

When Symptoms Persist: Clozapine Augmentation Strategies

by Peter Buckley, Alexander Miller, Jerry Olsen, David Garver,
Del D. Miller, and John Csernansky

Abstract

Recent data and clinical experience confirm that, in spite of superior efficacy for treatment-refractory schizophrenia, a substantial proportion of patients receiving clozapine will continue to experience disabling symptoms. Optimizing clozapine monotherapy is the first step in the management of "clozapine non-responders." Described here is a synthesis of the available literature on the range and efficacy of clozapine augmentation strategies that may be used when monotherapy fails. Treatment options include adjunctive antipsychotic medications, mood stabilizers, selective serotonin reuptake inhibitors, glycinergic agents, and electroconvulsive therapy. The evidence favoring one augmentation strategy over another is lacking; overall, adjunctive therapy is associated with only modest clinical improvement. Moreover, case series and open-labeled clinical trials dominate the extant literature, and there is a dearth of double-blind trials comparing these augmentation agents. Current systematic efforts to enhance the treatment of these patients with adjunctive therapies are worthy of being studied in carefully conducted clinical trials.

Keywords: Schizophrenia, antipsychotic response, treatment refractory, augmentation, clozapine.

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Clozapine has had a profound influence on the ability to treat individuals with severe mental illness. Carefully conducted pivotal studies (Claghorn et al. 1987; Kane et al. 1988), subsequent studies in a variety of "real-world" clinical settings (Naber and Hippius 1990; Wilson 1992; Essock et al. 1996; Rosenheck et al. 1997), and a recent authoritative meta-analysis (Wahlbeck et al. 1999) collectively confirm clozapine's stature as the treatment of choice for severe refractory schizophrenia. Among treatment-resistant patients who have failed to respond to two or more conventional antipsychotics, clozapine has often

provided substantial, and occasionally virtually complete, relief from positive, disorganized, and negative symptoms. At the present time, it is difficult to assess the real impact of other (nonclozapine) atypical antipsychotics on treatment-refractory schizophrenia; individual comparative studies of risperidone, olanzapine, or quetiapine and the conventional antipsychotics show superiority for the newer agents in more refractory populations (Conley et al. 1998; Wirshing et al. 1999; Emsley et al. 2000), although the magnitude of response is typically less than that observed with clozapine. Moreover, relatively few studies directly compare these atypicals with clozapine (Bondolfi et al. 1998; Bitter et al. 1999), and the efficacy of these (nonclozapine) atypicals relative to each other remains to be clearly determined (Tran et al. 1997; Conley et al. 1999; Mullen et al. 1999). The extent to which these drugs differ pharmacologically is also a major issue (Remington and Kapur 1999). There remain patients for whom both conventional and "atypical" neuroleptics, and clozapine alone, appear to yield little benefit. There are not enough data addressing how best to treat the group of patients who do not respond to clozapine. This paper is intended to provide a current, comprehensive, and critical account of the available literature on the adjunctive use of various psychotropic agents to enhance the response to clozapine in patients who are either partial or nonresponders to clozapine monotherapy. This review will also include the use of adjunctive electroconvulsive therapy (ECT) for this purpose. In order to organize this review of a large body of literature and also to briefly cover the related topics of optimizing clozapine monotherapy and defining response, the article is structured as follows: (1) optimizing clozapine monotherapy; (2) clozapine nonresponders: estimates of prevalence and economic impact; (3) clozapine polypharmacy: preliminary observations; (4) augmentation therapies and response expectations; (5)

Send reprint requests to Dr. Peter Buckley, Dept. of Psychiatry, Medical College of Georgia, 1515 Pope Avenue, Augusta, GA 30912; e-mail: PBuckley@mail.mcg.edu.

augmentation therapies: reviewing the literature (this section includes individual subsections on combination therapies for which there are some published data); (6) schizophrenia practice guidelines and augmentation therapies; and (7) concluding remarks.

Optimizing Clozapine Monotherapy

Maximizing the efficacy of clozapine and other new antipsychotics by combining the antipsychotic with other psychotropics is a difficult clinical matter that should be considered after monotherapy has been exhausted as an option (Weiden and Casey 1999). In the case of clozapine, inadequate medication compliance, dosing, blood levels of clozapine (< 450 ng/ml [Potkin et al. 1994]), and comorbid substance abuse may retard treatment response (Conley and Buchanan 1997; Conley 1998). Moreover, distressing and serious side effects such as seizures or sedation may make clozapine difficult to tolerate and thereby complicate efforts to achieve therapeutic dosing. Appropriate management of these side effects can assist in maximizing therapy. These issues should be assessed in such patients before embarking upon strategies to augment the effects of clozapine or other atypical antipsychotics (Barnes et al. 1996). Despite the best efforts to optimize clozapine monotherapy, an emergent group of patients—known as clozapine nonresponders or superrefractory patients with schizophrenia—now pose a substantial clinical dilemma. These patients, often those who have “revolving door” hospitalizations or are chronically hospitalized, are disproportionate users of mental health systems. In considering the differential economic burden of schizophrenia, Davies and Drummond (1993) concluded that 40 percent of patients with schizophrenia, those with refractory illnesses, accounted for 97 percent of the cost of schizophrenia.

Clozapine Nonresponders: Estimates of Prevalence and Economic Impact

As noted below, probably less than one-third of the patients who could benefit from clozapine have tried it. Some of these patients will likely refuse a clozapine trial under any circumstances, but some will be offered and accept a course of clozapine therapy. Many will respond satisfactorily, but a substantial percentage (perhaps 30%) will have an inadequate response. With this group, which will increase in size as more patients are tried on clozapine, clinicians will face the dilemma of how best to boost an insufficient improvement in clinical status.

Schizophrenia is a costly and major public health issue (Rice and Miller 1996), which makes the economics of treatment all the more meaningful. The upper and

lower limits of the number of inadequate clozapine responders in the United States can be estimated. As of mid-1999 approximately 190,000 patients had been tried on clozapine (Novartis data base), of whom 85–90 percent had schizophrenia spectrum disorders. If the size of the schizophrenia spectrum group tried on clozapine is 160,000 and their response rate is 50 percent (Claghorn et al. 1987; Lindstrom 1988; Lieberman et al. 1994), then about 80,000 schizophrenia spectrum patients have been tried on and failed with clozapine. In addition to these proven nonresponders to clozapine is a large group of treatment-resistant patients who have never had a trial of clozapine, either because it has not been recommended or because it has been refused. If the rate of treatment resistance of patients with schizophrenia to antipsychotics other than clozapine is 20–30 percent (Prien and Cole 1968; Davis and Casper 1977; Essock et al. 1996; Conley and Buchanan 1997) and the number of adults in the United States with schizophrenia is 2.6 million, then the number of treatment-resistant patients is about 650,000 (25%), of whom 325,000 would be expected to also be unresponsive to clozapine.

Pharmacoeconomic studies of the impact of clozapine have estimated the annual per patient medical cost of schizophrenia resistant to typical neuroleptics to be in the \$30,000–\$70,000 range (Rosenheck et al. 1997; Revicki 1999). Applying these costs to the estimated range of 80,000–325,000 patients with clozapine-refractory schizophrenia leads to calculated annual medical care expenditures of \$2.4 billion to \$23.0 billion for this group. Thus, even the most conservative set of assumptions leads to the conclusion that the number of clozapine-refractory patients is substantial and that the cost of their care is great.

It is an open question whether augmentation of clozapine with other agents can significantly reduce the number of clozapine-refractory patients. The studies reviewed in this article strongly indicate that more controlled studies are needed. Moreover, it is very evident that augmentation strategies are in widespread use, prompted no doubt by a lack of evidence and a lack of clinical experience favoring any other alternative. Certainly the tone of recent psychiatric literature toward switching patients from clozapine to other atypicals is very cautionary (Weiden et al. 1997).

There are, of course, reasons other than poor response of the symptoms of schizophrenia for patients to receive combinations of clozapine and other psychotropics. Some of these reasons might include coexisting mood or anxiety symptoms; prophylactic use of anticonvulsants (e.g., valproic acid); and the use of combinations to alleviate side effects (Miller 1996; Conley 1998). The focus of this review, however, is on the use of additional psychotropics and electroconvulsive therapy for the target symptoms of schizophrenia.

Clozapine Polypharmacy: Preliminary Observations

To estimate the extent of use of combinations of other psychotropics with clozapine, we surveyed the sites represented at a satellite symposium held at the Seventh International Congress on Schizophrenia Research, Santa Fe, New Mexico, in April 1999. This survey was not comprehensive, however, and did not attempt to determine the rationales for polypharmacy. Also, while the information was derived from several states, these centers were largely university affiliates and may not be broadly representative of prescribing practices at large. In sampling clozapine use in this survey, we characterized patients as being on clozapine, clozapine plus one or more other antipsychotics, or clozapine plus a mood stabilizer. The results showed how frequently combinations are used in a broad geographic base of public mental health facilities. A total of 906 patients were identified: 336 inpatients, 570 outpatients. For the group as a whole, 52 percent were on clozapine alone, 18 percent on clozapine plus another antipsychotic, and 30 percent on clozapine plus a mood stabilizer. The proportions were similar for inpatients and outpatients, although outpatients were somewhat more likely to receive another antipsychotic (21% versus 13%)

and somewhat less likely to receive a mood stabilizer (28% versus 33%). The overwhelming choice of mood stabilizers was divalproex sodium.

The survey was not systematic, but results were consistent across sites in showing that prescribing of a second antipsychotic is common and use of mood stabilizers is even more frequent (table 1). In Ohio's public mental health system during 1999, 36 percent of patients with a diagnosis of schizophrenia were receiving a combination of two antipsychotic medications (Dale P. Svendsen, M.D., personal communication, June 8, 2000). Data on concomitant use of antidepressants were not obtained from all sites in this survey of clozapine, but, where assessed, their use was also common (15%–20%). Thus, use of combination therapies with clozapine is very prevalent. Accordingly, a review of the evidence for these combinations is timely.

Augmentation Therapies and Response Expectations

Concomitant with the advent of clozapine and other atypicals, response criteria and definitions of treatment-refractory schizophrenia have become more complex (Kane et al. 1988) and now encompass broader dimensions of out-

Table 1. Number of patients receiving clozapine monotherapy and polypharmacy at U.S. treatment facilities (1999, see text)

| Site | Clozapine | | Clozapine + Antipsychotic | | Clozapine + Mood Stabilizer | |
|-----------------|-----------|------------|---------------------------|------------|-----------------------------|------------|
| | Inpatient | Outpatient | Inpatient | Outpatient | Inpatient | Outpatient |
| Iowa | 29 | 17 | 6 | 10 | 18 | 4 |
| Hillside, NY | | 60 | | 25 | | 50 |
| Maryland | 26 | | | | 15 | |
| Ohio | 22 | 16 | 14 | 8 | 57 | 18 |
| Michigan | | 138 | | 25 | | 32 |
| Missouri | 30 | | | 6 | | 6 |
| Dallas, TX | 2 | 10 | | 5 | | 9 |
| New York, NY | 55 | | | 27 | | 27 |
| San Antonio, TX | 16 | 48 | 23 | 14 | 23 | 12 |
| Totals | 180 | 289 | 43 | 120 | 113 | 158 |

| | Clozapine | | Clozapine + Antipsychotic | | Clozapine + Mood Stabilizer | |
|---------------------|-----------|------------|---------------------------|------------|-----------------------------|------------|
| | Inpatient | Outpatient | Inpatient | Outpatient | Inpatient | Outpatient |
| Patients | 125 | 91 | 43 | 43 | 113 | 49 |
| Percentage of group | 44 | 50 | 15 | 23 | 40 | 27 |

Note: Data from Iowa, Maryland, Ohio, Missouri, Dallas, and San Antonio: $n = 464$.

come (Kane 1999; Peuskens 1999). There are no widely agreed-upon criteria for antipsychotic response, and most investigators have used a predefined reduction in a standard rating scale measuring psychopathology. Clozapine response has generally been defined as greater than a 20 percent reduction in the Brief Psychiatric Rating Scale (BPRS) with a final BPRS total score of less than 35, a criterion that tends to emphasize improvement in positive symptoms. In recent years the importance of negative symptoms and cognitive impairment in schizophrenia has been recognized, but these have generally not been included in response criteria for clozapine response. Clinically most clinicians do not refer to response or non-response based on a change on a rating scale but rather on the presence of ongoing symptomatology. Persistent negative symptoms have become a clinical focus of treatment response (Carpenter et al. 1995). The presence of cognitive deficits is very relevant now in clinical practice because much attention is given to cognition as a key outcome measure. This is now important in determining long-term functional outcome (Green 1996), and there is now evidence of subtle, yet clinically meaningful, improvements in cognition during treatment with atypical antipsychotics (Keefe et al. 1999). Also, some initial data indicate that atypical antipsychotics may reduce aggressive, suicidal, and substance-abusing behaviors in patients with schizophrenia (Walker et al. 1997; Volavka 1999). Thus, the notion of treatment resistance is still an evolving one and, of course, the conceptualization of treatment resistance will influence prevalence rates of nonresponse for each new drug (see prior section). It is also likely to have a real impact in deciding the key features of response for any given individual and how these may be best addressed by antipsychotic monotherapy or augmentation strategies. Accordingly, adjunctive pharmacotherapy may address distinct target symptoms (e.g., cognition, aggression, suicidality) that are unresponsive to clozapine monotherapy or may aim to have a broad effect in diminishing the remaining psychotic symptoms. In weighing the relative merits of continued clozapine monotherapy versus augmentation, attention needs to be paid to effects on cognition, extrapyramidal symptoms, incidence of tardive dyskinesia, depression, agitation and aggression, incidence of substance abuse, quality of life, and back-to-work measures. Such methodological rigor has been stressed in critically evaluating the impact of novel antipsychotics (Collaborative Working Group on Clinical Trial Evaluations 1998a-c; Stahl 1999).

To date, the evaluation of augmentation strategies of clozapine in treatment-resistant patients with schizophrenia has been generally limited by a relative lack of prospective, double-blind, randomized, placebo-controlled clinical trials utilizing sufficient numbers of patients for meaningful statistical analysis. Methods of

establishing clozapine treatment resistance have not always been uniform, making interpretation of symptom response sometimes open to scrutiny. The length of treatment needed to establish treatment refractoriness to clozapine remains open to debate (Carpenter et al. 1995), an important consideration in evaluating adjunctive therapy. Although serum clozapine levels have gained greater acceptance in helping to determine whether a patient is taking a sufficient dose of clozapine, comparisons of serum clozapine levels on monotherapy versus combination therapy are often lacking. Such data would be useful to clarify whether drug-drug interactions (i.e., drug effects that result in higher clozapine levels) may be a reason for patient improvement. Moreover, adverse effects regarding both monotherapy and combination therapy are not regularly reported.

Augmentation Therapies: Reviewing the Literature

Clozapine and Antipsychotics

Typical antipsychotic medications. The best evidence for antipsychotic augmentation in clozapine nonresponders comes from Shiloh and colleagues' (1997) 12-week prospective, double-blind, randomized, add-on placebo-controlled study of sulpiride (600 mg) added to clozapine in 28 inpatients. The duration of clozapine therapy prior to the study was 75.6 ± 123.6 months for the sulpiride/clozapine group and 50.7 ± 36.8 months for the placebo/clozapine group; this difference was not statistically significant. Among other clinical and demographic variables, the total duration of hospitalization differed between the two groups (32.8 ± 30.3 for the sulpiride group, 70.8 ± 56.1 for the placebo group). Patients in the study received clozapine at an average dose of over 400 mg/day. Patients were considered partial or poor responders but not completely nonresponders to clozapine based on BPRS (0-6) scores greater than or equal to 25. Patients requiring scheduled concomitant antiparkinsonian or benzodiazepine medications were excluded from the study in order to avoid masking potential adverse effects on the combination treatment regimen. Weekly BPRS, Scale for the Assessment of Negative Symptoms (SANS), Scale for the Assessment of Positive Symptoms (SAPS), and Hamilton Depression Scale (HAM-D) scores were obtained. Overall group comparisons revealed a significantly greater improvement in BPRS, SAPS, and SANS scores but not HAM-D scores in the sulpiride/clozapine group compared with the placebo/clozapine group. Post-hoc analyses indicated a mean BPRS reduction of 20.7 percent in the sulpiride/clozapine group. Eight of these 16 patients had BPRS reductions of greater than 20 percent. On the other hand, 6 of the 16 sulpiride patients had a

minimal response of less than 5 percent reduction in their BPRS scores compared with baseline. Mean prolactin levels increased threefold in the 11 men (from 17.7 ± 15.8 ng/ml to 75.4 ± 19.8 ng/ml and 101.8 ± 41.0 ng/ml) in the sulpiride/clozapine group. Because this increase occurred in the absence of treatment of emergent galactorrhea or amenorrhea, the clinical significance of this rise in prolactin is unclear. There were no extrapyramidal side effects (EPS) in the sulpiride/clozapine group. However, this study was over a relatively short period of augmentation, and baseline demographic differences existed between the two groups with respect to time of inpatient hospitalization prior to study (i.e., add-on placebo patients had been hospitalized approximately twice as long as those in the sulpiride group). Pre- and poststudy serum clozapine levels were not obtained.

Pimozide, another primarily D2 receptor antagonist, was added by Friedman et al. (1997) in a open, nonrandomized clinical trial involving five outpatients with schizophrenia and two outpatients with schizoaffective disorder who had failed two adequate trials of conventional antipsychotics. They had been on clozapine, average daily dose of 425 mg/day (range, 325–600 mg/day), for 10 months ($n = 1$) and more than 1 year ($n = 6$) prior to addition of pimozide given at doses between 2 and 8 mg/day (average dose = 4 mg/day). Serum clozapine levels were not obtained during this study. Mean BPRS scores fell an average of 47 percent, from 51 to 27, over a mean treatment period of 32 days (range, 14–68 days). Again, this study is over a relatively short period of augmentation with no data given on any adverse events of the combination therapy.

Loxapine is an interesting compound to use as an adjunctive agent in view of recent speculation that it may be intermediate in its 5-HT_{2A}/D₂ receptor occupancy ratio between clozapine and the other newer atypical agents, and other traditional antipsychotic medications (Kapur et al. 1997). Mowerman and Siris (1996) conducted a prospective, open, nonrandomized clinical trial of loxapine (25–200 mg/day) in six outpatients with schizophrenia and one outpatient with schizoaffective disorder. Patients were on a mean dose of 821 mg/day clozapine, with five of the seven receiving 900 mg/day. Baseline clozapine levels averaged 872 ng/ml in three of the 900 mg/day patients and 634 ng/ml in one patient on 550 mg/day of clozapine. Total BPRS scores improved between 19 and 38 points when clozapine was being augmented with loxapine. Four patients with pre- and poststudy clozapine levels had an approximate average 45 percent reduction in their total BPRS scores without evidence of altered clozapine levels. Although outpatients, three of the seven patients progressed to higher level programs and three of the seven required less structured programs. Of the seven patients, two who had a history of aggressive

behaviors at home no longer exhibited these behaviors.

Atypical antipsychotic medications. There is little systematic information on the addition of other atypical antipsychotics (risperidone, olanzapine, or quetiapine) to clozapine. Henderson and Goff (1996) conducted a prospective, open, 4-week trial of risperidone (average daily dose of 3.8 mg/day [range, 2–6 mg/day]) in 12 outpatients with schizophrenia who were receiving clozapine (average daily dose = 479 mg/day). Prestudy serum clozapine levels averaged 479 ng/ml. Ten patients had baseline serum clozapine levels above 350 ng/ml. Total BPRS scores were reduced an average of 25.8 percent by the end of the 4-week study, with 10 of the 12 patients having a greater than 20 percent reduction. Adverse event monitoring indicated new onset of mild akathisia in four patients and an exacerbation of hypersalivation in five outpatients. Despite both clozapine and risperidone's strong affinities for the alpha-1 adrenoreceptor, neither dizziness nor orthostasis was noted. Six patients reported less sedation on combination therapy; only one patient had more fatigue. Available end-of-study serum clozapine concentrations in seven patients were nonsignificantly increased by 2.2 percent. Although the results of this trial are encouraging and demonstrate both clinical improvement and tolerability, the period of augmentation was relatively short, and the previous length of treatment with clozapine prior to addition of risperidone is unknown. In addition, the study was not double-blind.

There have been three case reports of use of adjunctive risperidone in clozapine nonresponders. Morera et al. (1999) reported on two cases. One involved a partial clozapine responder who after a year of 500 mg/day clozapine (without available serum levels) was switched to 6 mg/day risperidone, then back to clozapine because of deterioration. Ultimately, the patient received 6 mg/day risperidone in addition to 300 mg/day clozapine. He began to have clinical improvement within 10 days and a 50 percent reduction in his total BPRS score within 3 months, with no hospitalizations. A second patient, hospitalized for the past 4 years for persistent psychotic symptoms despite clozapine at 600 mg/day, was unchanged when switched to risperidone therapy at 6 mg/day. On a combination of 6 mg/day risperidone and 400 mg/day clozapine, his total BPRS score was reduced by 58.6 percent by the sixth week. Improved functioning was also noted.

McCarthy and Terkelsen (1995) reported on the addition of risperidone to the treatment regimen of two patients, one with a 4-year history of schizoaffective disorder and another with a 20-year history of schizophrenia, both of whom were clozapine intolerant at doses of 400 and 750 mg/day, respectively. In the first case, adjunctive lithium was tolerated, but severe hypotension and sedation necessitated a reduction in clozapine to 200 mg/day.

Addition of 25 mg/day of thiothixene did not improve the patient's frequency of hallucinations and delusions. However, when the patient was switched to 3 mg/day risperidone, hallucinations diminished and resolved over the next 2 weeks, and overall mood and social functioning improved. In the second case, a switch from clozapine 250 mg/day to risperidone 6 mg/day eliminated troublesome dysphagia but psychosis worsened, necessitating a restart of clozapine at 200 mg/day. Within 2 months, the patient was able to return to part-time employment.

A third case report by Chong and colleagues (1997) was complicated by fluctuation in the dosing of clozapine amid the addition of risperidone at 6 mg/day. Psychotic symptoms were essentially unchanged, although the patient experienced a reemergence of hoarding behaviors.

There is, thus far, only one report of olanzapine augmentation of clozapine therapy. Gupta and colleagues (1999) noted an approximately 35 percent improvement in BPRS scores in two patients when olanzapine (15 mg/day) was added to clozapine therapy (200 and 600 mg/day). So far, the only report of quetiapine addition to clozapine has been in treatment-responsive patients. This adjunctive therapy was an attempt to limit or reverse the impact of clozapine on weight gain and glycemic control (Reinstein et al. 1999).

Clozapine and Thymoleptics

Clozapine and lithium. A number of investigators have reported *uncontrolled* trials during which antipsychotic effects were enhanced when lithium was added to a stable dose of clozapine. Evidence is strongest for patients with major affective components to their illness (Fuchs 1994; Suppes et al. 1994; Puri et al. 1995). However, Bryois and Ferrero (1993) have reported on a series of patients, equally divided between schizophrenia and schizoaffective disorder, who responded well to a clozapine-lithium combination. Surveys in Denmark (Juul Povlsen et al. 1985; Peacock and Gerlach 1994) revealed that 2 percent of clozapine-treated patients were also receiving lithium. Discontinuation of lithium from the combination (because of side effects) often resulted in psychotic relapse despite continued stable levels of clozapine. Although there is substantial data on the efficacy of combining clozapine and lithium in the treatment of both bipolar and schizoaffective disorders, only uncontrolled studies address their interactive toxicity. Rare reports of neuroleptic malignant syndrome, myoclonus, and seizures have appeared. Lee and Yang (1999) reported reversible neurotoxicity (ataxia, coarse tremor, myoclonus, facial spasm, and increased deep tendon reflexes) despite lithium levels of less than 0.5 mEq/l. Garcia and colleagues (1994) have reported seizures in patients following the addition of lithium to a clozapine regimen. A tendency to augment the emergence of asterixis (reported for each of the drugs sep-

arately) was suggested during combined clozapine and lithium therapies (Rittmannsberger 1996). Although lithium has often been used to raise low leukocyte counts above the threshold required for patient continuation on clozapine (Blie et al. 1998), lithium may mask the detection of other myeloid processes associated with agranulocytosis (Gerson et al. 1994). Clinicians should monitor more closely when patients are treated with lithium and clozapine.

Clozapine and carbamazepine. Clozapine augmentation by carbamazepine should be avoided. Both drugs cause granulocytopenia at higher frequencies than most other medications (Junghan et al. 1993), and adjunctive carbamazepine has been implicated in fatal agranulocytosis during clozapine therapy (Gerson et al. 1994). Most anticonvulsants (except valproate) induce the oxidative metabolism of many antipsychotics and often lower their plasma concentrations to potentially subtherapeutic levels (Meyer et al. 1996). Addition of carbamazepine to clozapine reduces plasma levels of clozapine, presumably through a CYP2D6 induction (Taylor 1997), by 47–50 percent (Jerling et al. 1994). As with lithium, a tendency to increase the emergence of asterixis caused by each of the drugs separately was suggested during combination therapies (Rittmannsberger 1996).

Clozapine and valproate. The use of valproate as an augmentor of clozapine remains controversial, although its use in prophylaxis of clozapine-induced seizures is well accepted. Reinstein et al. (1998), from a retrospective chart review, compared the number of hospitalizations and the duration of hospitalization for 61 schizoaffective-bipolar patients for the 6 months prior to augmentation of clozapine with valproate with the following 6 months of augmentation. Mean number of hospitalizations was significantly reduced (44% reduction), as was length of stay (19.4% reduction) and total hospital days utilized (62.2% reduction) (all $p < 0.001$). Kando et al. (1994), in a retrospective study of six patients with treatment-refractory psychotic or manic symptoms, noted symptomatic benefit when valproate was added to clozapine. This combination was generally well tolerated, with sedation as the most troublesome adverse effect. In contrast, Wilson (1995), also from a retrospective study in treatment-resistant patients, reported data suggesting that patients receiving clozapine alone had a better outcome than those who were on concurrent anticonvulsants (phenytoin, carbamazepine, valproate, phenobarbital, or clonazepam). However, the Wilson (1995) study did not distinguish among the above-noted anticonvulsants. As noted above, many anticonvulsants (but not valproate) lower drug levels of clozapine by enzyme induction. Longo and Salzman (1995) reported that valproate significantly decreased levels of putative toxic clozapine metabolite, norclozapine, while affecting the parent drug

to a very small extent. Valproate acid caused a minor increase in total clozapine metabolites (Centorrino et al. 1994a,b). Thus, it is not clear that the impairment of response with the clozapine-anticonvulsant combinations reported by Wilson (1995) is relevant to the clozapine-valproate combination rather than enzyme induction by the other anticonvulsants. Still, in a recent survey of clozapine-treated patients in Denmark, 8 percent of clozapine-treated patients continued to receive augmentation with antiepileptics (carbamazepine, valproate, and phenobarbital) (Peacock and Gerlach 1994).

Clozapine and other anticonvulsants. The advent of a series of new anticonvulsants, including lamotrigine, gabapentin, topiramate, and vigabatrin, many of which are presently in trials for bipolar disease, also raises new possibilities for augmentation strategies with conventional antipsychotics, with other "atypical" antipsychotics, and with clozapine in treatment-resistant patients. Among the early trials in schizophrenia, Dursun and colleagues (1999), from an open study of adding lamotrigine to clozapine in six partially treatment-resistant patients with schizophrenia, described dramatic improvement in each. Such preliminary observations require replication under double-blind conditions. Topiramate, with its propensity to induce weight loss, might also emerge as a particularly useful agent if it can be shown to augment "atypical" antipsychotics in the treatment of psychotic symptoms.

Clozapine and selective serotonin reuptake inhibitors. The selective serotonin reuptake inhibitors (SSRIs) have often been used as an augmentation strategy to enhance efficacy of both typical (Christison et al. 1991) and atypical (Buckley and Schulz 1996) antipsychotic medications. The therapeutic rationale is to enhance treatment response to negative and positive residual symptoms. While these drugs are also widely used in the treatment of depressive symptoms in schizophrenia, their efficacy in this regard is unproven. Interestingly, there have been no comparative studies between SSRIs and conventional antidepressants in treating comorbid depression in schizophrenia; the evidence for efficacy with the older antidepressants is more convincing.

There are several studies, mainly open labeled, of SSRI augmentation in patients receiving typical antipsychotics (Goff et al. 1990; Silver and Nassar 1992; Goff et al. 1995a; Goldman and Janecek 1990). These studies have provided evidence that this strategy can enhance negative symptom response (Silver and Nassar 1992; Goff et al. 1995a) and, in one study (Goldman and Janecek 1990), lead to an improvement in overall level of functioning. It was also observed that coadministration of SSRIs with typical antipsychotics could elevate the plasma concentration of the antipsychotic (Goff et al. 1990), an effect that could itself account for any potential therapeutic benefit. The use of typical antipsychotics in the maintenance pharmacother-

apy of schizophrenia is in rapid decline and, therefore, patients heretofore considered for augmentation with SSRIs or other agents are now more appropriately considered candidates for clozapine therapy. Research on SSRI augmentation with typical antipsychotics has effectively stopped, and while these initial open trials were suggestive of efficacy, we are left with no firm conclusions from this literature.

Paradoxically, more information is available on the coadministration of SSRIs with clozapine than on SSRI augmentation of typical antipsychotics. These agents (especially fluvoxamine) are observed to elevate the plasma concentration and its primary metabolite, nor-clozapine (Byerly and Devane 1996). In a cross-sectional study, Centorrino and colleagues (1996) examined plasma levels in patients receiving clozapine monotherapy ($n = 40$) or SSRI combination of either paroxetine ($n = 16$), fluoxetine ($n = 14$), or sertraline ($n = 10$), and they observed that overall clozapine plasma levels were 40 percent higher in the combination therapy group. Wetzel and colleagues (1998) added fluvoxamine (50 mg/day) or paroxetine (20 mg/day) in a sample of 30 patients who were receiving clozapine. Threefold increases in clozapine and its metabolites were observed with the addition of fluvoxamine, whereas paroxetine induced only minor nonsignificant increases. In another study, clozapine plasma levels increased up to fivefold when fluvoxamine (50 mg/day) was added to clozapine therapy. However, there was no emergence of side effects or electroencephalographic abnormalities as a result of this addition. On the other hand, pronounced worsening of clozapine's side effects has been noted with coadministration of SSRIs, especially fluvoxamine.

The evidence for efficacy with SSRI augmentation is neither substantial nor compelling. Silver and colleagues (1995) reported a superior response for negative symptoms in 11 patients with schizophrenia who were cotreated with clozapine and fluoxetine; positive and depressive symptoms were unchanged. The trial lasted 12 weeks, and fluoxetine was given in an open-labeled, add-on fashion, such that observer bias cannot be discounted as an explanation for the observed effect. Moreover, the plasma concentration of clozapine was not measured. Buchanan and colleagues (1996) conducted the most rigorous study to date on this topic. Treatment response, as measured on the SANS, the BPRS, and the HAM-D, was assessed during an 8-week double-blind comparative trial between clozapine monotherapy ($n = 15$; mean daily dose of 511 mg) and clozapine augmentation with fluoxetine ($n = 18$; mean daily clozapine dose of 457 mg). Fluoxetine was given at 20 mg for 3 weeks, with flexible dosing thereafter up to a limit of 80 mg daily. The mean fluoxetine dose at 8 weeks was 49 mg daily. There was no difference in efficacy between the two groups. Specifically, there was no evidence of superior improvement for the augmentation group on the SANS.

There was also no difference in adverse effects between the two groups. Unfortunately, data on clozapine plasma levels are not reported for this study. Also, the authors caution that the sample size (while larger than those of other studies) may have been insufficient to detect changes in negative symptoms. Nevertheless, the conclusion from this double-blind study is that SSRI augmentation of clozapine therapy is not beneficial.

On the other hand, SSRIs can be helpful in the treatment of clozapine-induced obsessive-compulsive disorder (OCD) symptoms (Chang and Berman 1999). Approximately 5 percent of clozapine-treated patients develop clear and usually new-onset OCD phenomena. Although there is an absence of formal studies on this potentially informative patient subgroup, case reports (Buckley et al. 1992) point to a role for SSRI treatment of these symptoms.

Clozapine and Glycinergic Agents. The rationale for adding glycinergic agents to antipsychotic medication is based on the N-methyl-D-aspartate (NMDA) receptor hypofunction hypothesis of schizophrenia (Olney and Farber 1995). Because activation of a glycine site on the NMDA receptor complex is necessary for the normal function of the receptor system, it has been postulated that if the system is hypofunctional because of underactivation of the glycine site, agonists acting at this site may restore the system to a more normal function. Results from double-blind, placebo-controlled trials combining glycine, D-cycloserine, or D-serine with conventional antipsychotics have shown consistent improvement in negative symptoms (Javitt et al. 1994; Goff et al. 1995b, 1999a; Heresco-Levy et al. 1996, 1999; Tsai et al. 1998). Given these positive results, investigators have studied the effect of adding these agents to clozapine in treatment-refractory subjects (Goff et al. 1996, 1999; Potkin et al. 1999; Tsai et al. 1999).

Currently, four double-blind, placebo-controlled studies are examining the effect of adding glycinergic agents to clozapine, one involving glycine, two with D-cycloserine, and one with D-serine. Potkin and colleagues (1999) conducted a 12-week, double-blind, placebo-controlled trial in which 19 subjects with treatment-resistant schizophrenia were maintained on an optimal dose of clozapine (400–1200 mg/day) and were administered either glycine (30 g/day) or placebo. They reported that the addition of glycine to clozapine was not effective in decreasing positive or negative symptoms as measured by the BPRS and SANS. In contrast, the patients treated with clozapine and placebo had a 35 percent reduction in positive symptoms. Adjunctive glycine did not significantly affect clozapine levels and was well tolerated. They concluded that glycine may interfere with the antipsychotic efficacy of clozapine.

As glycine poorly penetrates the blood-brain barrier, another approach to activating the glycine recognition site

of the NMDA receptor has been the use of D-cycloserine, a drug that readily crosses the blood-brain barrier and that, at low concentrations, acts as a partial agonist at the glycine recognition site. Goff and colleagues (1996, 1999b) have completed two trials adding D-cycloserine to clozapine. The first trial was an open-label, dose-finding study in which 10 patients with schizophrenia who were receiving clozapine entered consecutive 2-week trials of placebo and four different doses of D-cycloserine (Goff et al. 1996). Clinical evaluations were videotaped and rated blind to treatment. The patients were on a mean dose of 450.0 mg/day clozapine. Baseline clozapine levels averaged 484.4 ng/ml and did not change significantly with the addition of D-cycloserine. There was a significant dose effect of D-cycloserine on SANS negative symptoms scores, with higher doses producing a worsening of negative symptoms. Goff and colleagues (1999b) subsequently conducted a double-blind, placebo-controlled trial in which 11 patients with schizophrenia receiving treatment with clozapine were assigned in random order to 6-week trials of D-cycloserine (50 mg/day) and placebo in a crossover design separated by a 1-week placebo washout. The patients were on a mean dose of 490.9 mg/day clozapine. Serum clozapine levels were not reported. D-cycloserine significantly worsened SANS negative symptoms scores compared to placebo but did not significantly affect ratings of psychotic symptoms.

To study the difference between full and partial agonists at the NMDA receptor glycine recognition site, the clinical effects of adding D-serine, a full agonist, to clozapine were assessed. Tsai and colleagues (1999) conducted a 6-week, double-blind, placebo-controlled trial in which 20 subjects with treatment-resistant schizophrenia receiving stable doses of clozapine were randomized to D-serine (30 mg/kg/day) or placebo. The patients were on a mean dose of 339 mg/day clozapine. Serum clozapine levels were not reported. The patients exhibited no improvement in Positive and Negative Syndrome Scale positive, cognitive, or general psychopathology subscales; SANS negative symptom scores; Wisconsin Card Sorting Test scores; or Clinical Global Impression scores with D-serine, nor did their symptoms worsen.

While the results from the double-blind, placebo-controlled trials combining glycine, D-cycloserine, or D-serine with conventional antipsychotics have been positive, the studies combining these agents with clozapine have been disappointing. A possible explanation as to why glycinergic agents do not improve symptoms in clozapine-treated patients but improve negative symptoms in patients receiving conventional antipsychotics may be related to the pharmacological properties of clozapine. It has been speculated that clozapine may have agonist, or partial agonist, activity at the NMDA receptor, contributing to its unique clinical efficacy. Thus, the addition of a

glycinergic agent does not further enhance the NMDA neurotransmission already influenced by clozapine, and partial agonists such as D-cycloserine may antagonize NMDA receptor neurotransmission secondary to saturation of the NMDA glycine recognition site, leading to worsening of symptoms (Tsai et al. 1999).

In summary, the current evidence suggests that combining clozapine with glycinergic agents is of little clinical benefit and may even worsen negative symptoms in some patients.

Clozapine and ECT. The premise for using ECT in combination with clozapine in treatment-refractory patients with schizophrenia stems from both earlier reports that ECT may add to the efficacy of typical antipsychotic drugs (Hertzman 1992; Krueger and Sackheim 1995) and some earlier work on the use of ECT alone in patients with schizophrenia (Salzman 1980).

The mechanism of ECT remains unknown. A variety of hypotheses have been put forward, including modifications to subcortical dopaminergic and serotonergic transmission (Mann and Kapur 1991). However, so long as the mechanism of action of ECT is either synergistic with, or independent of, the mechanism of action of a drug treatment, there is potential for a beneficial additive effect.

A number of promising case reports suggest that ECT may add to the efficacy of clozapine in treatment-resistant patients with schizophrenia (Klapheke 1991; Safferman and Munne 1992; Frankenberg et al. 1993; Cardwell and Nakai 1995; Benatov et al. 1996; Bhatia et al. 1998; James and Gray 1999; Kales et al. 1999). In most of these successful case reports, ECT was added to clozapine treatment after clozapine had already been used for several days or weeks to further reduce psychotic symptoms. However, James and Gray (1999) report that this combination of treatments may also be useful for producing a faster antipsychotic effect in patients who are uncooperative with the complex protocols usually required for clozapine treatment. Perhaps understandably, there are no controlled trials of ECT in combination with clozapine. The complexity of clozapine administration combined with practical and ethical problems that occur in designing placebo treatments for ECT make such trials unlikely even in the future. Reviews of case reports to date show that usual doses of clozapine (300–500 mg/day) are used in combination with ECT (Kales et al. 1999). In addition, bilateral ECT has most commonly been used in combination with both typical and atypical drug therapies.

Combined therapy with clozapine and ECT appears to be reasonably safe. Early reports suggested that prolonged seizures could occur as a result of the threshold-lowering effects of clozapine (Masiar and Johns 1991; Bloch et al. 1996). However, other authors reported that

modest lengthening of seizure duration because of concurrent clozapine can be safely managed (Poyurovsky and Weizman 1996; James and Gray 1999).

In summary, preliminary evidence from single case studies suggests that ECT can safely enhance the efficacy of clozapine. However, this information is derived from open-labeled case series or single case reports. It is noteworthy that ECT augmentation in schizophrenia has not been studied under the same (e.g., sham conditions) methodological rigor as in the current studies of transcranial magnetic stimulation in depression. The mechanism of action for any beneficial interaction of ECT with clozapine is unknown, but combined actions on brain dopaminergic and serotonergic systems are worthy of investigation.

Schizophrenia Practice Guidelines and Augmentation Therapies

Several recent guidelines for the treatment of schizophrenia reflect a lack of clarity as to the next step for the clozapine nonresponder. The Texas Medication Algorithm Project (Miller et al. 1999) places equal weight on augmentation with the various psychotropics and ECT cited in this article. The Expert Consensus Series (Treatment of Schizophrenia 1999) addresses this issue by way of weight responses. The choice of augmentation agent is listed in the following order: (1) add an anticonvulsant medication to clozapine, (2) combine a typical antipsychotic with clozapine, (3) combine another atypical antipsychotic with clozapine, (4) add lithium to clozapine, (5) add ECT to clozapine, or (6) add a benzodiazepine to clozapine. While this authoritative document represents the collective wisdom of experts, there is no literature to support this sequential and preferential choice of adjunctive agents. This point is underscored in the more academic-derived practice guidelines on schizophrenia, drafted by the American Psychiatric Association (APA 1997). This authoritative document does provide some guidance and relevant literature on augmentation strategies but is almost exclusively confined to adjunctive treatment of patients receiving conventional antipsychotic medications. The most recently available guidelines, those of the Royal College of Psychiatrists in England (2001), are unclear as to what to do when the patient is not responding well to clozapine.

Concluding Remarks

To date, no single adjunctive approach emerges as a primary choice for the clinician who wishes to augment clozapine therapy before switching to another antipsychotic. On the other hand, while the available literature

is sparse, at this juncture there is little evidence to encourage clinicians to discontinue clozapine therapy in favor of an expected and subsequent superior response to any of the other atypical antipsychotics. It is within the context of this present therapeutic void that the role of augmentation of clozapine nonresponders comes to the fore. This is a significant clinical dilemma. In the absence of evidence of superiority of other atypical antipsychotics in this patient subgroup, the proportion of clozapine nonresponders is likely to increase over time. Moreover, at the present time, clinicians are resorting to polypharmacy with greater frequency (Suppes et al. 1999; Weiden and Casey 1999). It should be appreciated, however, that the study of augmentation strategies is still at a nascent stage and has been confounded by small sample sizes and open-labeled study designs. The accruing number of clozapine nonresponders, the relative lack of efficacy of other atypicals in this group, and the increasing trend of polypharmacy provide a propitious environment for the systematic study of clozapine augmentation strategies.

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The Authors

Peter Buckley, M.D., is Professor and Chairman, Department of Psychiatry, Medical College of Georgia, Augusta, GA; Alexander Miller, M.D., is Professor of Psychiatry and Jerry Olsen, M.D., is Assistant Professor of Psychiatry, University of Texas Health Science Center at San Antonio, TX; David Garver, M.D., is Professor of Psychiatry, University of Louisville, Louisville, KY; Del D. Miller is Associate Professor of Psychiatry, University of Iowa, Iowa City, IA; and John Csernansky is Professor of Psychiatry, Washington University, St. Louis, MO.