Update on the Clinical Efficacy and Side Effects of Clozapine

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Abstract

Clozapine (CLOZ) is an atypical antipsychotic drug being used with increasing frequency throughout the world and has recently been commercially marketed in the United States. Its unique properties make it a promising but challenging drug to use in the treatment of schizophrenia. In order to use CLOZ most effectively and efficiently, clinicians must be aware of its potential benefits and risks. This report is a review and critical evaluation of current knowledge regarding the clinical efficacy and side effects of CLOZ. Although CLOZ has proven to be effective in some treatment-refractory schizophrenic patients and to produce relatively few extrapyramidal side effects compared to classical neuroleptic drugs, several issues require further investigation including what defines neuroleptic intolerance, the optimal dose range, and the appropriate duration of a CLOZ treatment trial. Similarly, studies are needed to determine what role CLOZ should have in the treatment of patients with predominantly negative symptoms and those patients who are only partially responsive to standard neuroleptics. In addition, important questions remain as to what other conditions might be indications for CLOZ, for example, schizoaffective disorder, affective psychoses, and idiopathic Parkinson's disease.

Although clozapine (CLOZ) was first synthesized in 1960, it has taken three decades to be commercially marketed in the United States. The development of CLOZ was delayed and the conditions for which it is indicated have been limited by its potential for hematologic toxicity. Despite these serious risks, the combination of the tremendous interest generated by CLOZ's novel properties and the dearth of other bona fide atypical neuroleptic compounds available for clinical use has fueled efforts to determine the extent of CLOZ's clinical utility. Consequently, the body of information on CLOZ has continued to accumulate from its initial clinical testing and use in Europe and Scandinavia through its Food and Drug Administration (FDA) approval and introduction to the commercial market in the United States. This report is intended to provide an overview of current knowledge of clinical effects of CLOZ, both therapeutic and adverse. This is a rapidly evolving area of investigation, but numerous questions remain unanswered.

Review of Efficacy

Acute Treatment Studies. Many of the acute treatment studies of CLOZ (< 12 weeks) employed an open-label design and were often uncontrolled (Matz et al. 1974; Simpson and Varga 1974; Chouinard and Annable 1976; Panteleeva et al. 1987). Conclusions to be drawn from some of these studies were also limited by a variety of methodological problems including small sample size, inappropriate dosing, inadequate duration of treatment, and differences in diagnostic criteria. The generally favorable results of these studies, including the relative lack of extrapyramidal side effects (EPS), provided an impetus to conduct double-blind studies.

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Double-Blind Studies. Four important double-blind studies were reviewed by Honigfeld et al. (1984). In these trials CLOZ was compared to chlorpromazine (CPZ) or haloperidol (HPL) in various groups of patients including the treatment refractory and neuroleptic intolerant, those with tardive dyskinesia (TD), and acute schizophrenics (Fisher–Cornelssen and Ferner 1976; Shopsin et al. 1979; Claghorn et al. 1987; Sandoz 1987). All of these studies used the Brief Psychiatric Rating Scale (BPRS; Overall and Gorham 1962) to quantify improvements in behavioral status, thus allowing more meaningful comparisons across studies. The results of these studies demonstrated that at the endpoint of each study (range = 28–56 days) CLOZ was generally superior to either HPL or CPZ on at least some of the individual BPRS items. These differences were more pronounced if the more severely ill group of patients was analyzed separately.

Other double-blind studies evaluated the efficacy of CLOZ versus standard agents in acutely ill and not necessarily refractory or intolerant schizophrenic patients (Chiu et al. 1976; Van Praag et al. 1976; Guirguis et al. 1977). These studies provided evidence that CLOZ was essentially comparable in efficacy to other agents. Gelenberg and Doller (1979) prematurely terminated their double-blind comparison of CLOZ with CPZ in acutely ill schizophrenic patients (all with histories of drug-induced EPS) due to concerns about CLOZ-induced agranulocytosis. Although their small sample size precluded an analysis for statistical significance, the results suggested that CLOZ was at least as effective as CPZ.

Efficacy in Treatment-Refractory Patients. Following the initial reports of agranulocytosis associated with CLOZ, clinical use was generally restricted. However, experience in Europe suggested that deaths associated with CLOZ-induced agranulocytosis could largely be prevented by weekly blood count monitoring (Sandoz 1987). Given CLOZ's potential value in treatment-refractory patients, coupled with its risk of producing agranulocytosis, it became clear that this compound could be marketed in the United States only if a carefully designed, well-controlled trial demonstrated statistically significant superiority over a currently available neuroleptic. Such a trial was conducted and reported by Kane et al. (1988).

Patients were eligible for this study if they met the following criteria for treatment refractoriness: (1) at least three periods of treatment in the preceding 5 years with neuroleptic agents (from at least two different chemical classes) at dosages equivalent to or greater than 1,000 mg/day of CPZ for a period of 6 weeks, each without significant symptomatic relief; and (2) no period of good functioning within the past 5 years. Subjects had to be rated at least moderately ill on the Clinical Global Impressions scale (CGI; Guy 1976) (CGI > 3) and score at least 45 on the total BPRS. In addition, item scores of at least 4 (moderate) were required on at least two of the following items: conceptual disorganization, suspiciousness, hallucinations, and unusual thought content. To confirm the lack of drug responsiveness, all patients were treated single-blind with HPL 60 mg/day for up to 6 weeks before entering the double-blind, controlled trial. Improvement criteria were defined in advance as a decrease of BPRS score by at least 20 percent and either CGI < 4 or BPRS < 36. Only 2 percent of the patients were considered responders to the HPL trial, confirming the accuracy of historically designating patients as nonresponders. Of the 319 patients initially recruited into the study, 268 were randomized to a double-blind 6-week course of either CLOZ or CPZ plus benztropine. Average mean peak doses were 600 mg/day for CLOZ and 1,200 mg/day for CPZ.

Using a priori response criteria, 30 percent of the CLOZ-treated patients were judged treatment responders compared to only 4 percent of the CPZ group. Total BPRS scores, as well as the four positive-symptom BPRS items mentioned earlier, showed CLOZ to be significantly superior to CPZ. In addition, CLOZ demonstrated superiority on BPRS items that represent negative symptoms of schizophrenia. This study demonstrated that CLOZ was clearly superior to CPZ in a well-defined group of severely ill, treatment-refractory schizophrenic patients. It also served as the pivotal study to gain FDA approval to market CLOZ in the United States. Some investigators participating in this multicenter trial have also reported results from their individual study sites elsewhere (Borison et al. 1988; Conley et al. 1988).

Followup and Long-Term Studies. Followup studies involving CLOZ are very important in answering questions about whether therapeutic gains are maintained over long periods of time and whether CLOZ is safe and well tolerated when taken over extended periods of time. Most of the followup studies of CLOZ have been retrospective in nature (Leon 1979; Povlsen et al. 1985; Kuha and Miettinen 1986; Lindstrom...
Some of these studies looked at various markers of efficacy including behavioral improvement (e.g., BPRS), ability to be discharged from the hospital, and social adjustment (e.g., Quality of Life Scale [Heinrichs et al. 1984], ability to work). While it is beyond the scope of this article to describe each of these studies in detail, we will note some of the important results.

Lindstrom (1988) reported on a long-term followup study of 96 patients (89 schizophrenic, 7 schizoaffective) treated with CLOZ for up to 13 years. The patients were designated as either treatment refractory (85%) or neuroleptic intolerant (15%). The results showed that 85 percent of all patients could be discharged from the hospital. Of those 62 patients who were still on CLOZ after 2 years, up to 39 percent were employable on at least a part-time basis. A global evaluation described 43 percent as significantly improved and 36 percent as moderately improved. Povlsen et al. (1985) reported on 216 patients who received CLOZ for up to 12 years. Of this group, 85 received CLOZ alone and 51 percent of these patients were judged to have a better therapeutic outcome compared to previous treatment with standard agents. The 131 patients who received CLOZ in combination with a typical antipsychotic fared no better than those who were treated with CLOZ alone. The overall therapeutic efficacy across all groups ranged between 30 and 50 percent. Kuha and Miettinen (1986) reported on a group of 108 schizophrenic patients treated with CLOZ for up to 7 years. Most of the patients had been designated as treatment resistant. Approximately 33 percent of the patients were reported to have a distinct favorable effect with CLOZ and 23 percent were able to be discharged from the hospital. Leon (1979) performed a comparative followup study of patients receiving either CLOZ (n = 18) or CPZ (n = 19). He reported that the CLOZ group required fewer rehospitalizations and outpatient visits.

Prospective Followup Studies. While it may be concluded from the studies cited that at least 30–40 percent of neuroleptic-refractory patients derived sustained, clinically significant, long-term benefit from CLOZ treatment, the studies did not focus on the time course of response to CLOZ. In an attempt to determine the onset of response time beyond 6 weeks in treatment-refractory patients, Meltzer et al. (1989) conducted an open-label, uncontrolled study involving 51 retrospectively defined treatment-refractory patients for up to 35 months (mean duration approximately 10 months). The results will be discussed in detail in the sections on risks and benefits. The point to be made here was that approximately 60 percent of these patients were considered to be CLOZ responders after 1 year of treatment. Response was defined as a 20 percent decrease in BPRS scores from baseline. Mattes (1989) reported results in a small group of patients who received CLOZ for up to 2 years. Of the 14 patients who started the study, 6 were still taking CLOZ after 2 years and had statistically significant improvement on BPRS scores compared with baseline ratings. Interestingly, only about 50 percent of the eventual BPRS improvement was noted after 12 weeks of treatment. Owen et al. (1989) followed a group of schizoaffective or schizophrenic patients who received ongoing open-label CLOZ treatment for up to 4 years. Of the treatment-refractory patients in this study, 50 percent had improved significantly at 12 weeks. Although the therapeutic effects were maintained for the duration of the study, there was no significant further improvement in the BPRS ratings beyond this point.

All of the followup studies had significant flaws in design and methodology. A partial list of problems in the studies just mentioned includes reliance on incomplete or inaccurate medical records; small sample size; and lack of a control group, lack of blind ratings, lack of dosage standardization, lack of a precise definition of what constitutes an adequate response to treatment, and lack of treatment standardization (e.g., differences in efforts at adjunctive nonpharmacologic treatment such as psychosocial rehabilitation or use of concomitant antipsychotic medication).

Efficacy of CLOZ in Other Disorders. CLOZ has been reported to have efficacy in patients diagnosed with schizoaffective disorder (Lindstrom et al. 1988; Owen et al. 1989). While CLOZ appears to be an effective agent for this disorder, more research is needed. Little can be said about what role CLOZ may have in the long-term treatment of patients with major depression with psychotic features or bipolar disorder, since there is insufficient literature to draw any meaningful conclusions.

CLOZ has also been successfully used for those patients who were determined to be neuroleptic intolerant because of severe EPS or tardive dyskinesia (TD) (Claghornt et al. 1987; Small et al. 1987; Lindstrom et al. 1988). These patients were not treat-
ment refractory and therefore could be expected to respond to CLOZ at least as well as they did to typical antipsychotic agents. Indeed, CLOZ is indicated for schizophrenics with neuroleptic intolerance.

Several investigators have studied CLOZ’s effects on preexisting TD (Simpson and Varga 1974; Caine et al. 1979; Gerbino et al. 1980; Small et al. 1987; Kane et al. 1988; Lieberman et al. 1989b). Although the studies were either small, uncontrolled, or just case reports (Van Putten et al. 1990) some found a therapeutic effect in reducing TD when at least moderate doses of CLOZ were given. The extent to which CLOZ suppresses TD, corrects the underlying pathophysiology, or spares the striatum of chronic D_2 dopamine (DA) blockade (thereby allowing a spontaneous remission) needs to be determined by carefully designed studies.

CLOZ has been evaluated for its effects in treating tremor or L-dopa-induced psychosis. Pakkenberg and Pakkenberg (1986) evaluated the efficacy of low-dose CLOZ in the treatment of benign essential tremor, tremor of idiopathic Parkinson’s disease (IPD), alcohol tremor, and “tremor” of multiple sclerosis. They concluded that CLOZ in doses of 75 mg or less was effective in reducing tremor in all of these disorders. Similarly, Friedman and Lannon (1990) found low-dose CLOZ to be effective in reducing tremor of IPD. Wolters et al. (1989) state that while low-dose (25–50 mg/day) CLOZ may be effective in treating L-dopa-induced psychosis in IPD, higher doses (100–250 mg) may exacerbate the parkinsonism. This stands in contrast to the case report by Friedman et al. (1987) describing the successful treatment of a patient with coexistent schizophrenia and IPD who took both Sinemet and CLOZ (300 mg/day) with good effect. There are several other case reports in which CLOZ has been used to treat tremor in IPD (Pfeiffer et al. 1990). Clearly, more work is needed to determine CLOZ’s place in these and other neurologic or neuropsychiatric disorders.

Review of Adverse Effects

Were it not for its relatively high propensity to induce agranulocytosis, CLOZ could likely be a first or second choice, rather than the last resort, in the treatment of schizophrenia and other psychotic disorders. Many of the side effects that have been observed with CLOZ could be predicted from its pharmacologic properties. Other side effects (i.e., agranulocytosis) could not have been predicted or observed until CLOZ was administered to large numbers of patients for extended periods of time.

In addition to its effects on DA neuronal systems, CLOZ exhibits actions on multiple neurotransmitters including antimuscarinic, antiserotonergic (5HT_2), antihistaminic (H_1) activity. In addition, CLOZ has a weaker affinity for D_2 DA receptors compared to classical neuroleptics (Richelson 1985). At the same time CLOZ has a level of affinity to D_1 receptors that is significantly greater than most classical neuroleptics (Anderson and Braestrup 1986). In addition, CLOZ’s affinity for D_1 relative to D_2 receptors is proportionally greater than other classical neuroleptics (Farde et al. 1989).

The incidence of side effects reported with the use of CLOZ varies widely in some cases due to differences in reporting methods, study design and duration (retrospective, prospective), dosing and titration strategies, definitions for a particular adverse reaction, frequency of monitoring for that particular side effect, and concomitant medications. Keeping this in mind, table 1 includes some of the more frequently observed side effects of CLOZ treatment in premarketing studies in the United States.

### Agranulocytosis

The most serious adverse effect of CLOZ is agranulocytosis. (Agranulocytosis is often defined as a granulocyte count

### Table 1. Frequently observed adverse reactions reported with clozapine (n = 842)

<table>
<thead>
<tr>
<th>Reaction</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drowsiness or sedation</td>
<td>39</td>
</tr>
<tr>
<td>Salivation</td>
<td>31</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>25</td>
</tr>
<tr>
<td>Dizziness</td>
<td>19</td>
</tr>
<tr>
<td>Constipation</td>
<td>14</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>11</td>
</tr>
<tr>
<td>Hypotension</td>
<td>9</td>
</tr>
<tr>
<td>Sweating</td>
<td>6</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>6</td>
</tr>
<tr>
<td>Urinary problems</td>
<td>6</td>
</tr>
<tr>
<td>Tremor</td>
<td>6</td>
</tr>
<tr>
<td>Visual disturbance</td>
<td>5</td>
</tr>
<tr>
<td>Fever</td>
<td>5</td>
</tr>
<tr>
<td>Hypertension</td>
<td>4</td>
</tr>
<tr>
<td>Weight gain</td>
<td>4</td>
</tr>
<tr>
<td>Seizures</td>
<td>3</td>
</tr>
<tr>
<td>Akathisia</td>
<td>3</td>
</tr>
<tr>
<td>Rigidity</td>
<td>3</td>
</tr>
<tr>
<td>Agranulocytosis</td>
<td>1</td>
</tr>
</tbody>
</table>

**Note.**—Not reported: acute dystonic reactions, tardive dyskinesia, menstrual dysfunction, galactorrhea. From Sandoz, Inc. 1990.

1,700 patients.
During clinical trials in Europe from 1962 to 1972, four cases of CLOZ-induced agranulocytosis were reported. This translated into a frequency of 4 in 2,900 patients or 1.38 in 1,000 (Griffith and Saameli 1975), a figure that was comparable to the agranulocytosis rates reported with the phenothiazines (1 in 1,300) (Pisciotta 1973). However, 16 cases of agranulocytosis (out of an estimated 2,500-3,200 patients) were reported in the first 6 months of 1975 in the southern and western regions of Finland (Idänpää–Keikkilä et al. 1977). Despite the uneven geographic distribution and apparently higher rate of CLOZ agranulocytosis in Finland than elsewhere, no genetic or environmental risk factors could be determined (de la Chapelle et al. 1977). These events prompted Sandoz to withdraw CLOZ from the market in some countries and limit its use in others to treatment-resistant or neuroleptic-intolerant schizophrenic patients in whom regular WBC monitoring was performed. Close hematologic monitoring significantly reduced the mortality rate.

Krupp and Barnes (1989) reviewed 185 cases of CLOZ agranulocytosis or neutropenia. The following observations were made. The greatest risk of CLOZ agranulocytosis was between 4 and 18 weeks after starting CLOZ; 77 percent of the cases occurred within the first 18 weeks of treatment. The current rate of agranulocytosis among patients treated for 6 weeks or longer is 1 percent; however, if cumulative incidence is calculated after 1 year of treatment, the rate is 1.6 percent. The mean onset of agranulocytosis was after 67 days of exposure (range = 2–1,065 days) and the ratio of female to male cases was 1:0.56. The authors concluded that mortality rate is significantly decreased in cases in which CLOZ is immediately discontinued when agranulocytosis occurs and is detected before signs of infection develop; and regular WBC monitoring is essential in preventing fatalities.

In U.S. premarketing studies before September 1989, the number of cases of agranulocytosis was 16 out of 1,743 patients. As of December 21, 1990, there was a total of 7,981 patients in the United States who had received CLOZ, including those who continued on the drug from the premarketing period. During the period from September 1989 through December 21, 1990, there were 48 additional reported cases of agranulocytosis in the United States (J. Petrie, Sandoz, personal communication, December 1990). It would not be accurate to calculate an agranulocytosis incidence rate of 48+16 of 7,981 or 0.8 percent because these patients have been on CLOZ for varying intervals and many have not yet entered or completed the full period of maximum risk for agranulocytosis. Accurate estimates of risk require a cumulative incidence that takes into account the length of exposure of those receiving the drug. The U.S. premarketing experience with CLOZ agranulocytosis is similar to that of Europe's with an estimated cumulative incidence of 2 percent after 1 year of treatment (Lieberman et al. 1988). As of December 31, 1990, there had been one death in the United States from presumed CLOZ-induced agranulocytosis (J. Schwimmer, Sandoz, personal communication, 1991). Lieberman et al. (1988) described the natural history of CLOZ agranulocytosis that developed in five patients, all of Jewish descent. This provided evidence that there might be a genetically determined, selective vulnerability to this adverse effect. Onset of agranulocytosis was usually gradual and in all cases reversible over a period of about 2 weeks. A loss of granulocyte stem cells was found in bone marrow aspirates while other cell lines were unaffected. Since these patients had been treated with numerous psychotropic medications before CLOZ and after recovery without return of agranulocytosis, it was suggested that there is no cross-reactivity between CLOZ and other drugs. In a followup study, Lieberman et al. (1990) examined the human leukocyte antigen types of patients who developed CLOZ agranulocytosis and found that the incidence of HLA–B38, DR4, DQW3 (5 of 5 patients) was significantly increased in Jewish patients who developed CLOZ agranulocytosis compared to those who did not (only 2 of 17 patients). This is an important finding because it provides evidence for genetic vulnerability to developing CLOZ agranulocytosis and may lead to more efficient methods to reduce the risk (e.g., genetic screening). However, this study needs to be replicated and expanded to other patient groups.

Guidelines and parameters for the management of a drop in the WBC have been published by the manufacturer (Sandoz 1990). Any fever or sign of infection (e.g., pharyngitis) is an immediate indication for a WBC count especially within the first 18 weeks of treatment. If the patient has a WBC count below 2,000 or a granulocyte count below 1,000, CLOZ must be discontinued. Two U.S. and nine European patients who developed agranulocytosis on CLOZ were
subsequently rechallenged with CLOZ following their hematologic recovery (Sandoz 1990). All redeveloped agranulocytosis sooner and at lower doses than in their initial exposure. Thus, patients who develop agranulocytosis should not be reexposed to CLOZ following recovery.

Although a WBC level below 3,500 is not a proven risk factor, it is suggested that patients with these low levels not receive CLOZ because of the difficulty that would be involved in the early identification of agranulocytosis. In addition, drugs that have a relatively high likelihood of causing agranulocytosis or leukopenia (e.g., carbamazepine [CBZ]) should not be coadministered with CLOZ. Other hematologic changes that have been described with CLOZ include leukocytosis (0.6%) (Lieberman et al. 1988), eosinophilia (1%), and leukopenia/neutropenia/decreased WBC (3%) (Sandoz 1990) and rarely, thrombocytopenia (Panteleeva et al. 1987).

Seizures and Other Central Nervous System (CNS) Effects. Like other antipsychotic medications, CLOZ has been found to produce electroencephalogram (EEG) changes (Koukkou et al. 1979; Small et al. 1987; Schmauss et al. 1989) that are dose related (Leppig et al. 1989) and grand mal seizures (Simpson and Cooper 1978; Pavlsen et al. 1985; Lieberman et al. 1989a; Haller and Binder 1990). Similarly, the risk of seizures is dose related: doses up to 300 mg/day, 1–2 percent risk; 300–600 mg/day, 3–4 percent; 600–900 mg/day, 5 percent (Sandoz 1990). A preexisting seizure disorder or history of head trauma places the patient at even higher risk (Povlsen et al. 1985; Haller and Binder 1990). Various guidelines have been suggested to minimize or manage this risk including obtaining an EEG before raising the dose above 600 mg/day; combining CLOZ with anticonvulsants at doses where a seizure occurred before (Haller and Binder 1990); monitoring CLOZ blood levels (Simpson and Cooper 1978); reducing the dose to 50 percent of the dose at which a seizure occurred and obtaining a neurology consult (Lieberman et al. 1989a). As a general rule it is important to look for other causes of seizures and avoid combining CLOZ with other drugs that lower the seizure threshold. Although it is sometimes necessary to give anticonvulsants along with CLOZ, the combination can significantly alter blood levels of each drug. The use of CBZ is to be avoided, given its risk of agranulocytosis. There have also been a few reports of myoclonic movements and rarely, cataleptic-like events (Lindstrom 1988; Lieberman et al. 1989a) in which the patient experiences a sudden loss of muscle tone in a part of the body without loss of consciousness. Other investigators contend that this side effect is often subtle and hence underreported (Chiles et al. 1990). This problem can be managed by reducing the CLOZ dose.

Sedation is the most common side effect seen with CLOZ, with a reported incidence of 39 percent (Sandoz 1990). It is most prominent early in treatment, but fortunately tolerance develops over the first few days or weeks (Lindstrom 1988; Lieberman et al. 1989a). Sedation may be minimized by giving the larger portion or the entire dose at bedtime and avoiding coadministration of other CNS depressants. The sedative effects associated with CLOZ may be related to its anti-histaminic (H1) and antiadrenergic (alpha2) properties.

Other CNS effects reported include dizziness (19%), syncope (6%), and confusion (3%) (Sandoz 1990). Dizziness and syncope are probably caused by orthostatic hypotension. As with sedation, tolerance may occur with continued treatment. Patients should be instructed to avoid rising suddenly from a seated or supine position early in treatment. Confusion or toxic delirium may occur with CLOZ (Banki and Vojnik 1978; Grohmann et al. 1989; Naber et al. 1989) and has been successfully, albeit transiently, reversed by intravenous physostigmine (Schuster et al. 1977; Gerbino et al. 1980). This provides evidence that the delirious states associated with CLOZ may in some cases be a manifestation of CNS anticholinergic toxicity.

Hypersalivation. Sialorrhea, which occurs in 31 percent of those treated with CLOZ, is a common side effect that develops early in the course of treatment (Sandoz 1990). This is an unexpected adverse reaction because CLOZ is anticholinergic and has a low incidence of EPS. Hypersalivation is most pronounced during sleep and may be voluminous. Patients can be told to cover their pillow with a towel or cloth. Treating this problem with anticholinergic agents may be effective (Ereshefsky et al. 1989) but will heighten the risk of toxicity and therefore cannot be recommended (Lieberman et al. 1989a). It is an infrequent cause of discontinuing treatment and although some tolerance occurs, the effect is often persistent even after several years of treatment. Different receptors located on salivary glands including alpha and beta adrenergic (Mandel et al. 1975), muscarinic (Ukai et al. 1989), and increased concentrations of the tachykinin, substance P (Kaniucki et al. 1984), can alter salivary flow or
composition. It is conceivable that the contribution of alterations in peripheral adrenergic tone and substance P can override the antimuscarinic effects of CLOZ at the level of the salivary glands. Sweating (6%), dry mouth (6%), and visual disturbances (e.g., blurred vision, 6%) have also been observed.

Cardiovascular Effects. Cardiovascular side effects frequently encountered are tachycardia (25%) and postural hypotension (9%). The tachycardia may be related to CLOZ’s direct vagolytic effects. Tachycardia can occur when the patient is resting in a supine position, and it is therefore not simply due to orthostatic changes. Increased pulse rates of 20–25 beats per minute were found when CLOZ was titrated to 300 mg/day over a 7-day period (Sandoz 1987). Although some tolerance may occur, in many cases the tachycardia will persist unless the dose is reduced. As an alternative, adding a beta-blocker such as atenolol may be helpful (Lieberman et al. 1989a) if the blood pressure permits it. Postural hypotension is related to CLOZ’s antiadrenergic properties. Early studies employing initial doses of > 75 mg/day resulted in a very high incidence of orthostatic collapse (Sandoz 1987). Tolerance often develops over time; this problem may be avoided when the initial dose is low (e.g., 25 mg/day) and the titration schedule is gradual. It can usually be managed by a dose reduction or adjunctive treatment such as support stockings, increased sodium intake, or fludrocortisone (Lieberman et al. 1989a). Sinus tachycardia is the most commonly encountered abnormal electrocardiogram (EKG) finding. Reversible nonspecific ST–T wave changes, T wave flattening, or inversions (repolarization effects) are seen infrequently but in most instances are of no clinical significance. These EKG findings are comparable to those seen with other antipsychotics (Sandoz 1987) and are dose dependent. Sudden death has not been seen more frequently with CLOZ than with other available antipsychotic agents. Hypertension (4%) has also been reported. Because CLOZ frequently produces clinically relevant hemodynamic changes, it should be used with caution in patients with preexisting cardiovascular disease (e.g., history of myocardial infarction, arrhythmias). Close monitoring of vital signs is advised in all patients during the first few weeks of treatment.

Gastrointestinal Effects. The most common gastrointestinal side effect is constipation (14%). Nausea, heartburn, and vomiting occur less frequently. The antimuscarinic effects of CLOZ are believed to be largely responsible for causing constipation, which should be treated symptomatically with stool softeners, laxatives, fiber supplements, and adequate fluid intake. Failure to treat constipation could result in intestinal obstruction. Nausea and, less frequently, vomiting may be managed by dose reduction or antacids. Metoclopramide has been suggested (Lieberman et al. 1989a) to manage these effects, but others suggest avoiding this and other DA D₂ blockers because of their EPS effects (Jenkins and Metzer 1990). Liver function abnormalities (1%) have been reported (Kirkegaard and Jensen 1979; Kane et al. 1988; Leppig et al. 1989; Naber et al. 1989). These changes were relatively mild, transient, and of no clinical consequence; however, at least one case report of CLOZ-induced cholestatic jaundice has been reported (Dorta et al. 1989). It is prudent to obtain baseline liver function tests and to monitor them periodically, especially during the initial stages of treatment and after dose increments.

Urogenital Effects. Urogenital effects (6%) seen with CLOZ have included incontinence (enuresis), frequency/urgency, hesitancy, urinary retention, and impotence. Because these symptoms may be embarrassing for patients and not readily volunteered, it behooves the physician to inquire about them. Failure to do so may result in medical complications, noncompliance, and a further deterioration in the quality of life for these patients. CLOZ may produce these effects through alterations in muscarinic and adrenergic transmission. Because CLOZ may produce urinary retention, it is suggested that the drug be avoided in patients with symptomatic prostatic hypertrophy and other preexisting conditions that involve incomplete voiding of urine from the bladder. It is difficult to accurately quantify the incidence of sexual dysfunction (decreased libido, impotence, ejaculatory dysfunction, or anorgasmia) in chronically psychotic patients (Sullivan and Lukoff 1990). CLOZ’s weak D₂ receptor blocking effects, coupled with increased activity of tuberoinfundibular DA neurons (Gudelsky and Meltzer 1989) may explain its inability to produce sustained hyperprolactinemia (Meltzer et al. 1979; Kane et al. 1981). The loosely bound CLOZ on the D₂ receptors of the lactotrophs would be displaced by endogenously released DA. Therefore, the secondary effects of hyperprolactinemia, such as amenorrhea, galactorrhea, and gynecomastia, are not observed.

Thermoregulation. When it occurs, benign hyperthermia (5%) is seen...
within the first 3 weeks of starting CLOZ, with a peak incidence on the 10th day (Sandoz 1987). It usually involves an increase of 1 to 2 °F, which spontaneously resolves over a few days with continued CLOZ treatment and is of no clinical significance. However, in some cases temperature elevations well above 101 °F can be seen. When this occurs, CLOZ should be temporarily withheld and frequent hematologic monitoring should be performed. Differential diagnoses can include drug fever, intercurrent infection, infection secondary to agranulocytosis, dehydration, heat stroke, “lethal” catatonia, and possibly neuroleptic malignant syndrome (NMS). Patients who develop high fever may be offered CLOZ a second time, but the dose titration schedule should be more gradual. If this strategy is not successful, CLOZ may need to be avoided. Mild hypothermia is observed in a large proportion of patients (87%) on CLOZ. This effect is seen just as frequently with CPZ and presumably, by extension, with other classic neuroleptics. The precise mechanism by which CLOZ causes temperature dysregulation is not known, but it is believed to be mediated by the hypothalamus (Heh et al. 1988).

Weight Changes. Weight gain (4%) has been reported with CLOZ (Povlsen et al. 1985; Schmauss et al. 1989; Carson and Forbes 1990; Cohen et al. 1990; Leadbetter and Viewig 1990). CLOZ appears to cause weight gain like most antipsychotics and may prove to have a greater weight-increasing effect (Sandoz 1987; Lieberman et al. 1989a). This side effect may be related in part to CLOZ’s antiserotonergic and antihistaminic (H₁) activity.

Extrapyramidal System

Acute extrapyramidal effects. Unlike typical neuroleptic drugs, CLOZ causes a very low incidence of EPS (Matz et al. 1974; Povlsen et al. 1985; Claghorn et al. 1987; Kane et al. 1988; Lindstrom 1988). It is widely known that noncompliance with antipsychotic medication is an all too common problem. One important reason given for neuroleptic medication noncompliance is the occurrence of EPS, particularly akathisia (Van Putten 1974). Consistent with the reported low incidence of EPS with CLOZ, Claghorn et al. (1987) found that only 1 of 75 patients treated with CLOZ had to be terminated from their study because of EPS compared with 11 of 76 CPZ-treated patients. If hypersalivation is excluded as an EPS effect (Casey 1989), the frequency of EPS such as tremor (6%), akathisia (6%), and rigidity (3%) is significantly lower than that seen with standard antipsychotic agents (Ayd 1961). There are no published reports of acute dystonic reactions with CLOZ. On this basis alone, one can expect that patients will be more compliant with CLOZ than with typical agents. At the same time it might be suggested that there is an inherent bias toward selecting more compliant patients for CLOZ since they all must accept weekly phlebotomy in order to receive the drug.

Tardive dyskinesia. One large prospective study determined that the overall incidence of TD after cumulative exposure to typical neuroleptics is 18.5 percent after 4 years, 40 percent after 8 years (Kane et al. 1986), and 44 percent after 10 years (M. Woerner, personal communication, January 1991). The TD incidence is even higher in patients over 55 years of age with rates as high as 31 percent after only 43 weeks of cumulative neuroleptic exposure (Saltz, unpublished data). Thus, it is striking that, to date, there have been no confirmed cases of TD attributed to CLOZ even after prolonged treatment (Sandoz 1987; Casey 1989).

Neuroleptic malignant syndrome. In keeping with CLOZ’s weak D₂ blocking effects in the striatum, there have been no reports of typical NMS developing in patients where CLOZ was the sole agent. However, there are at least two case reports of apparent NMS when CLOZ was combined with lithium (Pope et al. 1986) and with CBZ (Muller et al. 1988). In both instances the patients had previously experienced NMS with typical neuroleptic agents. On the other hand, Stoudemire and Clayton (1989) reported that CLOZ was safely used in one patient with a prior history of NMS. It is therefore suggested that the best approach is to avoid giving CLOZ in combination with lithium or Tegretol (Tegretol should be discontinued in NMS (e.g., hyperthermia, cardiovascular effects, delirium, diaphoresis, elevations in creatine phosphokinase, leukocytosis [Levenson 1985]), increased vigilance is warranted in the identification and diagnosis of NMS in patients being treated with CLOZ. Indeed, some investigators have described “atypical” NMS in which a patient receiving CLOZ developed all the characteristic signs of the syndrome except rigidity. Controversy exists as to whether NMS without rigidity is really a valid subtype of NMS (Roth et al. 1986).
Rebound Psychosis. There have been a few reports of rapid return of psychotic symptoms after abrupt discontinuation of CLOZ (Ekblom et al. 1984; Perenyi et al. 1985; Eklund 1987; Borison et al. 1988). While these investigators have linked rebound psychosis to a supersensitivity psychosis (supersensitivity of the mesolimbic system) as described by Chouinard et al. (1978), others question its existence (Singh et al. 1990). We have observed seven patients abruptly withdrawn from CLOZ following the development of agranulocytosis and did not see any rebound psychosis. If this phenomenon does occur, it is probably quite rare and it is important to consider the nature of the patient population receiving CLOZ before assuming a specific drug effect. When clinical circumstances permit, CLOZ should be tapered gradually to avoid withdrawal symptoms such as diaphoresis, diarrhea, restlessness, and insomnia.

Discussion

The decision to use CLOZ represents a challenge to the clinician because of the complexities involved in accurately assessing its risks and benefits. This report has reviewed the two most important variables of the benefit risk equation: clinical efficacy and adverse effects of CLOZ.

Benefits and Advantages. Our review suggests that there is compelling evidence of CLOZ’s superior efficacy over typical antipsychotic agents in the treatment of severely ill, neuroleptic-refractory schizophrenic patients. The claim that CLOZ is superior in reducing the negative symptoms of schizophrenia requires further investigation. This advantage in treating negative symptoms has been conclusively demonstrated only within the context of “coexisting” positive symptomatology. Others conclude that CLOZ is comparable in efficacy to HPL in treating negative symptoms (Angst et al. 1989). To our knowledge, there is no direct proof that CLOZ is superior to other antipsychotics when negative symptoms are the sole or predominant psychopathology. In addition, when evaluating CLOZ’s effects on negative symptoms in the context of a comparative trial between CLOZ and a classical neuroleptic, the potentially confounding effects of acute EPS symptoms (e.g., akinesia) must be considered. Thus, the question of whether CLOZ has therapeutic effects on negative symptoms remains to be answered. CLOZ should not be given routinely to these patients until there is proof for this indication.

Another major advantage of CLOZ is its favorable acute EPS profile, even in those patients with a known sensitivity to this side effect. Very few patients who were treated with CLOZ in both short-term prospective and long-term retrospective studies discontinued treatment because of EPS. Because EPS are a major reason why patients do not comply with treatment with neuroleptic medications, CLOZ has another distinct advantage over typical antipsychotic agents in terms of its tolerability. Another aspect of its favorable acute EPS profile is that CLOZ may not produce TD. This claim will be put to the test as CLOZ’s use in large numbers of patients is extended over very long periods of time (Casey 1989). A small number of studies demonstrate that CLOZ may actually be an effective treatment for some TD patients, especially those with severe variants such as tardive dystonia. Further studies will determine if this is another advantage that CLOZ can offer.

Unlike typical agents, CLOZ also offers the advantage of not causing a sustained hyperprolactinemic state with its attendant secondary adverse effects. This may also serve to enhance medication compliance in some patients, particularly females who suffer from oligomenorrhea or amenorrhea from classical neuroleptic treatment.

Risks and Disadvantages. The most frequent adverse effects seen with CLOZ are sedation, hypersalivation, dizziness, tachycardia, hypotension, and constipation. These are usually manageable or tolerated and, in some cases, may disappear with continued treatment. Most side effects can be minimized or avoided by a gradual dose titration and by using the lowest effective dose. A recommended dose titration schedule has been published by Sandoz (Sandoz 1990). Titrating the CLOZ dose more quickly than the guidelines suggest may be problematic because the incidence and/or intensity of some side effects associated with its use rise dramatically.

The adverse effects of primary concern include agranulocytosis and, to a lesser extent, seizures. The period of maximum risk of CLOZ-induced agranulocytosis is from 4 to 18 weeks. However, it should be emphasized that although the risk of agranulocytosis appears to decline after this period, it does not fall to zero; therefore, the risk-benefit ratio may change over time. Fatalities can be prevented only if regular hematologic monitoring is strictly adhered to. Clearly, patients have to be willing to comply with this requirement on an ongoing basis and this may preclude its use in some patients.
Despite the controversy that has surrounded it, the Clozaril Patient Monitoring System (CPMS; Sandoz 1990) largely succeeded in preventing fatalities, thereby demonstrating that the risk associated with CLOZ-induced agranulocytosis is a manageable one. Recently, Sandoz indicated that CLOZ and its hematologic monitoring system will be "unbundled" and that it will allow alternatives to CPMS (New York Times, January 15, 1991). As alternatives to CPMS are developed and put into place, there will remain appropriate concern as to whether or not alternative methods will achieve the same high level of patient safety standards. To put this in perspective, a very small number of deaths associated with CLOZ-induced agranulocytosis are still reported each year in Europe. Most of these deaths occurred within the first 18 weeks of treatment and resulted from failure to closely monitor patients' hematologic status. Recently, the first death due to CLOZ-induced agranulocytosis occurred even though the patient was being followed by the CPMS. The persistence of fatalities, albeit in small numbers, emphasizes the need for careful surveillance.

Indications. Numerous questions remain as to who should receive a trial of CLOZ. The indications now approved by the FDA are for severely ill schizophrenic patients who have failed to respond adequately to treatment with appropriate courses of standard antipsychotic drugs, either because of insufficient effectiveness or inability to achieve an effective dose due to intolerable adverse effects from these drugs. Clearly several issues require clinical judgment, for example, like how should adequate response or intolerable adverse effects be defined or measured. In addition, it is well recognized that drug labeling is only one of several sources of prescribing information on which a physician must base a judgment regarding the treatment of an individual patient.

No clearly established, well-validated criteria are available for defining treatment refractoriness. However, the criteria in the Kane et al. (1988) study did succeed in selecting individuals who failed to respond to trials of HPL and CPZ, but among whom 30 percent benefited from CLOZ. As emphasized by Marder and Van Putten (1988), it should be kept in mind that these patients were severely ill with a mean BPRS total score of 61 at baseline.

Whether or not these criteria are too stringent remains to be determined and, as Marder and Van Putten (1988) point out, there is a very large population of inpatients and outpatients suffering from schizophrenia who have had a suboptimal response to neuroleptics but who would not necessarily meet the Kane et al. (1988) criteria for refractoriness. The indications for CLOZ in these patients remain to be determined, but some earlier trials with CLOZ seem to support its value among inpatient suboptimal respondents (Fischer-Cornelssen and Ferner 1976; Claghorn et al. 1987).

Questions also remain as to how many trials of how many different drugs and at what dosages should be used before considering a patient a candidate for CLOZ. Clinicians should also consider the possibility that patients may be noncompliant or idiosyncratic metabolizers with resulting low blood levels despite what would generally be considered an adequate oral dose. The measurement of neuroleptic blood levels and the use of parenterally administered medication (to ensure compliance, increase bioavailability, and reduce first pass hepatic metabolism) are approaches to be considered in treatment nonresponders, perhaps before using CLOZ.

It is important to emphasize that not all patients will benefit from CLOZ. However, for the subgroup that does, the effects may be very positive, not just in terms of reducing psychopathology, but also in terms of making the patient more amenable and responsive to renewed efforts at psychosocial and vocational therapies. Obviously any improvement in psychopathology in a patient who has been chronically ill is only one step toward overcoming disabilities in a variety of areas.

Ideally we would like to have predictors of CLOZ response to help clinicians identify those patients most likely to benefit. Attempts at identifying such predictors have not been very rewarding to date (Honigfeld and Patin 1989), and further research is necessary.

Other Considerations in CLOZ Treatment. Debate and uncertainty as to what represents an adequate trial of CLOZ continue. To date there have been no well-designed, dose-ranging studies to determine what the optimal dose of CLOZ should be. Toward this end it is apparent that significantly different dosing practices have developed throughout the world. For example, clinicians in the United States have thus far tended to use higher doses than clinicians in most European countries (e.g., Germany). By extension, a related issue potentially affecting CLOZ's efficacy has been the question of CLOZ blood levels. While some studies examined vari-
ables that may affect CLOZ blood levels (Haring et al. 1990), there is little guidance from the literature as to what constitutes a therapeutic range or minimum threshold.

Investigators have attempted to determine the appropriate duration of a treatment trial. As mentioned earlier, Meltzer et al. (1989) conducted an open, uncontrolled, prospective study of 51 treatment-resistant patients with an average treatment duration of over 10 months. Only 45 percent of patients who ultimately responded could be identified within the first 6 weeks. Ultimately, about 60 percent of the patients responded when CLOZ treatment was extended up to 1 year. They therefore suggest that a 6- to 12-month trial of CLOZ be given to identify all responders. Doing this, however, would put patients through the period of maximum risk for developing CLOZ-induced agranulocytosis. Nearly 75 percent of the patients were identified as responders by the third month of treatment. In addition, all of the improvement in Quality of Life Scale scores was seen by the 12th week of CLOZ treatment. Owen et al. (1989) also suggested that the largest amount of improvement in the BPRS score occurred within the first 12 weeks of treatment. In open, uncontrolled trials taking place in the context of high expectations and intensive psychosocial therapy, it is difficult to know what factors are responsible for gains occurring over a period of many months. Therefore, given CLOZ’s risks and current cost, we believe there is more justification for a 3-month trial of CLOZ.

It is essential that clinicians identify and assess target signs and symptoms in order to make a considered judgment whether or not to continue CLOZ beyond the initial acute treatment trial. There are no guidelines for this decision and each case should be viewed individually, weighing benefit and risk. Patients and their families should be involved in the decision to use CLOZ. The potential benefits and risks as well as the monitoring required should be clearly explained, and this process should be documented in the medical record.

It is hoped that the availability of CLOZ will stimulate further research to help evaluate other potential indications for its use. In the meantime, clinicians who use this drug for indications not currently included in the labeling should have compelling and carefully documented reasons as well as informed consent.

Hopefully, ongoing research will help to clarify the most appropriate dose range for acute treatment, the length of trial that should be employed, and predictive factors that might help to identify potential responders. After more extensive experience with the drug, it may be possible to clarify the time course of agranulocytosis risk. If, for example, the risk of agranulocytosis occurring after 1 year is no greater than that associated with phenothiazines, the frequency of required WBC monitoring could be reduced. At the same time, if further progress is made in identifying risk factors for or the pathophysiologic mechanism of agranulocytosis, strategies might be developed to reduce overall incidence of this adverse reaction. Any increase that can be achieved in the benefit-to-risk ratio will in all likelihood expand the indications for and the use of CLOZ. Clearly, this drug continues to present both opportunity and challenge to the field.

References


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