the proposition that clozapine has differential efficacy for schizophrenia patients who do not respond to traditional neuroleptics.

Second, the studies provide conflicting data on the efficacy of clozapine for negative symptoms. Two studies report a positive effect; however, one used a proxy measure composed of mainly depressive symptoms (Meltzer 1992), and the other found negative symptom change related to change in positive and extrapyramidal symptoms (Lieberman et al. 1994). The latter finding is similar to observations from uncontrolled short-term treatment studies (Tandon et al. 1993; Miller et al. 1994). Thus, the data suggest that clozapine's effect on negative symptoms may be limited. None of the studies that examined this effect differentiated deficit from secondary negative symptoms.

Third, clozapine treatment appears to be effective in preventing exacerbations of psychotic symptoms and is associated with decreased rates of hospitalization (Leon 1979; Meltzer et al. 1990; Breier et al. 1993). However, it is unclear if this advantage exists in patients who are not treatment resistant, nor is it known to what extent the weekly monitoring required for clozapine treatment may be related to the decrease in hospitalizations that occurs with treatment.

Fourth, long-term clozapine treatment is associated with improved social and occupational functioning and quality of life. Fifth, clozapine treatment is associated with a significant decrease in suicidal behavior (Meltzer and Okayli 1995). Sixth, the major reasons for discontinuing clozapine treatment are lack of adequate treatment response, noncompliance, and severe side effects.

Is Clozapine Efficacious for Schizophrenia Patients Who Fail to Respond to Conventional Antipsychotics? Selected characteristics and study samples of the three studies that examined the efficacy of clozapine in treatment-resistant schizophrenia patients and met review criteria are presented in table 3. Two studies examined the efficacy of clozapine in hospitalized treatment-resistant patients (Kane et al. 1988; Pickar et al. 1992), and one study examined it in treatment-resistant outpatients (Breier et al. 1994). These studies, primarily Kane et al. (1988) and Breier et al. (1994), provide strong
Table 2. Efficacy of clozapine for maintenance treatment

<table>
<thead>
<tr>
<th>Study</th>
<th>Characteristics: design, location, duration, sample size</th>
<th>Comparison treatment</th>
<th>Positive symptoms</th>
<th>Negative symptoms</th>
<th>Global</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leon (1979)</td>
<td>Retrospective chart review; location not specified; 3–4 years; n = 31–37</td>
<td>Chlorpromazine (CPZ)</td>
<td>Clozapine (CLZ) &gt; CPZ</td>
<td>Not assessed (NA)</td>
<td>NA</td>
<td>CLZ &gt; CPZ for hospitalization reduction</td>
</tr>
<tr>
<td>Juul-Poulsen et al. (1985)</td>
<td>Retrospective chart review; inpatient; up to 12 years; n = 216</td>
<td>Prior treatment with conventional antipsychotics</td>
<td>NA</td>
<td>NA</td>
<td>Compared with prior treatment on conventional antipsychotics: 51% better, 47% unchanged, 2% worse</td>
<td>NA</td>
</tr>
<tr>
<td>Kuha and Miettinen (1986)</td>
<td>Retrospective follow-up; inpatient and outpatient; 30 days–7 years; n = 108</td>
<td>Prior treatment with conventional antipsychotics</td>
<td>30% marked reduction; 36% modest reduction</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Lindstrom (1988)</td>
<td>Retrospective follow-up; inpatient and outpatient; mean = 44 months; n = 96</td>
<td>Prior treatment with conventional antipsychotics</td>
<td>NA</td>
<td>NA</td>
<td>43% global improvement; 38% moderate improvement</td>
<td>Employment rate increased from 3% to 38%</td>
</tr>
<tr>
<td>Leppig et al. (1989)</td>
<td>Retrospective chart review; outpatient; mean = 21 months; n = 121</td>
<td>Prior treatment with conventional antipsychotics</td>
<td>Decreased delusions and incoherence</td>
<td>Decreased anergia</td>
<td>12% complete remission; 57% markedly improved; 24% mildly improved</td>
<td>Decreased depression</td>
</tr>
<tr>
<td>Mattes (1989)</td>
<td>Case reports, open trial; inpatient and outpatient; variable followup; n = 14</td>
<td>Prior treatment with conventional antipsychotics</td>
<td>Decreased BPRS psychosis</td>
<td>Decreased BPRS emotional withdrawal</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Meltzer et al. (1990); Meltzer (1992)</td>
<td>Prospective open trial; inpatient; 6 months; n = 38</td>
<td>Prior treatment with conventional antipsychotics</td>
<td>Decreased BPRS psychosis</td>
<td>Decreased BPRS anergia</td>
<td>NA</td>
<td>Improved quality of life; enhanced employment; 83% decrease in hospitalization</td>
</tr>
<tr>
<td>Davies et al. (1991)</td>
<td>Prospective open trial; inpatient and outpatient; 1 year; n = 24</td>
<td>Prior treatment with conventional antipsychotics</td>
<td>NA</td>
<td>NA</td>
<td>Overall symptom reduction (type not specified)</td>
<td>NA</td>
</tr>
</tbody>
</table>
support for the proposition that clozapine exhibits differential efficacy for treatment-resistant schizophrenia patients, especially inpatients. The relatively small sample in the Breier et al. (1994) study precludes definitive conclusions on this score, but the study’s results, when combined with the results from the maintenance studies, provide strong presumptive evidence.

Clozapine was found to be effective for both positive and negative symptoms. Its effect on negative symptoms is restricted to secondary negative symptoms, and this effect is related to its enhanced efficacy for positive symptoms and the decreased incidence of EPS. In the only study that examined clozapine’s effect on deficit symptoms, Breier et al. (1994) report no effect.

Both Kane et al. (1988) and Breier et al. (1994) found clozapine to be effective for reducing symptoms of hostility but not of anxiety/depression. The findings of clozapine’s efficacy for hostility symptoms are similar to the findings from the studies examining the effect of clozapine in acutely psychotic patients. Kane et al. (1988) note that clozapine exhibits its differential efficacy by the first week of treatment. Breier et al. (1994) do not report any time-of-onset data.

What Are the Side Effects and Risks Associated With Clozapine?
Clozapine treatment is associated with a broad range of side effects, yet it offers the advantage of lower rates of EPS than those observed with conventional antipsychotics. The most serious of clozapine’s side effects is agranulocytosis. Other important side effects include weight gain, sedation, constipation, and orthostatic hypotension. However, the most severe side effect is the risk of agranulocytosis, which requires regular blood count monitoring.

Table 2. Efficacy of clozapine for maintenance treatment—Continued

<table>
<thead>
<tr>
<th>Study</th>
<th>Comparison treatment</th>
<th>Positive symptoms</th>
<th>Negative symptoms</th>
<th>Global</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breier et al. (1993)</td>
<td>Prospective open trial; outpatient; 1 year; n = 35</td>
<td>Prior treatment improved on clozapine</td>
<td>No significant improvement</td>
<td>NA</td>
<td>Decreased hospitalization; improved social and occupational function</td>
</tr>
<tr>
<td>Lieberman et al. (1994)</td>
<td>Prospective open trial; inpatient; 1 year; n = 84</td>
<td>Prior treatment with conventional antipsychotics</td>
<td>Decrease in BPRS thought disorder</td>
<td>50% response rate</td>
<td>NA</td>
</tr>
<tr>
<td>Meltzer and Okuyi (1995)</td>
<td>Prospective open trial; inpatient; 6 months; n = 42</td>
<td>Prior treatment with conventional antipsychotics</td>
<td>Decrease in BPRS thought disorder</td>
<td>NA</td>
<td>Decreased suicidality, hopelessness, and depression</td>
</tr>
</tbody>
</table>

Note—BPRS = Brief Psychiatric Rating Scale (Overall and Gorham, 1962); SANS = Scale for the Assessment of Negative Symptoms (Andreasen, 1984).
Table 3. Efficacy of clozapine for treatment-resistant patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Characteristics: design, location, duration, sample size</th>
<th>Comparison treatment</th>
<th>Positive outcomes</th>
<th>Negative symptoms</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kane et al. (1988)</td>
<td>Double-blind, parallel; inpatient (multi-center); 6 weeks; n = 268</td>
<td>Chlorpromazine (CPZ)</td>
<td>Clozapine (CLZ) &gt; CPZ on BPRS</td>
<td>CLZ &gt; CPZ on BPRS anergia; CLZ = CPZ on BPRS hostility</td>
<td>Not assessed</td>
</tr>
<tr>
<td>Pickar et al. (1992)</td>
<td>Double-blind, placebo-controlled, crossover; inpatient; variable trial duration; n = 21</td>
<td>Fluphenazine (FLU)</td>
<td>CLZ &gt; FLU on BPRS psychosis</td>
<td>CLZ &gt; FLU on BPRS anergia; CLZ = FLU on SANS</td>
<td>Not assessed</td>
</tr>
<tr>
<td>Breier et al. (1994)</td>
<td>Double-blind, parallel groups; outpatient; 10 weeks; n = 45</td>
<td>Haloperidol (HDL)</td>
<td>CLZ &gt; HDL on BPRS psychosis</td>
<td>CLZ &gt; HDL in non-deficit patients; CLZ &gt; HDL in deficit patients</td>
<td>CLZ &gt; HDL on BPRS hostility; CLZ = HDL on BPRS depression and anxiety</td>
</tr>
</tbody>
</table>

Note.—BPRS = Brief Psychiatric Rating Scale (Overall and Gorham 1962); SANS = Scale for the Assessment of Negative Symptoms (Andreasen 1984).

effects include orthostatic hypotension and tachycardia, sedation, seizures, weight gain, and rebound psychosis.
Hypotension and tachycardia. Clozapine treatment is commonly associated with orthostatic hypotension (secondary to clozapine's alpha-adrenergic antagonism; rate of occurrence: 8%–13%) and tachycardia (secondary to clozapine's anticholinergic activity; rate of occurrence: 12%–25%) (Borison and Diamond 1990; Baldessarini and Frankenburg 1991; Safferman et al. 1991; Meltzer 1993), and both are dosage dependent. Patients tend to develop tolerance to these side effects with time (Fitton and Heel 1990; Jann 1991).

Sedation. Sedation, the most common side effect (20%–50%), is probably related to clozapine's antihistaminergic and anti-alpha₁-adrenergic properties (Grohmann et al. 1989; Leppig et al. 1989; Borison and Diamond 1990; Stephens 1990; Safferman et al. 1991). Sedation occurs early in treatment, and patients typically become tolerant to it (Fitton and Heel 1990; Baldessarini and Frankenburg 1991).

Seizures. Clozapine treatment, as compared with traditional neuroleptic treatment, is associated with a relatively high risk of grand mal seizures (1%–10%) (Fitton and Heel 1990; Stephens 1990; Baldessarini and Frankenburg 1991; Devinsky et al. 1991; Leppig et al. 1989). There are also reports of myoclonic and atonic activity and/or seizures with clozapine treatment (Lemus et al. 1989; Chiles et al. 1990; Gouzoulis et al. 1991; Safferman et al. 1991; Berman et al. 1992; Szarek and Goethe 1992). The presence of myoclonic jerks may presage the development of future grand mal seizures (Berman et al. 1992). Seizure activity is a potential complication of clozapine overdoses (Jann 1991); concurrent neuroleptic treatment may increase the risk of seizures (Liukkonen et al. 1992).

Electroencephalogram changes and seizures appear to be dosage related (Simpson and Cooper 1978; Leppig et al. 1989; Fitton and Heel 1990; Haller and Binder 1990; Stephens 1990; Baker and Conley 1991; Jann 1991; Safferman et al. 1991; Meltzer 1993). Devinsky et al. (1991) conducted a retrospective chart review of 1,418 clozapine-treated patients to examine the relationship between clozapine dosage and seizures. They report the following frequency rates: clozapine dosage below 300 mg per day (1%); clozapine dosage below 600 mg per day (2.7%); and clozapine dosage above 600 mg per day (4.4%). They also note that rapid upward titration and the use of concurrent medications that lower the seizure threshold were associated with an increased likelihood of developing seizures.

Weight gain. Significant weight gain is commonly observed with clozapine treatment (13%–23%) (Leppig et al. 1989; Carson and Forbes 1990; Cohen et al. 1990; Fitton and Heel 1990; Leadbetter and Vieweg 1990; Baldessarini and Frankenburg 1991; Safferman et al. 1991; Meltzer 1993). The weight gain may be related to clozapine's serotonergic antagonist actions, since serotonin agonists have been noted to suppress appetite (Leadbetter et al. 1992). Weight gain has been associated with clinical response; patients who exhibit the greatest weight gain also exhibit the best clinical response (Leadbetter and Vieweg 1990; Lamberti 1992; Leadbetter et al. 1992).

Rebound psychosis. There have been reports of rapid deterioration and the onset of new psychotic symptoms with abrupt clozapine withdrawal (Simpson et al. 1978; Ekbloom et al. 1984; Perenyi et al. 1985; Eklund 1987; Borison et al. 1988; Stephens 1990; Alphs and Lee 1991; Safferman et al. 1991; Parsa et al. 1993). The frequency of this phenomenon is unknown, but patients with higher baseline symptom levels (Borison et al. 1988) or longer duration of clozapine treatment may be more likely to exhibit the phenomenon. Exacerbations of psychosis following clozapine withdrawal have been shown to be associated with increased tardive dyskinesia (TD) (Alphs and Lee 1991), suggesting the possibility that supersensitivity of dopaminergic receptors may underlie this phenomenon.

Other side effects. Among other side effects of clozapine are nausea, vomiting, and constipation (Baldessarini and Frankenburg 1991; Safferman et al. 1991); elevation of liver enzymes (up to 10%) (Kirkegaard and Jensen 1979; Stephens 1990; Safferman et al. 1991); hypersalivation (12%–40%) (Stephens 1990; Baldessarini and Frankenburg 1991; Safferman et al. 1991; Meltzer 1993); confusion or delirium (3%) (Schuster et al. 1977; Banki and Vojnik 1978; Grohmann et al. 1989; Fitton and Heel 1990; Stephens 1990; Baldessarini and Frankenburg 1991; Safferman et al. 1991; Meltzer 1993); incontinence, frequency/urgency, hesitancy, urinary retention, or impotence (6%) (Safferman et al. 1991; Meltzer 1993); benign hyperthermia (5%–15%) (Fitton and Heel 1990; Stephens 1990; Baldessarini and Frankenburg 1991; Meltzer 1993); and development or exacerbation of obsessive-compulsive symptoms (Baker et al. 1992; Patil 1992; Meltzer 1993). This last phenome-
non may be related to clozapine's antiserotonergic properties (Baker et al. 1992; Patel 1992). There are no known teratogenic effects of clozapine (Meltzer 1993; Waldman and Safferman 1993).

Side effects of other antipsychotics less commonly seen with clozapine. Clozapine is associated with lower rates of certain side effects than are typically observed with conventional antipsychotics. The incidence of EPS is low (4%-7%) (Casey 1989; Fitton and Heel 1990; Stephens 1990; Baldessarini and Frankenburg 1991; Safferman et al. 1991; Meltzer 1993). Clozapine is also associated with a lower risk of neuroleptic malignant syndrome (NMS) (Borison and Diamond 1990; Fitton and Heel 1990; Safferman et al. 1991; Meltzer 1993). Although clozapine has been claimed not to cause NMS, there are case reports of clozapine-induced NMS in patients receiving only clozapine treatment (Nopoulos et al. 1990; Anderson and Powers 1991; Miller et al. 1991; Coates and Escobar 1992). In contrast, there are also case reports of clozapine being successfully used in patients with previous histories of NMS (Stoudemire and Clayton 1989; Windhager et al. 1990; Burrell et al. 1991; Weller and Kornhuber 1992), suggesting that clozapine may be a viable alternative for patients who develop NMS on traditional neuroleptics.

It is unclear if clozapine can cause TD (Kane et al. 1993). Several authors claim that there are no confirmed cases of clozapine-related TD (Casey 1989; Fitton and Heel 1990; Stephens 1990; Safferman et al. 1991; Meltzer 1993), but there are several case reports of clozapine exaggeration of TD and clozapine-induced TD (de Leon et al. 1991; Jann 1991; Kane et al. 1993). If clozapine causes TD, it appears that the incidence of TD with clozapine treatment is markedly less than that with traditional neuroleptics.

There have been several case reports and studies examining the potential therapeutic effect of clozapine for TD, with some studies documenting the therapeutic value of clozapine for diminishing TD (Simpson et al. 1978; Meltzer and Luchins 1984; Small et al. 1987; Van Putten et al. 1990; Lieberman et al. 1991; Bajulaiye and Addonizio 1992; Littrell and Magill 1993; Tamminga et al. 1994); however, others have not found evidence supporting this effect (Gerlach et al. 1975; Carroll et al. 1977; Caine et al. 1979; Wirshing et al. 1990).

Discussion

The quality of the studies evaluating clozapine's clinical efficacy for positive and negative symptoms in acutely psychotic and in treatment-resistant schizophrenia patients, and as a maintenance treatment for positive and negative symptoms, varies widely within each area. Multiple double-blind studies have been conducted examining the efficacy of clozapine for the treatment of acutely ill schizophrenia patients; however, most of these studies are characterized by small sample sizes or the use of low dosages of either clozapine or the comparison drug. Only three double-blind studies have examined the efficacy of clozapine in treatment-resistant schizophrenia patients. The majority of studies examining clozapine's efficacy as a maintenance treatment are retrospective. These studies are limited by their dependence on medical records as their major source of information, their lack of objective symptom ratings, and their failure to use objective criteria to define treatment response. The prospective studies are characterized by small sample sizes and lack of nonblind ratings of outcome measures.

The general quality issue with respect to the studies examining the effect of clozapine on other outcome measures is that none of the studies are double-blind. In addition, there is a relative paucity of literature in each of the areas, especially that of clozapine's effect on cognitive impairments (not reviewed in this article).

With regard to clozapine's efficacy for the active symptoms of schizophrenia, it can be said with substantial confidence that it is (1) as effective as traditional neuroleptics for the reduction of positive symptoms in acutely psychotic patients, (2) an effective treatment for reducing psychotic symptoms in 30 to 60 percent of schizophrenia patients who fail to respond to adequate trials of traditional neuroleptics, (3) an effective maintenance treatment for positive symptoms, and (4) an effective treatment for hostility.

There is suggestive evidence that clozapine (1) improves social and occupational functioning, (2) improves patients' quality of life, (3) decreases the rate and length of hospitalizations, (4) reduces affective symptoms, (5) reduces secondary negative symptoms, and (6) reduces TD.

As to clozapine's side effect profile, there is substantial evidence that clozapine is associated with an increased risk for agranulocytosis and seizures; that it is associ-
ated with a reduced likelihood of developing EPS, NMS, and TD; and that it may cause rebound psychosis if abruptly discontinued.

**Needs for Future Research**

Several measurement issues need to be addressed in future studies. The first is assessment of negative symptoms. There has been a general lack of attention paid to differentiation of deficit from other negative symptoms. Future studies need to incorporate assessments of deficit symptoms (Kirkpatrick et al. 1989) in order to be able to evaluate the effect of clozapine on these symptoms. Second, future studies should use instruments that provide detailed evaluations of role functioning, quality of life, and family burden. Third, the evaluations of clozapine's effect on cognitive functions should be organized according to specific cognitive functions observed to be abnormal in schizophrenia patients, with detailed evaluations of each function included in the neuropsychological assessment battery.

Future investigations should focus on the following areas of substantive interest:

1. Double-blind studies to examine clozapine's efficacy (1) for negative symptoms, including whether such efficacy includes both deficit and secondary negative symptoms and, if limited to secondary negative symptoms, what the underlying mechanisms are for this beneficial effect; (2) for cognitive impairments; (3) for quality of life, social and occupational role functioning, and family burden; and (4) as a maintenance treatment, including its effect on relapse and hospitalization rates.

2. Double-blind studies to evaluate what constitutes an optimal clozapine treatment trial and who should be eligible for clozapine treatment; that is, what is the operational definition of treatment resistance?

3. Double-blind studies to evaluate pharmacological augmentation strategies for patients who do not have an adequate response to clozapine.

4. The interaction between clozapine treatment and nonpharmacological treatment interventions.

5. The effectiveness of clozapine in nonresearch settings, including evaluations of factors affecting the patient’s acceptance of or non-compliance with clozapine treatment, and factors affecting the physician's clozapine prescription practices.

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