Clozapine Augmentation: Safety and Efficacy

by Siow-Ann Chong and Gary Remington

Abstract

While clozapine has been demonstrated to be efficacious in refractory schizophrenia and possibly schizoaffective as well as bipolar disorders, a substantial number of patients still remain unresponsive. One strategy in treating these refractory patients is to augment clozapine with other somatic treatments. This article reviews the efficacy and safety of the combination of clozapine with other somatic treatments. A total of 70 articles were obtained from a manual, as well as computerized (Medline), search of the English language literature from 1978 to March 1998. Few controlled studies exist; most were case reports/series. From these data, the greatest risk of adverse effects seems to be associated with clozapine combined with benzodiazepines, valproate, or lithium, but no currently evaluated combination is absolutely unsafe. In terms of efficacy, the data suggest a number of potential augmentation strategies, although controlled data are few. Combination therapies with clozapine are common in clinical practice, despite a lack of empirical data, and the benefits and risks of these combinations need to be systematically reviewed.

Keywords: Clozapine, augmentation, combination.

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Clozapine has been reported to be effective in 30 to 60 percent of schizophrenia patients who do not respond to typical neuroleptics (Kane et al. 1988; Kane 1992). In addition, it has been reported to be efficacious in patients with schizoaffective and bipolar disorder who have not responded to conventional pharmacotherapies (Zarate et al. 1995). However, there are patients who do not respond to clozapine, and the need to treat these severely ill patients frequently compels clinicians to adopt therapeutic innovations that lack a sound empirical basis. One strategy is the combination of various other somatic treatments with clozapine, although expert consensus guidelines often have been lacking and frequently reticent about augmentation strategies with clozapine (Frances et al. 1996). For example, the Practice Guidelines for the Treatment of Patients With Schizophrenia by the American Psychiatric Association makes no comments on the therapeutic potential of such strategies other than to caution against the combined use with carbamazepine or benzodiazepines (American Psychiatric Association 1997). Similar warnings were made by members of the Schizophrenia Patient Outcomes Research Team (PORT), and though they suggest adjunctive pharmacotherapy for patients with inadequate response to clozapine, no specific recommendations are made (Lehman and Steinwachs 1998). Nonetheless, combination of other agents with clozapine is not uncommon in clinical practice. In one report of 656 patients in Denmark who were on clozapine, 35 percent were receiving concomitant neuroleptics, 28 percent benzodiazepines, 19 percent anticholinergics, 11 percent antidepressants, 8 percent antiepileptics, and 2 percent lithium (Peacock and Gerlach 1994). Joffe et al. (1996) found that 40 percent of their 39 outpatients were also on other drugs: 23 percent on additional neuroleptics and 17 percent on other medications, usually benzodiazepines.

For this article, we reviewed the literature regarding efficacy and safety of clozapine in combination with other somatic therapies for the treatment of schizophrenia, schizoaffective disorder, bipolar disorder, and major depression. We did not review the drug-drug interaction of those adjunctive drugs that are used to counter the side effects of clozapine or any medications used to treat any concurrent physical illness, as this is beyond the scope of the present review. Reviews on other drug-drug interactions have been done elsewhere (Goff and Baldessarini 1993; Johns and Thompson 1995; Taylor 1997). We sought to evaluate the quantity and quality of the pub-

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lished data and to extrapolate from these data the efficacy and safety of the various combinations.

Method

Because clozapine was first introduced into clinical practice in 1978 (Lehmann and Ban 1997), we performed a manual and computerized (Medline) search from that year to March 1998 of the English language literature. The following terms were cross-referenced with clozapine in the computerized search: adjunctive, antidepressants, augmentation, benzodiazepines, carbamazepine, combination, ECT (electroconvulsive therapy), lithium, neuroleptics, olanzapine, risperidone, SSRIs (selective serotonin reuptake inhibitors), and valproate.

A total of 70 reports involving clozapine with ECT and other medications that have documentation of either efficacy and/or adverse events were reviewed (table 1). There are five controlled studies and three prospective open-label studies, with the remaining reports being retrospective chart analyses or case reports/series. Unfortunately, in most cases well-controlled studies are lacking, making the interpretation of existing data difficult. To arrive at a summary of the findings, we have distinguished the data from controlled studies versus uncontrolled studies and ranked the data in two dimensions: efficacy and safety. For each, a quantitative estimate has been assigned that is based on ranking according to specific operational criteria (table 2). In the case of controlled studies and where there is only a single case report in the extant literature, we have adopted a dichotomous classification of summarizing the efficacy: yes or no.

Results

ECT. There are no controlled trials of ECT and clozapine, although eight anecdotal reports and two retrospective chart analyses state that this combination is effective in schizophrenia (Safferman and Munne 1992; Cardwell and Nakai 1995; Benatov et al. 1996), schizoaffective disorder (Klapheke 1991; Frankenburg et al. 1993; Cardwell and Nakai 1995), bipolar disorder, and depression with psychotic symptoms (Frankenburg et al. 1993; Lurie 1996).

Tachycardia during concurrent clozapine and ECT has been reported but in all these cases, there were no further sequelae (Klapheke 1991; Landy 1991; Safferman and Munne 1992). Beale et al. (1994) documented the occurrence of supraventricular tachycardia during caffeine-augmented ECT in a 66-year-old woman with a history of myocardial infarction who was also receiving clozapine. Subsequent ECT without caffeine was uneventful. Prolonged seizures during ECT were reported in one patient who was on 50 mg/day of clozapine (Bloch et al. 1996), and Masiar and Johns (1991) reported that a patient who had been receiving 800 mg/day of clozapine until 4 days before ECT experienced a prolonged seizure and two tardive grand mal seizures on days 4 and 6 after this first and only ECT treatment. This case was complicated as the individual was also being tapered from long-term diazepam treatment, which had been reduced from 20 mg/day to 5 mg/day in the 2 weeks before ECT. In a retrospective chart analysis, Cardwell and Nakai (1995) did not find any increased seizure activity in their seven patients who had received concurrent clozapine and ECT. The maximum clozapine dosage during ECT was a mean of 580 mg/day (range of 300–800 mg/day) for this group of patients. No clozapine blood levels were measured in these cases.

It is difficult to attribute the aforementioned cardiac complications solely to the combination of clozapine and ECT, as either clozapine monotherapy (Lieberman et al. 1989) or ECT (Abrams 1992) can give rise to tachycardia and cardiac arrhythmias. Clozapine and ECT could, however, have an additive effect when given together. Clozapine may lower seizure threshold and prolong seizure duration during ECT, although clinical states such as premorbid seizure disorder and withdrawal from sedative-hypnotics are probably predisposing factors as well (Klapheke 1993).

Overall, the limited data suggest that ECT during clozapine therapy is generally safe and may be efficacious; however, controlled trials of neuroleptics plus ECT versus clozapine alone versus clozapine plus ECT are needed, as the present data are inconclusive. Duration of effect, the need for maintenance ECT treatment, appropriate clozapine dose, and predictors of response also need to be addressed.

Neuroleptics. Retrospective surveys of the European experience in a naturalistic setting have indicated that the combination of clozapine and typical neuroleptics is common. Povlsen et al. (1985) in a retrospective study found that of 216 patients on clozapine, 120 received other typical neuroleptics, and 30 percent of these patients were reported to have a "better effect" than with previous treatment. Naber et al. (1992), in a chart review of 480 inpatients, found that 18.5 percent were being treated concomitantly with typical neuroleptics. Compared with those receiving clozapine monotherapy, there were significantly more side effects such as delirious states, electroencephalograph alterations, and hypersalivation in those receiving combined therapy. Peacock and Gerlach (1994) found in their survey of psychiatric hospitals in Denmark that 35 percent of 656 patients treated with clozapine also received typical neuroleptics; however, the authors did not describe any adverse effects or response for these patients.

Table 1. Studies of clozapine in combination with other somatic treatments

Combination	*n*	Patient population	Rating scales	Results	Adverse effects
Clozapine and ECT					
Retrospective studies					
Frankenburg et al. 1993	12	Schizophrenia ($n = 2$), schizoaffective disorder ($n = 7$), bipolar disorder ($n = 1$), major depression ($n = 2$)	None	Marked improvement ($n = 3$), moderate improvement ($n = 1$), and minimal improvement ($n = 4$)	None reported
Cardwell and Nakai 1995	7	Schizophrenia ($n = 4$), schizoaffective disorder ($n = 3$)	BPRS	27% improvement in total BPRS, 25% in positive symptoms, and 21% in negative symptoms	None reported
Case reports/series					
Klapheke 1991	1	Acute psychosis	None	Clinical improvement	Tachycardia
Masiar and Johns 1991	1	Schizophrenia	None	None	Grand mal seizures
Bloch et al. 1996	1	Refractory psychosis	None	None	Prolonged seizure
Landy 1991	2	Psychotic depression	None	Relief of affective symptoms	Tachycardia
Saffermann and Munne 1992	1	Schizophrenia	None	Clinical improvement	None reported
Beale et al. 1994	1	Psychotic depression	None	None	Supraventricular tachycardia
Lurie 1996	1	Bipolar disorder	None	Clinical improvement	None reported
Benatov et al. 1996	4	Schizophrenia	BPRS	3 > 40% of total BPRS	None reported
Clozapine and neuroleptics					
Double-blind controlled studies					
With chlorpromazine					
Potter et al. 1989	57	Schizophrenia	BPRS	Significant improvement on withdrawal, conceptual disorganization, unusual thoughts, and hostility items when compared with chlorpromazine alone	None reported
With sulpiride					
Shiloh et al. 1997	28	Schizophrenia	BPRS, SAPS, SANS, HAM-D	Significant reduction in BPRS, SAPS, and SANS but not HAM–D in clozapine-sulpiride group vs. clozapine-placebo group	Hypersalivation, aggravation of tardive dyskinesia, increase in serum prolactin

Table 1. Studies of clozapine in combination with other somatic treatments (Continued)

Combination	*n*	Patient population	Rating scales	Results	Adverse effects
Open-label studies					
With loxapine					
Mowerman and Siris 1996	7	Schizophrenia, schizoaffective	BPRS	Reduction in BPRS ranging from 19–38 points	None reported
With risperidone					
Henderson and Goff 1996	12	Refractory schizophrenia	BPRS	10 < 20% reduction in BPRS	Mild akathisia in 4 patients; hypersalivation in 5 patients
Retrospective studies					
With pimozide					
Friedman et al. 1997	7	Refractory schizophrenia, schizoaffective disorder	BPRS	Significant improvement from baseline BPRS	None reported
Case reports/series					
With risperidone					
McCarthy and Terkelsen 1995	2	Refractory schizoaffective disorder, refractory schizophrenia	None	Clinical improvement	None reported
Koreen et al. 1995	1	Refractory schizophrenia	None	None reported	Mild oculogyric crises
Tyson et al. 1995	1	Refractory schizoaffective disorder	None	Clinical improvement	None reported
Godleski and Sernyak 1996	1	Refractory schizophrenia	None	None	Agranulocytosis
Chong et al. 1996	1	Refractory schizophrenia	None	None	Exacerbation of hoarding behavior
Chong et al. 1997*b*	1	Refractory schizophrenia	None	None	Atrial ectopics
Clozapine and benzodiazepines					
Retrospective studies					
Sassim and Grohmann 1988	39	Schizophrenia (n = 31), organic psychosis (n = 3), affective disorders (n = 3), alcohol addiction (n = 1), movement disorder (n = 1)	None	None reported	Cardiorespiratory collapse (8%), dizziness (28%), sedation (44%)
Faisal et al. 1997	Novartis data base	Schizophrenia (82%); the rest not stated	None	None reported	Cardiorespiratory collapse in 0.3% of those with clozapine-benzodiazepine

Case reports/series					
Cobb et al. 1991	2	Schizoaffective disorder, refractory schizophrenia	None	None reported	Sedation, hypersalivation, and ataxia
Bredbacka et al. 1993	2	Refractory schizophrenia, diagnosis not given in second patient	None	None reported	Cardiorespiratory dysregulation; sudden death in second patient
Klimke and Klieser 1994	1	Refractory schizophrenia	None	None reported	Sudden death
Jackson et al. 1995	3	Schizophrenia, psychotic depression, schizoaffective disorder	None	None	Delirium
Clozapine and mood stabilizers					
Retrospective studies					
With carbamazepine					
Junghan et al. 1993	147	Schizoaffective disorder, bipolar disorder	None	None reported	No significant difference in frequency of agranulocytosis in those with clozapine-carbamazepine vs. clozapine alone
With valproate					
Kando et al. 1994	55	Schizophrenia (n = 17), schizoaffective disorder (n = 23), bipolar disorder (n = 12), psychotic disorder, NOS (n = 2), delusional disorder (n = 1)	None	"Effective" in 41 (87%) of 47 patients	Sedation (62%), enuresis (9%), nausea (9%), hypersalivation (6%), mild elevation of liver function values (24%)
With lithium					
Bender et al. 1996	27	Schizophrenia (n = 13), schizoaffective disorder (n = 13), borderline personality disorder (n = 1)	None	"Effective" in 23 patients	Reversible myoclonus, fatigue
Case reports/series					
With carbamazepine					
Muller et al. 1988	1	Bipolar disorder	None	None	Neuroleptic malignant syndrome
Gerson et al. 1991	1	Schizophrenia	None	None	Fatal agranulocytosis
Rittmannsberger and Leblhuber 1992	2	Schizophrenia	None	None	Myoclonus

Table 1. Studies of clozapine in combination with other somatic treatments (Continued)

Combination	*n*	Patient population	Rating scales	Results	Adverse effects
With valproate					
Costello and Suppes 1995	1	Schizoaffective disorder	None	None	Neurotoxicity (confusion, sedation, slurred speech)
Wirshing et al. 1997	1	Schizoaffective disorder	None	None	Hepatic encephalopathy
With lithium					
Pope et al. 1986	1	Bipolar disorder	None	None	Neuroleptic malignant syndrome
Lemus et al. 1990	1	Schizophrenia	None	None	Myoclonus
Blake et al. 1992	4	Schizophrenia ($n = 2$), schizoaffective disorder ($n = 2$)	None	None	Reversible neurologic symptoms
Valevski et al. 1993	1	Schizoaffective disorder	None	None	Agranulocytosis
Suppes et al. 1994	3	Refractory bipolar disorder	CGI, GAF	Improvement in all 3 patients	None reported
Fuchs 1994	1	Refractory bipolar disorder with obsessive-compulsive disorder	None	Clinical improvement	None reported
Koval et al. 1994	1	Schizophrenia	None	None	Diabetic ketoacidosis
Garcia et al. 1994	2	Schizoaffective disorder ($n = 1$), schizophrenia ($n = 1$)	None	None	Seizures
Puri et al. 1995	1	Bipolar disorder	None	Clinical improvement	None reported
Peterson and Byrd 1996	1	Schizophrenia	None	None	Diabetic ketoacidosis
Clozapine and tricyclic antidepressants					
With clomipramine					
Stoll et al. 1991	1	Bipolar disorder	None	None	Grand mal seizure
With nortriptyline					
Smith and Riskin 1994	1	Schizoaffective disorder	None	None	Neurotoxicity (delirium, confusion, and memory impairment)
Clozapine and SSRIs					
Double-blind controlled studies					
With fluoxetine					
Buchanan et al. 1996	33	Refractory schizophrenia	BPRS, SANS,	No significant difference in positive, negative, and depressive symptoms	No difference between the 2

			HAM–D	between adjunctive fluoxetine vs. placebo	groups
Open-label studies					
With fluvoxamine					
Silver et al. 1996	11	Chronic schizophrenia with persistent negative symptoms	BPRS, SANS, CGI	8 completed 6 weeks trial, 4 > 20% reduction in BPRS, 2 > 20% reduction in SANS	None reported
Case reports/series					
With fluoxetine					
Cassady and Thaker 1992	1	Chronic schizophrenia with obsessive thoughts	None	Clinical improvement	None reported
Eggert et al. 1994	1	Chronic schizophrenia with compulsive behavior	None	Resolution of compulsive behavior	None reported
Kingsbury and Puckett 1995	1	Schizophrenia with depression	None	None reported	Myoclonic jerks
Purdon and Snaterse 1998	1	Schizophrenia	PANSS, BDI	Substantial improvement in psychosis and cognition but not in depression	None reported
With fluvoxamine					
Hiemke et al. 1994	3	Schizophrenia	None	Improvement reported in 1 patient	Slight nausea and dizziness in 1 patient
Silver et al. 1995	1	Refractory schizophrenia	BPRS	54% improvement on BPRS	None reported
Szegedi et al. 1995	1	Chronic schizophrenia	None	Marked improvement in negative symptoms	Sedation, hypersalivation
Dequardo and Roberts 1996	2	Schizophrenia	None	No clinical improvement	Somnolence, slurred speech, ataxic gait, and hypotension in 1 patient
Koponen et al. 1996	2	Schizophrenia with depressive symptoms	None	Improvement of psychotic and depressive symptoms in 1 patient	Hypersalivation, sedation, constipation
Markowitz et al. 1996	1	Schizophrenia and obsessive-compulsive disorder	None	Improvement of both psychotic and obsessive symptoms	Increased anxiety and sedation
Armstrong and Stephans 1997	1	Bipolar disorder	None	None	Dizziness and hypotension
Chong et al. 1997*a*	1	Schizophrenia	BPRS	None	Worsening of psychosis
With sertraline					
Suppes and Rush 1996	1	Schizoaffective disorder with compulsive behavior	None	Improvement of compulsive behavior	None reported

Table 1. Studies of clozapine in combination with other somatic treatments (Continued)

Combination	*n*	Patient population	Rating scales	Results	Adverse effects
Chong et al. 1997*a*	1	Schizophrenia with obsessive-compulsive symptoms	BPRS	None	Worsening of psychosis
With paroxetine					
George et al. 1998	2	Schizoaffective disorder	None	None	Leukopenia
Clozapine and NMDA agonists					
Double-blind controlled studies					
With D-cycloserine					
Goff et al. 1996	10	Schizophrenia	BPRS, SANS	Worsening of negative symptoms in D-cycloserine group	None reported
With glycine					
Potkin et al. 1997	24	Chronic schizophrenia	BPRS	No improvement in negative symptoms	None reported
Clozapine with other agents					
Retrospective studies					
With chlorate hydrate, amobarbital sodium					
Dickson et al. 1994	14	Schizophrenia	None	Reduction in agitation, anxiety and restlessness	None reported
Case reports/series					
With bromocriptine					
Al-Semaan 1996	1	Schizophrenia with pituitary adenoma	None	Improvement in negative symptoms	None reported
With reserpine					
Healy et al. 1997	1	Refractory schizoaffective disorder	None	Clinical improvement	None reported
With ondansetron					
Briskin and Curtis 1997	1	Schizophrenia with Hodgkin's lymphoma	BPRS	Marked improvement in psychosis	None reported

Note.—BDI = Beck Depression Inventory Scale (Beck 1978); BPRS = Brief Psychiatric Rating Scale; CGI = Clinical Global Impression Scale; ECT = electroconvulsive therapy; GAF = Global Assessment of Functioning Scale (Endicott et al. 1976); HAM-D = Hamilton Rating Scale for Depression; NOS = not otherwise specified; PANSS = Positive and Negative Syndrome Scale (Kay et al. 1987); SANS = Scale for Assessment of Negative Symptoms; SAPS = Scale for Assessment of Positive Symptoms; SSRI = selective serotonin reuptake inhibitor.

Table 2. Summary of the types, efficacy, and safety of studies

Combination	Controlled studies	Efficacy	Uncontrolled studies	Efficacy[1]	Safety[2]
Clozapine and ECT	None	—	2 retrospective studies 8 case reports/series	3	2
Clozapine and typical neuroleptics	1 (with chlorpromazine)	No	1 open label study 1 retrospective study	3	2
Clozapine and atypical neuroleptics	1 (with sulpiride)	Yes	1 retrospective study 6 case reports	3	1
Clozapine and benzodiazepines	None	—	2 retrospective studies 4 case reports/series	—	1
Clozapine and carbamazepine	None	—	1 retrospective study 3 case reports	—	1
Clozapine and lithium	None	—	1 retrospective study 10 case reports/series	3	1
Clozapine and valproate	None	—	1 retrospective study 2 case reports	3	1
Clozapine and tricyclic antidepressants	None	—	2 case reports	—	1
Clozapine and SSRIs	1 (with fluoxetine)	No	1 open label study 15 case reports/series	3	1
Clozapine with NMDA agonists	1 (with D-cycloserine) 1 (with glycine)	No	None	—	3
Clozapine and chloral hydrate/ sodium amytal	None	—	1 retrospective study	3	3
Clozapine and reserpine	None	—	1 case report	Yes	3
Clozapine and bromocriptine	None	—	1 case report	Yes	3
Clozapine and ondansetron	None	—	1 case report	Yes	3
Clozapine and dextroamphetamine	None	—	1 case report	Yes	3

Note.—ECT = electroconvulsive therapy; NMDA = N-methyl-D-aspartate; SSRI = selective serotonin reuptake inhibitor.

[1] 3 = generally efficacious, > 50% reports with positive results; 2 = possibly efficacious, < 50% reports with positive reports; 1 = does not appear efficacious

[2] 3 = no adverse effects reported; 2 = adverse effects reported but not life-threatening; 1= adverse reports with at least one report of a life-threatening event

— = no data

A controlled trial conducted at the Shanghai Mental Health Center (Potter et al. 1989) randomized 57 inpatients with schizophrenia to either chlorpromazine alone (n = 20), clozapine alone (n = 17), or clozapine plus chlorpromazine (n = 20). Using a flexible dosing design, the doses of chlorpromazine and clozapine were allowed to reach a maximum of 600 mg/day depending on side effects or response in each of the monotherapy arms, and 400 mg/day of each in the clozapine-chlorpromazine arm. Patients were evaluated over 8 weeks, using the Brief Psychiatric Rating Scale (BPRS; Overall and Gorham 1962) by psychiatrists blind to the medications. No significant differences were found in total BPRS scores among the three treatment groups, but the clozapine and clozapine-chlorpromazine groups demonstrated greater improvement on the withdrawal, conceptual disorganization, unusual thoughts, and hostility items of the BPRS.

In a double-blind study (Shiloh et al. 1997), 28 patients with schizophrenia who were partially responsive to clozapine were randomized to treatment with either clozapine plus 600 mg/day of sulpiride (n = 16) or clozapine plus placebo (n = 12). The patients were rated at the end of 10 weeks on the BPRS, Scale for the Assessment of Positive Symptoms (SAPS; Andreasen 1984), Scale for the Assessment of Negative Symptoms (SANS; Andreasen 1983), and Hamilton Rating Scale for Depression (HAM–D; Hamilton 1960). The clozapine-sulpiride group showed significant improvement in total BPRS scores, with 8 (50%) of the 16 clozapine-sulpiride patients demonstrating more than 20 percent reduction, compared with one (8.3%) of the 12 clozapine-placebo patients. Similar trends were also seen for the SAPS (reduction of > 20% in 37.5% vs. 8.3%, $p = 0.08$) and for the SANS (25% vs. 0%, $p = 0.06$). No differences were found in either group on the HAM–D. The clozapine-sulpiride group did not show any additional extrapyramidal side effects (EPS) but demonstrated a four- to sevenfold increase in serum prolactin levels. It is noteworthy that although the patients were randomized, the control group had a significantly longer hospitalization period before the start of the trial.

Friedman et al. (1997) retrospectively evaluated five patients with schizophrenia and two patients with schizoaffective disorder who had persistent psychotic symptoms despite being on clozapine for 10 months or longer (mean dosage 425 mg/day, range 325–600 mg/day). These patients subsequently received pimozide (mean dosage 4 mg/day, range 2–8 mg/day) for periods varying from 14 to 68 days, and mean BPRS scores fell from 51 to 27 ($p = 0.003$).

Mowerman and Siris (1996) studied the addition of loxapine in a prospective open trial involving seven patients with chronic schizophrenia exposed to at least 9 months of clozapine treatment. In conjunction with a steady dose of clozapine, loxapine 25 mg/day was added for 18 to 50 weeks. All the patients showed clinical improvement with decrease in BPRS total scores ranging from 19 to 38 points (no statistical analyses were done). Plasma clozapine concentrations were assayed in four of the seven patients, and none showed any significant change from baseline.

Of the atypical antipsychotics, there are at present reports of clozapine-risperidone combinations but none involving clozapine-olanzapine. Case reports have cited the efficacy of adding risperidone to ongoing clozapine treatment (McCarthy and Terkelsen 1995; Tyson et al. 1995). Others have reported adverse events: mild oculogyric crisis (Koreen et al. 1995), agranulocytosis (Godleski and Sernyak 1996), exacerbation of hoarding behavior (Chong et al. 1996), and atrial ectopics (Chong et al. 1997*a*). An open 4-week trial involving 12 patients with schizophrenia found that the addition of risperidone (to a maximum of 6 mg/day) was relatively free of adverse effects other than mild akathisia in four patients and a return of hypersalivation in five patients (Henderson and Goff 1996). Total BPRS scores decreased significantly from baseline, with 10 patients showing a ≥ 20 percent reduction. Plasma clozapine levels in seven patients did not show any significant change from baseline.

A limitation common to all the above studies is the lack of information on any prior exposure of the patients to the neuroleptic used for augmentation purposes. This leaves open the question of whether the response observed could have resulted from the second neuroleptic alone.

The mechanisms underlying the apparent enhanced therapeutic effect may involve a synergistic pharmacodynamic interaction. Positron emission tomography (PET) studies have indicated that these agents effect antipsychotic response at doses that result in greater than 60–70 percent dopamine D_2 occupancy (Kapur et al. 1995, 1999). PET studies have shown that the degree of D_2 occupancy in patients treated with clozapine is low (38 to 65%) (Farde et al. 1992), even at serum clozapine concentrations up to 1770 ng/ml (Nordstrom et al. 1995). The augmentation effect of other neuroleptics might therefore result from an additive effect on the low D_2 occupancy, increasing it beyond the identified threshold of 60–70 percent. Indeed, increased D_2 occupancy was indirectly evidenced in the report by Shiloh et al. (1997) through a rise in serum prolactin for patients treated with the clozapine-sulpiride combination. Unfortunately, this additional D_2 occupancy may also induce EPS and perhaps a greater risk of tardive dyskinesia (TD) given that EPS has been associated with D_2 occupancy in excess of 80 percent (Farde et al. 1992; Nordstrom et al. 1993; Kapur and Remington 1996) and risk of TD has been associated with

persistent EPS (Kane et al. 1986). However, it is also possible that clozapine's potent cholinergic and serotonergic antagonism may counter the risk of EPS and therefore TD. On the basis of these findings, there is a rationale to hypothesize that adding a compound that effects its response through higher D_2 occupancy may augment clozapine's clinical response, which appears to be mediated by mechanisms other than high D_2 blockade.

At odds with this explanation are the findings of a 6-week trial of clozapine in individuals switched from oral or depot neuroleptics (Carpenter et al. 1998). Although neuroimaging data were not gathered, the argument is made that D_2 occupancy would be higher during clozapine treatment in those previously treated with depot neuroleptics. However, evaluation of the clinical response failed to distinguish differences based on pretreatment with depot versus oral neuroleptics.

Pharmacokinetic interactions may play a role as well. Tyson et al. (1995) and Koreen et al. (1995) reported an increase in plasma clozapine levels after risperidone augmentation, although this was not shown in a study by Henderson and Goff (1996); a further study involving the addition of loxapine also indicated no significant changes in plasma clozapine concentrations (Mowerman and Siris 1996).

In conclusion, the published data suggest that the combination of clozapine and other neuroleptics is safe and may be potentially efficacious in schizophrenia and schizoaffective disorder when clozapine alone has produced less than optimal improvement. Controlled data, however, still are lacking.

Benzodiazepines. Adjunctive benzodiazepines are often used to treat agitation, irritability, and anxiety in psychosis. Although there is a substantial body of evidence examining the efficacy of adjunctive benzodiazepine treatment with typical neuroleptics (Johns and Thompson 1995), no studies to date have systematically examined this question with clozapine. However, the concomitant use of benzodiazepines and clozapine in clinical practice is not uncommon. Baldessarini and Frankenburg (1991) reported that up to a third of 200 patients whom they had treated with clozapine for the past 10 years were also taking benzodiazepines, with no increase in side effects. Naber et al. (1992), in reviewing the charts of 480 patients treated with clozapine, reported that 82 were on clozapine-benzodiazepine combinations and did not manifest any increase in side effects compared with patients on clozapine monotherapy. Peacock and Gerlach (1994) found that 28 percent of 656 patients treated with clozapine were also receiving benzodiazepines.

In contrast, there are anecdotal reports of adverse drug interactions including hypersalivation, lethargy, delirium, ataxia, and loss of consciousness (Sassim and Grohmann 1988; Grohmann et al. 1989; Cobb et al. 1991; Jackson et al. 1995). Two deaths have been reported, one following three 2-mg doses of intravenous lorazepam over 9 hours (Klimke and Klieser 1994), and the other after rapid institution of clozapine treatment a week following the discontinuation of clonazepam (Bredbacka et al. 1993).

A potentially serious complication with this combination is cardiorespiratory collapse, although rates vary between reports and the data to date reflect anecdotal reports rather than controlled trials. Sassim and Grohmann (1988) found 3 (7.7%) of 39 patients had collapsed while on combined treatment compared with only 1 patient (2.6%) on clozapine monotherapy, while Grohmann et al. (1989) reported a rate of 2.1 percent. Faisal et al. (1997), reviewing the data on file from Novartis Pharmaceuticals Corporation, found that 11 percent of 15,311 patients who were treated with clozapine during the first 18 months of its use in the United States received benzodiazepines as well. Of these, 6 (0.36%) experienced respiratory depression/arrest. The etiologic role of benzodiazepines in this adverse reaction is uncertain. Faisal et al. (1997) suggested that benzodiazepines may increase blood levels of clozapine, but Jerling et al. (1994) compared the ratio of clozapine concentration to dose in matched groups of patients with clozapine alone and clozapine-benzodiazepine combinations and found no such differences. A synergistic pharmacodynamic interaction must also be considered.

Most of the reported cases of cardiorespiratory collapse occurred shortly after adding clozapine to an existing benzodiazepine regimen. On the basis of this observation, Faisal et al. (1997) have suggested that if adjunct benzodiazepines are used, they should be cautiously added only if a therapeutic dose of clozapine has been attained. They also suggest the alternative of either a slow tapering of previous neuroleptics or the addition of a small dose of typical neuroleptic while switching to clozapine to reduce the emergence of anxiety or agitation during the switch.

Mood Stabilizers

Carbamazepine. Gerson et al. (1991) reported a patient who died from sepsis following agranulocytosis while on a multiple drug regime that included clozapine and carbamazepine, leading to the suggestion that the concomitant use of carbamazepine with clozapine has an additive toxic effect on the bone marrow (Gerson and Meltzer 1992). Despite this, Jerling et al. (1994) noted that the use of carbamazepine with clozapine may be common in clinical practice, both to counter the epileptogenic action of clozapine and to augment antipsychotic action. A survey of 656 patients treated with clozapine

found that 8 percent were receiving antiepileptics, and all but one were taking carbamazepine (Peacock and Gerlach 1994). Data from a therapeutic drug monitoring service found that 11 percent of 168 patients on clozapine were also receiving carbamazepine (Jerling et al. 1994). In a retrospective study of 147 patients, Junghan et al. (1993) reported that the frequency of granulocytopenia in patients treated with a clozapine-carbamazepine combination was not significantly different from those on either clozapine alone or clozapine combined with other drugs. Although the authors concluded that an increased risk of agranulocytosis cannot be established from their data, neither can it be denied.

Other reports in the extant literature suggest that this combination may be problematic. Muller et al. (1988) reported a case of neuroleptic malignant syndrome (NMS) that developed 3 days following the addition of clozapine to carbamazepine. However, the NMS resolved after clozapine was stopped, which suggests that it might have been caused by this drug alone. Asterixis was also described in four patients with this combination (Rittmannsberger and Leblhuber 1992). Raitasuo et al. (1993) reported elevation of plasma clozapine levels in two patients subsequent to carbamazepine withdrawal. Carbamazepine induces the cytochrome CYP3A4 (Jerling et al. 1994) and possibly CYP1A2 enzymes (Taylor 1997), and both have been implicated in clozapine's metabolism (Wetzel et al. 1998). This induction could result in a lowering of clozapine levels, which in turn might compromise therapeutic effect (Ereshefsky 1996). These considerations, and in particular the potential risk of haematological complications, pose ethical problems in any prospective study on the efficacy of carbamazepine in combination with clozapine. In the United States, the adjunct use of carbamazepine with clozapine is proscribed.

Valproate. Valproate has been suggested to be a better option than carbamazepine as prophylaxis against the risk of clozapine-induced seizures or as an anticonvulsant with possible additive or synergistic therapeutic effects (Kando et al. 1994). In a retrospective study, Kando et al. (1994) reviewed 55 patients with schizophrenia (n = 17), schizoaffective disorder (n = 23), bipolar disorder (n = 12), psychotic disorder not otherwise specified (n = 2), and delusional disorder (n = 1) who received a combination of clozapine and valproate. The outcome in 87 percent of the patients was assessed to be "effective" with this combination. The side effects noted were sedation (62%), mild elevation of liver function values (24%), enuresis (9%), nausea (9%), and excessive salivation (6%). One patient subsequently developed hepatic dysfunction. Wirshing et al. (1997) also reported a patient who developed acute liver failure with secondary encephalopathy following this combination. Another case of neurotoxicity presenting with sedation and confusion has also been described (Costello and Suppes 1995). In a retrospective study of patients who received clozapine for refractory psychosis, Wilson (1995) judged that 20 patients who also received concurrent anticonvulsants (valproate, carbamazepine, phenobarbital, or clonazepam) had a poorer clinical outcome than the 68 patients who were on clozapine alone. The author suggested that the anticonvulsants might hinder clozapine treatment through pharmacodynamic or pharmacokinetic interactions. The effect of valproate on the metabolism of clozapine is conflicting (Taylor 1997); Centorrino et al. (1994) found a small but significant increase in clozapine plasma levels, while Longo and Salzman (1995) noted a decrease in both clozapine and norclozapine levels.

Lithium. The combination of clozapine and lithium has been anecdotally reported to be effective in cases of refractory bipolar disorder (Fuchs 1994; Suppes et al. 1994; Puri et al. 1995). A retrospective study (Bender et al. 1996) of 27 patients with schizophrenia (n = 13), schizoaffective disorder (n = 13), and borderline personality disorder (n = 1), with a mean duration of 4.1 years and 2.2 years of clozapine and lithium treatment respectively, found the combination to be effective in 23 patients. One patient had reversible myoclonus and five others complained of fatigue. No controlled studies have specifically examined the efficacy of this combination in treatment-refractory schizophrenia or schizoaffective disorder.

Naber et al. (1992), in their review of 480 patients treated with clozapine, found that of those who were also taking lithium (n = 106) there was no increase in side effects. However, there is a report of four patients on this combination experiencing reversible neurological symptoms including spasms, tremor, unsteady gait, confusion, and memory impairment (Blake et al. 1992). There are also reports of myoclonus (Lemus et al. 1990), NMS (Pope et al. 1986), diabetic ketoacidosis (Peterson and Byrd 1996), and agranulocytosis (Valevski et al. 1993). The attribution of these adverse effects to the combination of clozapine and lithium is uncertain, as they have also been reported with clozapine monotherapy (Lieberman and Alvir 1992; Koval et al. 1994; Rames and Christie 1994; Sachdev et al. 1995). The mechanisms underlying the interaction of these two drugs are unknown. Blake et al. (1992) suggested that it is unlikely to be pharmacokinetic in nature as lithium has no effect on the cytochrome P450 enzymes, but instead implicated a possible interaction through the shared serotonergic effects of both medications.

In summary, although there is evidence supporting the efficacy of this combination, there may be potential adverse drug interactions.

Antidepressants

Tricyclic antidepressants. No studies have specifically addressed the efficacy of tricyclic antidepressants with clozapine, but there are two anecdotal reports of adverse effects. Stoll et al. (1991) reported the occurrence of grand mal seizures in two patients receiving clozapine and clomipramine. In a patient with schizoaffective disorder who was taking nortriptyline, the addition of clozapine led to an elevation of plasma nortriptyline levels and the development of delirium, confusion, and memory loss, all of which cleared after nortriptyline was stopped (Smith and Riskin 1994). It has been suggested that combining tricyclic antidepressants with clozapine could exacerbate adverse effects related to increased anticholinergic activity (Wetzel et al. 1998).

SSRIs. Cassady and Thaker (1992) suggested that adding fluoxetine to clozapine in the treatment of refractory schizophrenia may be potentially useful, although in the patient whom they reported, a dose reduction of fluoxetine from 80 mg/day to 60 mg/day was necessary because of the emergence of tremor and nervousness. Buchanan et al. (1996) performed a double-blind controlled study of adjunctive fluoxetine in clozapine-treated patients with residual positive and negative symptoms. Thirty-three patients who had been treated for at least 6 months with clozapine (at doses of 300 mg/day or higher) were randomized to treatment with either adjunctive fluoxetine (n = 18) or placebo (n = 15). Fluoxetine was started at 20 mg/day and held steady for 3 weeks before dose adjustments (maximum of fluoxetine 80 mg) were made according to clinical response. No further dose adjustments were allowed after week 6. At the end of week 8, there were no group differences on the BPRS, SANS, and the HAM–D scores from baseline ratings, nor were there any differences in side effects between the two groups. No assay of blood clozapine concentrations was done. Purdon and Snaterse (1998) reported a patient with refractory schizophrenia who showed improved cognitive functioning with a clozapine-fluoxetine combination but not with sertraline.

Anecdotal reports have suggested the efficacy of a clozapine-fluvoxamine combination in schizophrenia (Hiemke et al. 1994; Silver et al. 1995; Szegedi et al. 1995; Koponen et al. 1996). In an open study, Silver et al. (1996) added fluvoxamine (mean daily dose of 50 mg, range 25–100 mg) to 11 patients with chronic schizophrenia who had received a mean daily dose of 470.5 mg of clozapine for an average of 1.4 years before the trial. Three patients dropped out—two were uncooperative and the other cited tremulousness and weakness. Of the eight who completed the 6-week study, seven showed more than a point improvement on the Clinical Global Impression Scale (CGI; Guy 1976), four showed > 20 percent improvement in BPRS scores, and two showed > 20 percent improvement in SANS scores. Blood levels of clozapine were not evaluated, and no significant changes were noted on laboratory and physical examinations, including assessment of EPS. However, other case reports of clozapine-SSRI combinations have indicated adverse effects such as hypersalivation, sedation, constipation, urinary retention, memory impairment, dizziness, hypotension, worsening of psychotic symptoms, and leukopenia (Hiemke et al. 1994; Koponen et al. 1996; Markowitz et al. 1996; Chong et al. 1997*b*; George et al. 1998).

Although the data from the open study and case reports suggest an apparent accentuation of therapeutic efficacy, the single double-blind study with fluoxetine did not support this. The effect of adjunct SSRI treatment may have different pharmacokinetic and/or pharmacodynamic interactions with clozapine. Silver et al. (1995) suggested that the addition of fluvoxamine may have a modulating effect on the serotonergic-dopaminergic balance, which could result in improved efficacy. Fluvoxamine has also been shown to interfere with the degradation of N-desmethylclozapine and clozapine N-oxide (Wetzel et al. 1998). Compared with clozapine, N-desmethylclozapine has higher affinities for 5-HT_{1C}, 5-HT_2, and D_2 receptors (Kuoppamaki et al. 1993), which could produce a synergistic pharmacodynamic effect with clozapine.

A number of reports have demonstrated that SSRIs such as fluvoxamine, fluoxetine, and sertraline exert a pharmacokinetic effect on clozapine metabolism, leading to an increase in blood clozapine levels (Cassady and Thaker 1992; Hiemke et al. 1994; Centorrino et al. 1996; Wetzel et al. 1998). A probable exception is citalopram, where co-administration with clozapine in five patients did not elevate mean clozapine levels (Taylor et al. 1998). The putative mechanism whereby other SSRIs elevate plasma clozapine levels is through the inhibition of the CYP1A2, CYP2C9, and CYP3A4 isozymes by which clozapine is metabolized (Wetzel et al. 1998). This effect on clozapine levels must be viewed in the context of evidence indicating a correlation between blood clozapine concentrations and clinical response. Miller (1996), in a review of this topic, reported that five of six studies indicated that clozapine plasma concentrations above 350 to 420 ng/mL significantly increase the likelihood of clinical response in patients with treatment-refractory schizophrenia. It is possible, therefore, that the addition of an SSRI elevates clozapine levels in nonresponders to this particular range. In the four case reports that cited enhanced efficacy and where blood clozapine levels were available (Hiemke et al. 1994; Szegedi et al. 1995; Koponen et al. 1996; Markowitz et al. 1996), the reported pre-SSRI blood clozapine concentrations were below 300 ng/mL in

three patients, while the fourth had a level of 400 ng/mL. Subsequent to fluvoxamine augmentation, increased levels of clozapine were noted, together with clinical improvement (Hiemke et al. 1994). While there is the potential of enhancing therapeutic response, increased blood levels may also increase the risk of side effects through anticholinergic and anti-adrenergic activity, and anecdotal reports have cited the occurrence of adverse events in association with high levels (> 900 ng/mL) of clozapine concentrations (Hiemke et al. 1994; Koponen et al. 1996; Markowitz et al. 1996; Chong et al. 1997*b*). Furthermore, risk of seizures has been associated with high circulating clozapine serum levels (Simpson and Cooper 1978).

The limited data to date suggest that combining an SSRI with clozapine can lead to enhanced clinical response. Whether the improvement is subsequent to an increase in blood clozapine concentrations (which could be attained by increasing the dosage of clozapine) is yet to be resolved. The other caveat with this strategy relates to the increased likelihood of side effects with elevated clozapine levels.

N-methyl-D-aspartate (NMDA) agonists. Two studies have used such agents, in line with the NMDA hypothesis of schizophrenia, which postulates that inactivation of NMDA receptors gives rise to certain features of schizophrenia (Olney and Nuri 1995; Coyle 1996). Goff et al. (1996) studied the effect of adding D-cycloserine (a partial agonist of the glycine modulation site) to clozapine. Ten schizophrenia patients were treated consecutively with 2-week trials of placebo and then 15, 50, and 250 mg/day of D-cycloserine. Negative symptoms worsened as shown by a mean increase of 21 percent on the SANS from baseline with 50 mg/day of D-cycloserine. In the other study using glycine as an adjunctive, Potkin et al. (1997) randomized 24 schizophrenia patients to either placebo or glycine for a 12-week period. A significantly greater improvement in positive symptoms was noted with the placebo group while no difference in negative symptoms was found. Both these studies suggest no clinical advantage with the augmentation of clozapine by agents with NMDA agonist–like action. Clozapine has been reported to interact with glutamatergic neurotransmission and found to reverse animal behavior mediated by NMDA receptor antagonists (Brunello et al. 1995). This agonist-like action, if present, might buffer any potential additional benefits that could occur with addition of agents that work through similar mechanisms.

Chloral hydrate/amobarbital sodium. Addressing the potential risk of using benzodiazepines with clozapine, Dickson et al. (1994) conducted a retrospective chart review of 15 schizophrenia patients who were admitted for clozapine initiation. Of these, 5 were given chloral hydrate, and 5 were given sodium amytal for agitation and anxiety. No adverse effects were reported with either, leading the authors to suggest that both drugs may be viable alternatives to benzodiazepines for sedative-hypnotic purposes in patients treated with clozapine. In a case series of five patients on clozapine who developed myoclonus, one of the patients had received concomitant chloral hydrate occasionally (Bak et al. 1995).

Other combinations. In some other combinations there are only single case reports. Healy et al. (1997) suggested that reserpine may be an effective adjunctive to clozapine based on a patient with schizoaffective disorder who showed clinical improvement with this combination. However, this patient had also received valproate and was on clozapine for an unstated period of time. Al-Semaan (1996) reported a patient who initially demonstrated no improvement in negative symptoms after a 6-month trial with clozapine. This patient was later diagnosed as having a pituitary adenoma as well, for which bromocriptine was prescribed. Subsequent to this, an improvement of negative symptoms was seen. Another report described clinical improvement after the addition of ondansetron, a selective 5-HT_3 antagonist, in a patient with schizophrenia who was on clozapine (Briskin and Curtis 1997). This individual was receiving chemotherapy for Hodgkin's lymphoma, and ondansetron was given for the treatment of nausea and vomiting. In another patient with the diagnoses of bipolar disorder, borderline personality disorder, hypothyroidism, and alcoholism in remission, a combination of clozapine and dextroamphetamine was reported to be effective in treating psychotic and affective symptoms (Privitera et al. 1993).

Discussion

At present, there is a lack of compelling evidence to support any specific augmentation strategy with clozapine. However, drawing firm conclusions based on the existing literature reflects difficulties over and above the paucity of controlled studies. Even in those studies available, differences in methodologies, patients' diagnoses and characteristics, outcome measures, and the multiplicity of different drug combinations make comparison of results difficult. The criteria used for initiation of augmentation strategies are often unclear, with no consensus as to when a patient is designated as resistant to clozapine monotherapy. What constitutes an optimal dose and therapeutic plasma level of clozapine remains uncertain (American Psychiatric Association 1997), as is the time course required to evaluate clozapine response (Conley and Buchanan 1997), with the recommended length of an adequate therapeutic trial varying from 12 weeks (American Psychiatric Association 1997) to at least 6 months (Meltzer 1992).

Taking both controlled and uncontrolled reports together, there is evidence to suggest a number of promising augmentation strategies when patients respond poorly to clozapine alone. Tempering this optimism, however, is the fact that controlled reports, albeit few in number, have provided support for only one combination to date: clozapine and sulpiride. At the same time, it is very likely premature to make conclusions on a single report, or conversely to dismiss other combinations given the lack of existing data, particularly controlled studies.

From a safety standpoint, no combination reviewed is absolutely unsafe. Much of the existing literature involves case reports, and while case reports may provide limited validity regarding any inferred therapeutic effects, they have been generally accurate in reporting adverse reactions (Venning 1982). The combined use of benzodiazepines may give rise to potential cardiorespiratory collapse, valproate may cause hepatic dysfunction, lithium may cause neurotoxicity and seizures, and at least some SSRIs appear to elevate plasma clozapine to supratherapeutic levels, resulting in an increased risk of adverse effects. Interestingly, the combination of clozapine and carbamazepine is seen as potentially dangerous by many, although reports to date do not substantiate a significant risk associated with this particular combination. Long-term followup studies are needed to evaluate the safety of any combination, as in the case of clozapine and adjunctive neuroleptics where the risk of TD or other events related to higher D_2 occupancy is not clear.

A pattern related to the reporting of potentially useful augmentation strategies is worthy of note; indeed, it is typical of the evolution of new pharmacological treatments. Routinely, single case reports appear, noting efficacy with a specific combination in the face of relative safety. Findings are skewed toward favorable results as it is common to see only positive reports at this level. As the data expand, usually in the form of case series or uncontrolled investigations, the evidence becomes more qualified. Individuals failing to respond to this particular strategy begin to accumulate, as do reports of side effects. The next step, one of controlled studies, represents the final stage in evaluating the potential benefit of a particular combination. Unfortunately, as seen with clozapine augmentation strategies, evidence frequently falls short at this point. This sequence of events can readily be identified in table 2 if one moves from the single case reports to case series/uncontrolled studies and finally to the controlled trials.

What recommendations can be made for clinicians at this point? Up to 40 percent of individuals tried on clozapine will fail to demonstrate the desired clinical response, and in these cases a decision must be made as to whether clozapine was superior to previous neuroleptics before consideration is given to augmentation strategies. Because of clozapine's cost, risk of agranulocytosis, and requirement for routine hematologic monitoring, it may be preferable to try another atypical neuroleptic or return to treatment with a previous agent that has demonstrated at least an equivalent clinical response (which may or may not have included trials of other atypical compounds). This is said with the caveat that other factors beyond clinical efficacy, such as risk of TD, may continue to favor the choice of clozapine, particularly if a return to a conventional antipsychotic is being considered.

In those patients maintained on clozapine despite less than optimal response, the data are inadequate regarding choice of drug strategy. The clinician's decision may relate to limitations in global improvement, or to specific symptoms within a particular domain, such as persistent negative symptoms, anxiety, or depression. Whichever agent is chosen, clinicians are best advised to proceed with caution regarding untoward, and perhaps unexpected, adverse events. The definitive means to establish whether the observed adverse effect(s) can be attributed to the combination therapy is to rechallenge the patient with the same medications, but the benefit of this has to be weighed against the risk as well as any medicolegal implications (Edge et al. 1997). Any such augmentation trial should state clearly the indications for such intervention—for example, persistent psychotic symptoms, anxiety, or depression—as well as the duration, dosage, and blood levels of clozapine that were previously employed. Objective outcome measures should be used. As best as possible, the trial should be circumscribed with respect to dose and duration, and it should be discontinued if there is no clear evidence of benefit when compared with clozapine alone. Whether the refractory nature of this population necessitates that any treatment intervention, including augmentation strategies, be extended beyond the 1–2 months routinely employed in earlier stages of the illness needs to be more fully evaluated.

References

Abrams, R. *Electroconvulsive Therapy.* 2nd ed. New York, NY: Oxford University Press, 1992.

Al-Seeman, Y. Bromocriptine as adjunctive therapy to clozapine in treatment-resistant schizophrenia. [Letter]. *Canadian Journal of Psychiatry,* 41:484–485, 1996.

American Psychiatric Association. Practice guidelines for the treatment of patients with schizophrenia. *American Journal of Psychiatry,* 154(Suppl 4):1–62, 1997.

Andreasen, N.C. *The Scale for the Assessment of Negative Symptoms (SANS).* Iowa City, IA: The University of Iowa, 1983.

Andreasen, N.C. *The Scale for the Assessment of Positive Symptoms (SAPS)*. Iowa City, IA: The University of Iowa, 1984.

Armstrong, S.C., and Stephens, J.R. Blood clozapine levels elevated by fluvoxamine: Potential for side effects and lower clozapine dosage. [Letter]. *Journal of Clinical Psychiatry*, 58:499, 1997.

Bak, T.H.; Bauer, M.; Schaub, R.; Hellweg, R.; and Reischies, F. Myoclonus in patients treated with clozapine: A case series. *Journal of Clinical Psychiatry*, 56:418–422, 1995.

Baldessarini, R.J., and Frankenburg, F.R. Clozapine—A novel antipsychotic agent. [Review]. *New England Journal of Medicine*, 325:51, 1991.

Beale, M.D.; Pritchett, J.T.; and Kellner, C.H. Supraventricular tachycardia in a patient receiving ECT, clozapine and caffeine. *Convulsive Therapy*, 10:228–231, 1994.

Beck, A.T. *Depression Inventory*. Philadelphia, PA: Center for Cognitive Therapy, 1978.

Benatov, R.; Sirota, P.; and Megged, S. Neuroleptic-resistant schizophrenia treated with clozapine and ECT. *Convulsive Therapy*, 12:117–121, 1996.

Bender, S.A.; Wolstein, J.R.; Ortmann, K.; Blanke, J.U.; and Paulus, H.J. Treatment of schizophrenia and schizoaffective disorder with a combination of clozapine and lithium. *European Neuropsychopharmacology*, 6(Suppl 3):200, 1996.

Blake, L.M.; Marks, R.C.; and Luchins, D.J. Reversible neurologic symptoms with clozapine and lithium. [Letter]. *Journal of Clinical Psychopharmacology*, 12:297–299, 1992.

Bloch, Y.; Pollack, M.; and Mor, I. Should the administration of ECT during clozapine therapy be contraindicated? [Letter]. *British Journal of Psychiatry*,169:253–254, 1996.

Bredbacka, P.E.; Paukkala, E.; and Koponen, H. Can severe cardiorespiratory dysregulation induced by clozapine monotherapy be predicted? *International Clinical Psychopharmacology*, 8:205–206, 1993.

Briskin, J.K., and Curtis, J.L. Augmentation of clozapine therapy with ondansetron. [Letter]. *American Journal of Psychiatry*, 154:1171–1172, 1997.

Brunello, N.; Masotto, C.; Steardo, L.; Markstein, R.; and Racagni, G. New insights into the biology of schizophrenia through the mechanism of action of clozapine. *Neuropsychopharmacology*, 13:177–213, 1995.

Buchanan, R.W.; Kirkpatrick, B.; Bryant, N.; Ball, P.; and Breier, A. Fluoxetine augmentation of clozapine treatment in patients with schizophrenia. *American Journal of Psychiatry*, 153:1625–1627, 1996.

Cardwell, B.A., and Nakai, B. Seizure activity in combined clozapine and ECT: A retrospective view. *Convulsive Therapy*, 11:110–113, 1995.

Carpenter, W.T., Jr.; Conley, R.R.; Buchanan, R.W.; Brier, A.; and Tamminga, C.A. Patient response and resource management: Another view of clozapine treatment with schizophrenia. *American Journal of Psychiatry*, 152:827–832, 1995.

Carpenter, W.T., Jr.; Zito, J.M.; Vitrai, J.; and Volavka, J. Hypothesis testing: Is clozapine's superior efficacy dependent on moderate D2 receptor occupancy? *Biological Psychiatry*, 43:79–83, 1998.

Cassady, S.L., and Thaker, G.K. Addition of fluoxetine to clozapine. [Letter]. *American Journal of Psychiatry*, 149:1274, 1992.

Cavallaro, R.; Colombo, C.; and Smeraldi, E. A pilot, open study on the treatment of refractory schizophrenia with risperidone and clozapine. *Human Psychopharmacology: Clinical and Experimental*, 10:231–234, 1995.

Centorrino, F.; Baldessarini, R.J.; Frankenburg, F.R.; Kando, J.; Volpicelli, S.A.; and Flood, J.G. Serum levels of clozapine and norclozapine in patients treated with selective serotonin reuptake inhibitors. *American Journal of Psychiatry*, 153:820–822, 1996.

Centorrino, F.; Baldessarini, R.J.; Kando, J.; Frankenburg, F.R.; Kando, J.; Volpicelli, S.A.; Puopolo, P.R.; and Flood, J.G. Serum levels of clozapine and its major metabolite effects of cotherapy with fluoxetine or valproate. *American Journal of Psychiatry*, 151:123–125, 1994.

Chong, S.A.; Tan, C.H.; and Lee, H.S. Hoarding and clozapine-risperidone combination. [Letter]. *Canadian Journal of Psychiatry*, 41:315–316, 1996.

Chong, S.A.; Tan, C.H.; and Lee, H.S. Atrial ectopics with clozapine-risperidone combination. [Letter]. *Journal of Clinical Psychopharmacology*, 17:130–131, 1997*a*.

Chong, S.A.; Tan, C.H.; and Lee, H.S. Worsening of psychosis with clozapine and selective serotonin reuptake inhibitor combination: Two case reports. [Letter]. *Journal of Clinical Psychopharmacology*, 17:68–69, 1997*b*.

Cobb, C.D.; Anderson, C.B.; and Siedel, D.R. Possible interaction between clozapine and lorazepam. [Letter]. *American Journal of Psychiatry*, 148:1601–1602, 1991.

Conley, R.R., and Buchanan, R.W. Evaluation of treatment-resistant schizophrenia. *Schizophrenia Bulletin*, 23(4):663–674, 1997.

Costello, L.E., and Suppes, T. A clinically significant interaction between clozapine and valproate. [Letter]. *Journal of Clinical Psychopharmacology*, 15:139–141, 1995.

Coyle, J.T. The glutamate dysfunction hypothesis for schizophrenia. *Harvard Review of Psychiatry,* 3:241–253, 1996.

Dequardo, J.R., and Roberts, M. Elevated clozapine levels after fluoxamine initiation. [Letter]. *American Journal of Psychiatry,* 153:840–841, 1996.

Dickson, R.A.; Williams, R.; and Dalby, J.T. The use of chloral hydrate and sodium amytal during clozapine initiation. *Canadian Journal of Psychiatry,* 39:132–134, 1994.

Dumortier, G.; Lochu, A.; De Mello, P.C.; Ghribi, O.; Rabreau, D.R.; Degrassat, K.; and Desce, J.M. Elevated clozapine concentrations after fluvoxamine initiation. [Letter]. *American Journal of Psychiatry,* 153:738–739, 1996.

Edge, S.C.; Markowitz, J.S.; and Devane, C.L. Clozapine drug-drug interactions: A review of the literature. *Human Psychopharmacology: Clinical and Experimental,* 12:5–20, 1997.

Eggert, A.E.; Crismon, M.L.; and Dolson, P.G. Lack of effect of fluoxetine on clozapine plasma concentrations. [Letter]. *Journal of Clinical Psychiatry,* 55:454–455, 1994.

Endicott, J.; Spitzer, R.L.; Fleiss, J.L.; and Cohen, J. The Global Assessment Scale: A procedure for measuring overall severity of psychiatric disturbance. *Archives of General Psychiatry,* 33:766–771, 1976.

Ereshefsky, L. Pharmacokinetics and drug interactions: Update for new antipsychotics. *Journal of Clinical Psychiatry,* 57(Suppl 11):12–25, 1996.

Faisal, I.; Lindenmayer, J.P.; Taintor, Z.; and Cancro, R. Clozapine-benzodiazepine interactions. [Letter]. *Journal of Clinical Psychiatry,* 58:547–548, 1997.

Farde, L.; Nordstrom, A.L.; Wiesel, F.A.; Pauli, S.; Halldin, S.; and Sedvall, G. Positron emission tomographic analysis of central D1 and D2 dopamine receptor occupancy in patients treated with classical neuroleptics and clozapine: Relation to extrapyramidal side effects. *Archives of General Psychiatry,* 49:538–544, 1992.

Frances, A.; Docherty, J.P.; and Kahn, D.A. The expert consensus guideline series: Treatment of schizophrenia. *Journal of Clinical Psychiatry,* 57(12, Pt B):11–50, 1996.

Frankenburg, F.R.; Suppes, T.; and McLean, P.E. Combined clozapine and electroconvulsive therapy. *Convulsive Therapy,* 9:176–180, 1993.

Friedman, J.; Ault, K.; and Powchik, P. Pimozide augmentation for the treatment of schizophrenic patients who are partial responders to clozapine. *Biological Psychiatry,* 42:522–523, 1997.

Fuchs, D.C. Clozapine treatment of bipolar disorder in a young adolescent. *Journal of the American Academy of Child and Adolescent Psychiatry,* 33:1299–1302, 1994.

Garcia, G.; Crismon, M.L.; and Dorson, P.G. Seizures in two patients after the addition of lithium to a clozapine regimen. [Letter]. *Journal of Clinical Psychopharmacology,* 14:426–427, 1994.

George, T.P.; Innamorato, L.; Sernyak, M.J.; Baldessarini, R.J.; and Centorrino, F. Leukopenia associated with addition of paroxetine to clozapine. [Letter]. *Journal of Clinical Psychiatry,* 59:31, 1998.

Gerson, S.L.; Lieberman, W.R.; Friedenberg, D.; Lee, D.; Marx, J.; and Meltzer, H. Polypharmacy in fatal clozapine-associated agranulocytosis. [Letter]. *Lancet,* 338:262–263, 1991.

Gerson, S.L., and Meltzer, H. Mechanism of clozapine-induced agranulocytosis. *Drug Safety,* 7(Suppl 1):17–25, 1992.

Godleski, L.S., and Sernyak, M.J. Agranulocytosis after addition of risperidone to clozapine treatment. [Letter]. *American Journal of Psychiatry,* 153:735–736, 1996.

Goff, D.C., and Baldessarini, R.J. Drug interactions with antipsychotic agents. *Journal of Clinical Psychopharmacology,* 13:57–67, 1993.

Goff, D.C.; Midha, K.K.; Sarid-Segal, O.; Hubbard, J.W.; and Amico, E. A placebo-controlled trial of fluoxetine added to neuroleptic in patients with schizophrenia. *Psychopharmacology,* 117:417–423, 1995.

Goff, D.C.; Tsai, G.; Manoach, D.S.; Flood, J.; Darby, D.G.; and Coyle, J.T. D-cycloserine added to clozapine for patients with schizophrenia. *American Journal of Psychiatry,* 153:1628–1630, 1996.

Grohmann, R.; Ruther, E.; Sassim, N.; and Schmidt, L.G. Adverse effects of clozapine. *Psychopharmacology,* 99:S101–S104, 1989.

Guy, W., ed. *ECDEU Assessment Manual for Psychopharmacology, Revised.* (DHEW Publication No. [ADU] 76-338.) Rockville, MD: National Institute of Mental Health.

Hamilton, M. A rating scale for depression. *Journal of Neurology, Neurosurgery and Psychiatry,* 23:56–62, 1960.

Healy, D.J.; Dalack, G.W.; and Meador-Woodruff, J.H. Clozapine-reserpine combination for refractory psychosis. [Letter]. *Schizophrenia Research,* 25:259–260, 1997.

Henderson, D.C., and Goff, D.C. Risperidone as an adjunct to clozapine therapy in chronic schizophrenics. *Journal of Clinical Psychiatry,* 57:395–397, 1996.

Hiemke, C.; Weigmann, H.; Hartter, S.; Dahmen, N.; Wetzel, H.; and Muller, H. Elevated levels of clozapine in serum after addition of fluvoxamine. [Letter]. *Journal of Clinical Psychopharmacology,* 14:279–281, 1994.

Jackson, C.W.; Markowitz, J.S.; and Timothy, D.B. Delirium associated with clozapine and benzodiazepine combinations. *Annals of Clinical Psychiatry*, 7:139–141, 1995.

Jerling, M.; Linstrom, L.; and Bertilsson, L. Fluvoxamine inhibition and carbamazepine induction of the metabolism of clozapine: Evidence from a therapeutic drug monitoring service. *Therapeutic Drug Monitoring*, 16:368–375, 1994.

Joffe, G.; Venalaninen, E.; Tupala, J.; Hiltunen, O.; Wahlbeck, K.; Gadeke, R.; and Rimon, R. The effect of clozapine on the course of illness in chronic schizophrenia: Focus on treatment outcome in out-patients. *International Clinical Psychopharmacology*, 11:265–272, 1996.

Johns, C.A., and Thompson, J.W. Adjunctive treatments in schizophrenia: Pharmacotherapies and electroconvulsive therapy. *Schizophrenia Bulletin*, 21(4):607–619, 1995.

Junghan, U.; Albers, M.; and Woggan, B. Increased risk of hematological side-effects in psychiatric patients treated with clozapine and carbamazepine? [Letter]. *Pharmacopsychiatry*, 26:262, 1993.

Kando, J.C.; Tohen, M.; Castillo, J.; and Centorrino, F. Concurrent use of clozapine and valproate in affective and psychotic disorders. *Journal of Clinical Psychiatry*, 55:255–257, 1994.

Kane, J. Clinical efficacy of clozapine in treatment of refractory schizophrenia: An overview. *British Journal of Psychiatry*, 18(Suppl 17):41–54, 1992.

Kane, J.; Honigfeld, G.; Singer, J.; Meltzer, H.; and the Clozaril Collaborative Study Group. Clozapine for the treatment-resistant schizophrenic: A double-blind comparison with chlorpromazine. *Archives of General Psychiatry*, 45:789–796, 1988.

Kane, J.M.; Woerner, M.; Borenstein, M.; Weger, J.; and Lieberman, J. Integrating incidence and prevalence of tardive dyskinesia. *Psychopharmacology Bulletin*, 22:254–258, 1986.

Kapur, S., and Remington, G. Serotonin-dopamine interaction and its relevance to schizophrenia. *American Journal of Psychiatry*, 153:466–476, 1996.

Kapur, S.; Remington, G.; Zipursky, R.B.; Wilson, A.A.; and Houle, S. The D_2 dopamine receptor occupancy of risperidone and its relationship to extrapyramidal symptoms: A PET study. *Life Science*, 57:103–107, 1995.

Kapur, S.; Zipursky, R.B.; and Remington, G. Clinical and theoretical implications of 5-HT_2 and D_2 receptor occupancy of clozapine, risperidone, and olanzapine in schizophrenia. *American Journal of Psychiatry*, 156:286–292, 1999.

Kay, S.R.; Fiszbein, A.; and Opler, L.A. The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. *Schizophrenia Bulletin*, 13(2):261–276, 1987.

Kingsbury, S.J., and Puckett, K.M. Effects of fluoxetine on serum clozapine levels. [Letter]. American *Journal of Psychiatry*, 152:473, 1995.

Klapheke, M.M. Clozapine, ECT, and schizoaffective disorder, bipolar type. *Convulsive Therapy*, 7:36–39, 1991.

Klapheke, M.M. Follow-up on clozapine and ECT. [Letter]. *Convulsive Therapy*, 7:303–305, 1991.

Klapheke, M.M. Combining ECT and antipsychotic agents: Benefits and risks. *Convulsive Therapy*, 9:241–255, 1993.

Klimke, A., and Klieser, E. Sudden death after intravenous application of lorazepam in a patient treated with clozapine. [Letter]. *American Journal of Psychiatry*, 151:780, 1994.

Koponen, H.J.; Leinonen, E.; and Lepola, U. Fluvoxamine increases the clozapine levels significantly. *European Neuropsychopharmacology*, 6:69–71, 1996.

Koreen, A.R.; Lieberman, J.A.; Kronig, M.; and Cooper, T.M. Cross-tapering clozapine and risperidone. [Letter]. *American Journal of Psychiatry*, 152:1690, 1995.

Koval, M.S.; Rames, L.J.; and Christie, S. Diabetic ketoacidosis associated with clozapine treatment. [Letter]. *American Journal of Psychiatry*, 151:1520–1521, 1994.

Kuoppamaki, M.; Syvalahti, E.; and Hietala, J. Clozapine, N-desmethylclozapine are potent 5-HT_{1C} receptor antagonists. *European Journal of Pharmacology*, 245:179–182, 1993.

Lacey, R.L.; Preskorn, S.H.; and Jerkovich, G.S. Is risperidone a substitute for clozapine for patients who do not respond to neuroleptics? [Letter]. *American Journal of Psychiatry*, 152:1401, 1995.

Landy, D.A. Combined use of clozapine and electroconvulsive therapy. *Convulsive Therapy*, 7:218–221, 1991.

Lehman, A.F., and Steinwachs, D.M. Translating research into practice: The Schizophrenia Patient Outcomes Research Team (PORT) treatment recommendations. *Schizophrenia Bulletin*, 24(1):1–10, 1998.

Lehmann, H.E., and Ban, T.A. The history of the psychopharmacology of schizophrenia. *Canadian Journal of Psychiatry*, 42:152–163, 1997.

Lemus, C.; Lieberman, J.; and Johns, C. Myoclonus during treatment with clozapine and lithium: The role of serotonin. *Hillside Journal of Clinical Psychiatry*, 11:127–130, 1990.

Lieberman, J.A., and Alvir, J. Report of clozapine induced agranulocytosis in the United States, incidence and risk factors. *Drug Safety*, 7(Suppl 1):1–2, 1992.

Lieberman, J.A.; Kane, J.M.; and Johns, C.A. Clozapine: Guidelines for clinical management. *Journal of Clinical Psychiatry*, 50:329–338, 1989.

Longo, L.P., and Salzman, C. Valproic acid effects on serum concentrations of clozapine and norclozapine. [Letter]. *American Journal of Psychiatry*, 152:650, 1995.

Lurie, S.N. Combined use of ECT and clozapine. [Letter]. *Journal of Clinical Psychiatry*, 57:94–95, 1996.

Markowitz, J.S.; Gill, H.S.; Lavia, M.; Brewerton, T.D.; and DeVane, C.L. Fluvoxamine-clozapine dose-dependent interaction. [Letter]. *Canadian Journal of Psychiatry*, 41:670–671, 1996.

Masiar, S.J., and Johns, C.A. ECT following clozapine. [Letter]. *British Journal of Psychiatry*, 158:135–136, 1991.

McCarthy, R.H., and Terkelsen, K.G. Risperidone augmentation of clozapine. *Pharmacopsychiatry*, 28:61–63, 1995.

Meltzer, H.Y. Clozapine and ECT. [Reply]. *Archives of General Psychiatry*, 47:219, 1990.

Meltzer, H.Y. Treatment of the neuroleptic-nonresponsive schizophrenic patient. *Schizophrenia Bulletin*, 18(3):515–542, 1992.

Miller, D.D. The clinical use of clozapine plasma concentrations in the management of treatment-refractory schizophrenia. *Annals of Clinical Psychiatry*, 8:99–109, 1996.

Mowerman, S., and Siris, S.G. Adjunctive loxapine in a clozapine-resistant cohort of schizophrenic patients. *Annals of Clinical Psychiatry*, 8:193–197, 1996.

Muller, T.; Becker, T.; and Fritze, J. Neuroleptic malignant syndrome after clozapine plus carbamazepine. [Letter]. *Lancet*, 2:1500, 1988.

Naber, D.; Holzbach, R.; Perro, C.; and Hippus, H. Clinical management of clozapine patients in relation to efficacy and side effects. *British Journal of Psychiatry*, 160(Suppl 17):54–59, 1992.

Nordstrom, A.L.; Farde, L.; Nyberg, S.; Karlsson, P.; Halldin, S.; and Sedvall, G. D_1, D_2, and 5-HT_2 receptor occupancy in relation to clozapine serum concentration: A PET study of schizophrenic patients. *American Journal of Psychiatry*, 152:1444–1449, 1995.

Nordstrom, A.L.; Farde, L.; Weisel, F.A.; Forslund, K.; Pauli, S.; Halldin, C.; and Uppfeldt, G. Central D2-dopamine receptor occupancy in relation to antipsychotic drug effects: A double-blind PET study of schizophrenic patients. *Biological Psychiatry*, 33:227–235, 1993.

Olney, J.W., and Nuri, N.B. Glutamate receptor dysfunction and schizophrenia. *Archives of General Psychiatry*, 52:998–1007, 1995.

Overall, J.E., and Gorham, D.R. The Brief Psychiatric Rating Scale. *Psychological Reports*, 10:799–812, 1962.

Peacock, L., and Gerlach, J. Clozapine treatment in Denmark: Concomitant psychotropic medication and haematologic monitoring in system with liberal usage practices. *Journal of Clinical Psychiatry*, 55:44–49, 1994.

Perkins, D.O., and Lieberman, J.A. Medical complications and selectivity of therapeutic response to atypical antipsychotic drugs. *American Journal of Psychiatry*, 155:272–276, 1998.

Peterson, G.A., and Byrd, S.L. Diabetic ketoacidosis from clozapine and lithium cotreatment. [Letter]. *American Journal of Psychiatry*, 153:737–738, 1996.

Pope, H.G.; Cole, J.O.; Choas, P.T.; and Fulwiler, C.E. Apparent neuroleptic malignant syndrome with clozapine and lithium. *Journal of Nervous and Mental Disease*, 174:493–495, 1986.

Potkin, S.G.; Jin, Y.; Bunney, B.; Gulasekaram, B.; Costa, J.; Keator, D.B.; Telfor, J.; Wu, J.C.; Najafi, A.; and Bunney, W.E. Clinical and brain imaging effects of adjunctive high dose glycine with clozapine in schizophrenia. *Schizophrenia Research*, 24:187–188, 1997.

Potter, W.Z.; Ko, G.N.; Zhang, L.D.; and Yan, W. Clozapine in China: A review and preview of US/PRC collaboration. *Psychopharmacology*, 99:S87–S97, 1989.

Povlsen, U.J.; Noring, U.; Fog, R.; and Gerlach, J. Tolerability and therapeutic effect of clozapine. *Acta Psychiatrica Scandinavica*, 71:176–185, 1985.

Privitera, M.R.; Lamberti, J.S.; and Maharaj, K. Clozapine in a bipolar depressed patient. [Letter]. *American Journal of Psychiatry*, 150:986, 1993.

Purdon, S.E., and Snaterse, M. Selective serotonin reuptake inhibitor modulation of clozapine effects on cognition in schizophrenia. [Letter]. *Canadian Journal of Psychiatry*, 43:84–85, 1998.

Puri, B.K.; Taylor, D.G.; and Alcock, M.E. Low-dose maintenance clozapine treatment in the prophylaxis of bipolar affective disorder. *British Journal of Clinical Practice*, 49:333–334, 1995.

Raitasuo, V.; Lehtovaara, R.; and Huttunen, M.O. Carbamazepine and plasma levels of clozapine. [Letter]. *American Journal of Psychiatry*, 150:169, 1993.

Rames, L.J., and Christie, S. Diabetic ketoacidosis with clozapine treatment. [Letter]. *American Journal of Psychiatry*, 151:1520–1521, 1994.

Rittmannsberger, H., and Leblhuber, F. Asterixis induced by carbamazepine therapy. *Biological Psychiatry*, 32:364–368, 1992.

Sachdev, P.; Kruk, J.; Kneebone, M.; and Kasse, D. Clozapine-induced neuroleptic malignant syndrome review and report of new cases. *Journal of Clinical Psychopharmacology*, 15:365–371, 1995.

Safferman, A.Z., and Munne, R. Combining clozapine with ECT. *Convulsive Therapy*, 8:141–143, 1992.

Sassim, N., and Grohmann, R. Adverse drug reaction with clozapine and simultaneous application of benzodiazepines. *Pharmacopsychiatry*, 21:306–307, 1988.

Shiloh, R.; Zemishlany, Z.; Aizenberg, D.; Radwan, M.; Schwartz, B.; Dorfman-Etrog, P.; Modai, I.; Khaikin, M.; and Weizman, A. Sulpiride augmentation in people with schizophrenia partially responsive to clozapine. *British Journal of Psychiatry*, 171:569–573, 1997.

Silver, H.; Kaplan, A.; and Jahjah, N. Fluvoxamine augmentation for clozapine-resistant schizophrenia. [Letter]. *American Journal of Psychiatry*, 152:1098, 1995.

Silver, H.; Kushnir, M.; and Kaplan, A. Fluvoxamine augmentation in clozapine-resistant schizophrenia: An open pilot study. *Biological Psychiatry*, 40:671–674, 1996.

Simpson, G.M., and Cooper, T.A. Clozapine plasma levels and convulsions. *American Journal of Psychiatry*, 135:99–100, 1978.

Smith, R.C.; Chua, J.W.; Lipetsker, B.; and Bhattacharyya, A. Efficacy of risperidone in reducing positive and negative symptoms in medication-refractory schizophrenia: An open prospective study. *Journal of Clinical Psychiatry*, 57:460–466, 1996.

Smith, T., and Riskin, J. Effect of clozapine on plasma nortriptyline concentration. *Pharmacopsychiatry*, 27:41–42, 1994.

Still, D.J.; Dorson, P.G.; Crimon, M.L.; and Pousson, C. Effects of switching inpatients with treatment-resistant schizophrenia from clozapine to risperidone. *Psychiatric Services*, 47:1382–1384, 1996.

Stoll, A.L.; Pope, H.G.; and McElroy, S.L. High-dose fluoxetine: Safety and efficacy in 27 cases. [Letter]. *Journal of Clinical Psychopharmacology*, 11:225–226, 1991.

Suppes, T.; Philips, K.A.; and Judd, C.R. Clozapine treatment of nonpsychotic rapid cycling bipolar disorder: A report of three cases. *Biological Psychiatry*, 36:338–340, 1994.

Suppes, T., and Rush, A.J. Medication optimization during clozapine treatment. [Letter]. *Journal of Clinical Psychiatry*, 57:307–308, 1996.

Szegedi, A.; Wiesner, J.; and Heimke, C. Improved efficacy and fewer side effects under clozapine therapy after addition of fluvoxamine. [Letter]. *Journal of Clinical Psychopharmacology*, 15:141–143, 1995.

Taylor, D. Pharmacokinetic interactions involving clozapine. *British Journal of Psychiatry*, 10:9–12, 1997.

Taylor, D.; Ellison, L.; Ementon, S.; Wickham, H.; and Murray, R. Co-administration of citalopram and clozapine: Effect on plasma clozapine levels. *International Clinical Psychopharmacology*, 13:19–21, 1998.

Tyson, S.C.; Devane, C.L.; and Risch, S.C. Pharmacokinetic interaction between risperidone and clozapine. [Letter]. *American Journal of Psychiatry*, 152:1401–1402, 1995.

Valevski, A.; Modai, I.; Lahav, M.; and Weizman, A. Clozapine-lithium combined treatment and agranulocytosis. *International Clinical Psychopharmacology*, 8:63–65, 1993.

Venning, G.R. Validity of anecdotal reports of suspected adverse drug reactions: The problem of false alarms. *British Medical Journal (Clin Res Ed)*, 284:249–252, 1982.

Wetzel, H.; Anghelescu, I.; Szegedi, A.; Wiesner, J.; Weigmann, H.; Hartter, S.; and Heimke, C. Pharmacokinetic interactions of clozapine with selective serotonin reuptake inhibitors: Differential effects of fluvoxamine and paroxetine in a prospective study. *Journal of Clinical Psychopharmacology*, 18:2–9, 1998.

Wilson, W. Do anticonvulsants hinder clozapine treatment? *Biological Psychiatry*, 37:132–133, 1995.

Wirshing, W.C.; Ames, D.; Bisheff, S.; Pierre, J.M.; Mendoza, A.; and Sun, A. Hepatic encephalopathy associated with combined clozapine and divalproex. [Letter]. *Journal of Clinical Psychopharmacology* 17:120–121, 1997.

Zarate, C.A.; Tohen, M.; and Baldessarini, R.J. Clozapine in severe mood disorders. *Journal of Clinical Psychiatry*, 56:411–417, 1995.

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