When Symptoms Persist: Choosing Among Alternative Somatic Treatments for Schizophrenia

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Abstract

Many patients with schizophrenia continue to have significant disabling symptoms despite adequate trials of different types and doses of traditional neuroleptics. Clinicians treating these neuroleptic-resistant patients must look to other treatments in the hope of providing some relief. The literature on many of the alternative treatments is too scanty for firm conclusions. We offer criteria for deciding which treatments may warrant consideration. We review the evidence for the eight treatments we found to meet these criteria and discuss clinical points salient to their use in this population. Although not always conclusive, the data do offer clues for treatment guidelines and an approach to choosing among the available treatments is suggested.

Managing a patient with chronic schizophrenia involves combining somatic treatments and various adjunctive psychosocial therapies (Liberman and Mueser 1989). Among the somatic treatments, the efficacy of neuroleptics in alleviating psychotic symptoms is well documented. About 25 percent of schizophrenic patients, however, have significant symptoms on traditional neuroleptics that remain refractory despite trials of different classes and doses of neuroleptics and despite thorough searches for other contributory medical conditions and for medication side effects (Davis and Casper 1977).

These are the neuroleptic-resistant patients, many of whom are quite disabled by their refractory symptoms. Clinicians treating these patients are compelled to consider what other available treatments might offer some relief. Unfortunately, choices about which agents or treatments

to try are often made in a semirandom fashion, because the body of reliable data about most alternative treatments is not conclusive about the place of the treatment in neuroleptic-resistant schizophrenia. The lack of clearly conclusive data in the literature, however, does not mean that the clinician can or should ignore these treatments. Individual patients do respond, and the improvement can make a clear difference in the quality of life for them and their families. How, then, should a physician choose? Which treatments warrant consideration? Among them, which appear more likely to offer benefit and should therefore be considered first? These are the questions we address in this review. We believe the available data, although often insufficient for definite conclusions, do offer clues on which to build initial guidelines for treating these often difficult patients.

Which Treatments Warrant Consideration?

For this review, a treatment had to meet two criteria to be considered potentially useful.

1. Evidence from double-blind, controlled studies of consistent superiority to placebo (PBO) in patients with schizophrenia, or of benefit to a specific subgroup of patients. For many treatments, good results are described in case reports or open trials but are not found in subsequent controlled trials. Patients with chronic schizophrenia who are given

a new drug are as likely as other patients to have a PBO response. For a treatment to be included for consideration we therefore required that there be at least three double-blind, controlled trials in patients diagnosed with schizophrenia or schizoaffective illness, and that half or more of these studies report statistically significant benefit from the treatment. It is, however, fully conceivable that although a treatment might not be found effective in general populations of patients with schizophrenia, a specific subgroup might consistently benefit. Because some controlled data suggest that this possibility may be true for L-dopa, L-dopa is also included.

The treatments discussed were found in controlled studies to have some beneficial effect on positive or negative symptoms or aggressive outbursts in patients with schizophrenia. Aggressive outbursts were included because such behavior is important in clinical management and is often a target symptom for neuroleptics. Although depression is also a common symptom in patients with schizophrenia, it is not usually a symptom treated with neuroleptics, and discussion of its management is beyond the scope of this article.

2. Evidence of benefit to neuroleptic-resistant patients. Patients who respond poorly to traditional neuroleptics are, by definition, a subgroup with a pattern of drug responsivity different from that of most patients with schizophrenia. Thus, there is no reason to assume that nonneuroleptic treatments that are found to have some efficacy in general populations of patients with schizophrenia will have similar benefit in the neuroleptic-resistant subgroup. We therefore required that there be some evidence of benefit in neuroleptic-resistant patients. Unfor-

tunately, the literature addressing these patients is quite limited, with few controlled studies and no consistent definition of neuroleptic resistance. We have therefore included some treatments for which usefulness in this population is based on findings from uncontrolled or retrospective studies. For the purposes of this review, any study that described its patients as having prominent symptoms despite neuroleptic treatment (however poorly or thoroughly that treatment was documented) was categorized as a study that addressed "neuroleptic-resistant" patients.

Clozapine (CLOZ), lithium, benzodiazepines, electroconvulsive therapy (ECT), reserpine, carbamazepine (CBZ), possibly propranolol (PPL), and L-dopa fulfilled these criteria. Evidence for efficacy of each treatment and points relevant to its use are discussed. Finally, an approach to choosing among these treatments is presented.

Eight Alternative Treatments

Clozapine (CLOZ). Although CLOZ (table 1) is structurally related to loxapine, it is considerably different from conventional neuroleptics in its neurochemical effect (Richelson 1984) and its side-effect profile (Fisher-Cornelssen and Ferner 1976; Povlsen et al. 1985). Several studies have shown CLOZ to be an effective antipsychotic agent (Fisher-Cornelssen and Ferner 1976; Shopsin et al. 1979; Claghorn et al. 1987; Kane et al. 1988); particularly intriguing is the growing evidence that CLOZ benefits patients in whom other neuroleptics produce minimal improvement. In an impressive multicenter collaborative study, Kane et al. (1988) compared CLOZ with chlorpromazine (CPZ) plus benztropine in 268 patients with

schizophrenia, who were rigorously documented as minimally responsive to multiple neuroleptic trials, including a prospective 6-week haloperidol (HPL) trial performed by the investigators.

CLOZ produced superior improvement in ratings of positive and negative symptoms and in global ratings. The most impressive aspect of the results involved the use of predetermined rigorous criteria for classifying patients as responders. By these criteria, 30 percent of the CLOZ patients were found to have clinically significant improvement after a 6-week trial, versus 4 percent of CPZ patients.

These data strongly suggest that approximately one-third of neuroleptic-resistant patients will show considerable improvement with CLOZ, a major therapeutic advance in the treatment of this difficult patient population. The use of CLOZ has been the topic of recent excellent reviews (Kane 1989; Lieberman et al. 1989). Unfortunately, the incidence of agranulocytosis that occurs with CLOZ is reported by Kane (1989) to be 1.6 percent of patients who take the drug for 1 year. This side effect caused some fatalities after the initial release of the drug in other countries (Idänpään-Keikkilä et al. 1975), but it is apparently fully reversible if CLOZ is promptly discontinued (Kane 1989). Because agranulocytosis can appear more than 1 year after the start of treatment (Kane 1989), weekly complete blood counts are currently required.

The daily CLOZ doses used in the studies listed in table 1 ranged from 300 mg to 900 mg, but a markedly increased incidence of seizures is noted above 600 mg (Lieberman et al. 1989). Significant improvement has been reported by some investigators in the first 2 to 3 weeks of

Table 1. Double-blind studies of clozapine (CLOZ) in schizophrenia

Study	Number of patients	Patient description	Study design	Outcome measures	Results	Comments
Fisher-Cornelssen and Ferner (1976)	723	Moderate to severe, acute paranoid schizophrenics.	CLOZ (mean daily dose 300 mg) vs. CPZ (350 mg), trifluroperazine (30 mg), HPL (8 mg), or clopenthixol (100 mg).	BPRS, undefined global rating.	CLOZ found as effective as the other neuroleptics.	
Shopsin et al. (1979)	31	"Floridly psychotic" newly admitted patients with "acute schizophrenic symptoms."	PBO vs. CPZ (max. dose 1600 mg/d) vs. CLOZ (max. dose 900 mg/d) for 5 wks.	BPRS; CGI; NOSIE.	Both active treatments produced improvement; only CLOZ statistically superior to PBO.	Hypersalivation noticed in 11 of 13 CLOZ patients; only 12 of 31 patients completed study.
Claghorn et al. (1987)	151	Hospitalized patients with schizophrenia diagnosed by DSM-II.	CPZ (max. dose about 800 mg/d) vs. CLOZ (max. dose about 400 mg/d) for 3 wks.	BPRS; CGI; NOSIE.	CLOZ statistically superior to CPZ on all BPRS clusters, total BPRS, and CGI.	Hypersalivation noted in 30 of 75 CLOZ patients, interfered with treatment in 4 patients; no cases of agranulocytosis.
Kane et al. (1988)	268	Patients with DSM-III schizophrenia, rated at least "moderately ill," who had failed to respond to 3 neuroleptic trials and 1 prospective 6-wk HPL trial.	CLOZ (max. dose 900 mg/d) vs. CPZ (max. dose 1800 mg/d) plus benztropine (max. dose 6 mg/d) for 6 wks.	BPRS; CGI; NOSIE.	CLOZ superior to CPZ in reduction of ratings of positive symptoms, negative symptoms, and global scores. Prior criteria for global response met by 30% of CLOZ patients, 4% of CPZ patients.	

Abbreviations.—CLOZ = clozapine; CPZ = chlorpromazine; HPL = haloperidol; PBO = placebo.

Scales.—BPRS = Brief Psychiatric Rating Scale (Overall and Gorham 1962); CGI = Clinical Global Impressions (Guy 1976); NOSIE = Nurses Observation Scale for Inpatient Evaluation (Honigfeld et al. 1966); DSM-II = Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association 1968); DSM-III = Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association 1980).

CLOZ trials (Fisher-Cornelssen and Ferner 1976; Kane et al. 1988). Because risk of agranulocytosis is greatest between 6 weeks and 6 months of treatment (Kane 1989; Lieberman et al. 1989), discontinuing a CLOZ trial after 6 weeks has been recommended if no definite improvement has been seen (Kane et al. 1988). Meltzer (1989), however, reported the results of persisting with an uncontrolled trial of CLOZ in neuroleptic-resistant patients for up to 1 year. He noted that only 30 percent of eventual responders had clearly improved in the first 6 weeks and suggested that 9 months or more may be required for a fully adequate trial. These data await verification from PBO-controlled investigations, but they suggest that continuing a CLOZ trial in a carefully monitored fashion beyond 6 weeks may be warranted in some cases.

Lithium. There is considerable evidence that adding lithium (table 2) to neuroleptics will reduce symptoms for some patients with schizophrenia who respond poorly to neuroleptics alone. Of the 10 double-blind investigations into the use of lithium in schizophrenia (Johnson 1970; Shopsin et al. 1971; Prien et al. 1972; Small et al. 1975; Alexander et al. 1979; Biederman et al. 1979; Growe et al. 1979; Carmen et al. 1981; Braden et al. 1982; Lerner et al. 1988), only three specifically studied neuroleptic-resistant patients (Small et al. 1975; Growe et al. 1979; Carmen et al. 1981). Six of the seven other studies examined patients in the midst of acute psychotic exacerbation (Johnson 1970; Shopsin et al. 1971; Prien et al. 1972; Biederman et al. 1979; Braden et al. 1982; Lerner et al. 1988), and in six trials patients with a mixture of affective and schizophrenic symptoms were either

specifically chosen (Johnson 1970; Prien et al. 1972; Biederman et al. 1979; Braden et al. 1982) or were the majority of the patients studied (Shopsin et al. 1971; Alexander et al. 1979). Collectively these seven studies document that lithium alone is inferior to neuroleptics as a first-line agent in acutely psychotic patients but may be useful as an adjunct to neuroleptics in some patients with schizophrenia or schizoaffective illness.

The three studies (Small et al. 1975; Growe et al. 1979; Carmen et al. 1981) that examined the role of lithium as an adjunctive treatment in patients with symptoms resistant to neuroleptics were well designed. All used strict diagnostic criteria (Research Diagnostic Criteria [RDC; Spitzer et al. 1978] or Feighner Criteria [Feighner et al. 1972]) and employed a PBO-controlled, multiple crossover design whereby patients received two separate, 4-week trials of lithium alternating with two 4-week periods of PBO treatment. Most patients were diagnosed with schizophrenia, the remainder with schizoaffective illness; all had been frequently or chronically hospitalized. All three studies found statistically significant results favoring lithium. The study with the smallest number of patients (eight) found improvement on only one subscale (psychotic excitement) (Growe et al. 1979). The other two studies, both of which studied chronic, "poor prognosis" patients, reported clear clinical improvement with lithium in one-third to one-half of their patients (Small et al. 1975; Carmen et al. 1981). The improvement was large enough in some cases that patients were discharged to less restrictive living situations than had previously been possible (Small et al. 1975). The patients who responded to lithium

improved in multiple areas, including psychotic symptoms, cooperation, social competence, neatness, irritability, and excitement (Small et al. 1975; Carmen et al. 1981). These data are encouraging and suggest that a percentage of chronic, poor-prognosis schizophrenic and schizoaffective patients benefit from having lithium added to their neuroleptic regimen.

The literature is clear that affective symptoms need not be present for patients with schizophrenia to respond to lithium (Small et al. 1975; Alexander et al. 1979; Carmen et al. 1981) and that such a response does not demand a subsequent change of diagnosis to affective disorder. There is some evidence, however, that the presence of affective symptoms, including mild depression, predicts a greater likelihood of response to adjunctive lithium (Lerner et al. 1988). Research into biological predictors of response, reviewed by Donaldson et al. (1986), has yielded isolated findings that require replication and further study before they could be considered clinically useful.

Lithium may decrease not only chronic symptoms but also the rate of relapse in some schizoaffective patients. In a large collaborative prospective study over 2 to 4 years (Angst et al. 1970), lithium increased the interval between episodes by 30 percent in patients diagnosed as having schizoaffective disorder. Similar studies have not been carried out for schizophrenic patients without affective symptoms.

Investigators reporting the best results with lithium used doses sufficient to produce mean serum levels of 0.9 to 1.2 mEq/l (Prien et al. 1972; Alexander et al. 1979; Biederman et al. 1979; Carmen et al. 1981; Braden et al. 1982) in trials lasting from 3 to 5 weeks. Although some

Table 2. Double-blind studies of lithium in schizophrenia

Study	Number of patients	Patient description	Study design	Outcome measures	Results	Comments
Johnson (1970)	11	"Schizoaffective, excited phase."	Lithium alone vs. CPZ.	Undefined global rating.	1 patient showed global improvement on lithium.	5 lithium patients developed a confusional state with therapeutic levels.
Shopsin et al. (1971)	21	Acute admissions, hospital diagnosis; affective symptoms in 14 patients.	Lithium alone vs. 1200 mg CPZ, 3-wk trial.	CGI; BPRS; IMPS; SCI; NOSIE; a self-rating scale.	CPZ superior to lithium; lithium patients worsened on some psychosis scales.	6 of 11 lithium patients developed delirium at serum levels < 1.2 mEq/l.
Prien et al. (1972)	83	Acute admissions, DSM–II bipolar manic or SA with manic symptoms.	Lithium alone vs. CPZ. 3-wk trial.	BPRS; IMPS; PIP.	CPZ superior in "highly active" patients; improvement with both drugs in "mildly active" patients.	Early dropout rate 22% for lithium, 11% for CPZ, highest among hostile, active patients.
Small et al. (1975)	22	Neuroleptic-resistant, "very chronically ill," poor-prognosis patients, diagnosed by Feighner criteria; 8 also met criteria for affective disorder.	Lithium vs. PBO added to neuroleptic, 3 crossovers, 4 wks each phase.	CGI; BPRS; NOSIE; MSRS; neuropsychological tests.	10 of 20 completing study showed definite improvement on lithium, statistically significant in several areas on rating scales.	Cognitive tests showed no group neurotoxicity; one patient developed toxic confusion; no reliable predictors of good response to lithium.
Alexander et al. (1979)	13	RDC diagnosis, 5 schizophrenic, 8 SA (3 manic, 5 depressed).	Crossover design: lithium vs. PBO, 3 wks each phase, no neuroleptic.	BHGRS.	Favorable response in 2 of 5 schizophrenics, 5 of 8 SA; modest improvement, no complete remissions.	Improvement in 1st wk seemed to predict response at 3 wks.
Biederman et al. (1979)	36	Acute admissions, "schizo-manic": elevated mood or hyperactivity plus delusions or hallucinations; 13 had interepisode schizophrenic symptoms.	Lithium vs. PBO added to neuroleptic, 5-wk trial.	BPRS; CGI; MSRS.	Lithium superior in patients with good functioning between episodes, trend favoring lithium in patients with interepisode schizophrenic symptoms.	1 patient developed toxic confusion.

Table 2. Double-blind studies of lithium in schizophrenia—Continued

Study	Number of patients	Patient description	Study design	Outcome measures	Results	Comments
Growe et al. (1979)	8	RDC, 2 SA; median of 3 prior admissions; poor response to medication.	Lithium vs. PBO added to neuroleptic; 3 crossovers, 4 wks each phase.	PIP.	Only 1 of 8 areas (psychotic excitement) showed significant improvement; 2 areas showed improvement trend.	Small number of patients; no toxic confusion seen.
Carmen et al. (1981)	18	RDC, 7 SA, 11 schizophrenic; poor functioning; chronic or frequent hospitalizations.	Lithium vs. PBO added to neuroleptic; 3 crossovers, 4 wks each phase.	BPRS.	Clinically relevant changes: decreased psychosis in 5 (3 SA); decreased arousal in 8 (4 SA).	3 of 4 best lithium responders relapsed on removal of neuroleptic.
Braden et al. (1982)	78	Acute admission; at least 2 symptoms of mania; 12 schizophrenics, 31 SA, 30 bipolar, 5 "other" by RDC.	Lithium vs. CPZ, 3-wk trial.	BPRS; global severity ratings.	CPZ superior for physically overactive patients; lithium = CPZ for the remaining patients.	None of several diagnostic systems predicted outcome; 4 patients with toxic confusion; lithium affected both psychotic and affective symptoms.
Lerner et al. (1988)	41	Acutely admitted patients meeting RDC for schizophrenia or SA, mainly schizophrenic.	Lithium vs. PBO added to HPL.	BPRS.	Significant lithium-PBO difference seen only in patients with at least mild depressive symptoms.	

Abbreviations.—CPZ = chlorpromazine; PBO = placebo; SA = schizoaffective; HPL = haloperidol.

Scales.—CGI = Clinical Global Impressions (Guy 1976); BPRS = Brief Psychiatric Rating Scale (Overall and Gorham 1962); IMPS = Inpatient Multidimensional Psychiatric Scale (revised) (Lorr and Klett 1966); SCI = Structured Clinical Interview (Burdock and Hardesty 1968); NOSIE = Nurses Observation Scale for Inpatient Evaluation (Honigfeld et al. 1966); *DSM-II* = Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association 1968); PIP = Psychotic Inpatient Profile (Lorr and Vestre 1968); Feighner Criteria (Feighner et al. 1972); MSRS = Manic State Rating Scale (Beigel et al. 1971); RDC = Research Diagnostic Criteria (Spitzer et al. 1978); BHGRS = Bunney-Hamburg Global Rating Scale (Bunney and Hamburg 1963).

reported definite clinical improvement in the first week (Alexander et al. 1979), others noted transient worsening in the first 10 days—even in patients who eventually responded after 4 weeks (Carmen et al. 1981). It appears, therefore, that at least 3 to 4 weeks with serum lithium levels of 0.9 to 1.2 mEq/l are necessary to assess the effect of lithium fully.

Some patients may benefit from lithium alone, but the best results have come from studies using it in combination with neuroleptics. It is of interest that, in one study (Carmen et al. 1981) of adjunctive lithium use in chronic patients poorly responsive to neuroleptics, the four best lithium responders were subsequently given an open trial of lithium alone. Three relapsed in 6 to 8 months; all responded to reinstatement of their neuroleptic.

Reversible delirium at therapeutic lithium levels is seen sometimes with lithium-neuroleptic combinations (Johnson 1970; Shopsin et al. 1971; Small et al. 1975; Braden et al. 1982) and appears to be more frequent when high neuroleptic doses are used (Miller and Menninger 1987). This delirium resolves rapidly when the drug is discontinued and is distinct from the disabling, irreversible neurotoxic reactions described in some patients who receive lithium-neuroleptic combinations (Cohen and Cohen 1974). The severe reactions described were most likely cases of neuroleptic malignant syndrome (NMS) (Pope et al. 1986). Adjunctive lithium has been implicated in increasing NMS risk (Pope et al. 1986; Susman and Addonizio 1988), but this effect remains speculative. Certainly all clinicians using neuroleptics, perhaps especially when in combination with lithium, must be watchful for changes in cognitive

functioning or the development of new neurologic symptoms.

Benzodiazepines. Benzodiazepines (table 3) are often used in acute exacerbations of psychotic symptoms to reduce agitation, and some double-blind evidence suggests they may speed resolution of the exacerbation (Nestoros et al. 1982). Benzodiazepine trials in patients who were not in the midst of an acute exacerbation but who had more chronic psychotic symptoms have produced mixed results. We found 11 double-blind studies that investigated the use of a benzodiazepine in a study population composed solely of patients diagnosed with chronic schizophrenia (Hekimian and Friedhoff 1967; Holden et al. 1968; Kellner et al. 1975; Lingjaerde et al. 1979; Ruskin et al. 1979; Jimerson et al. 1982; Karson et al. 1982; Nestoros et al. 1982; Wolkowitz et al. 1986, 1988; Csernansky et al. 1988). The results are almost evenly split: six studies reported significant benefit relative to PBO (Kellner et al. 1975; Ruskin et al. 1979; Jimerson et al. 1982; Nestoros et al. 1982; Wolkowitz et al. 1986, 1988), and five did not (Hekimian and Friedhoff 1967; Holden et al. 1968; Ruskin et al. 1979; Karson et al. 1982; Csernansky et al. 1988). Drawing conclusions from this body of data is difficult, especially because several of these studies used a very small number of patients (Kellner et al. 1975; Ruskin et al. 1979; Jimerson et al. 1982; Wolkowitz et al. 1986), and several did not use standardized diagnostic criteria (Hekimian and Friedhoff 1967; Holden et al. 1968; Lingjaerde et al. 1979; Ruskin et al. 1979). Dosage and trial duration also varied widely—but neither higher doses nor longer trials were associated with more consistently positive results.

Several studies using crossover designs clearly document that some patients respond significantly better to having a benzodiazepine rather than a PBO added to their neuroleptic regimen (Kellner et al. 1975; Jimerson et al. 1982; Wolkowitz et al. 1986). These responders, however, are definitely in the minority (Kellner et al. 1975; Jimerson et al. 1982). Thus, the likelihood of a study finding a statistically significant group benefit may depend on what percentage of the study population happens to belong to the subgroup of responders.

Although there are no firm predictors of response, there is some evidence that patients with more severe anxiety or psychosis are more likely to respond. In one of the more detailed investigations of the addition of a benzodiazepine to a neuroleptic regimen, Kellner et al. (1975) studied six patients with schizophrenia who were selected for anxiety and a probable response to adjunctive chlordiazepoxide (known from an earlier open trial). The patients were switched from chlordiazepoxide to PBO and back as many as 10 times in a double-blind fashion. Three patients had a consistent antipsychotic response to chlordiazepoxide compared with PBO, and in two of these three the response was particularly dramatic. These two patients were the most floridly symptomatic, scoring higher than all other patients on global ratings as well as symptom ratings of anxiety, depression, thought disorder, hostility, hallucinatory behavior, and excitement. In addition, in the recent report by Wolkowitz et al. (1988), patients with higher baseline anxiety and psychosis ratings demonstrated the largest symptom reductions with adjunctive alprazolam.

Table 3. Double-blind studies of benzodiazepines in schizophrenia

Study	Number of patients	Patient description	Study design	Outcome measures	Results	Comments
Hekimian and Friedhoff (1967)	30	Hospital diagnoses of schizophrenia.	CDZP alone vs. 450 mg/d CPZ vs. PBO; mean max. dose 231 mg/d for 10–15 d.	Global ratings; IMPS.	CDZP no better than PBO on most measures, inferior to CPZ.	
Holden et al. (1968)	22	Chronically hospitalized patients, with clinical diagnosis of schizophrenia, ill for average of 8 yrs, active symptoms despite neuroleptics.	Crossover study: 1 mg/kg CDZP vs. 5 mg/kg thioridazine vs. combination of the 2 vs. PBO; 8 wks in each phase.	A global rating scale; BPRS; and a scale with 132 items designed by the authors.	On global ratings, CDZP no better than PBO, combination no better than thioridazine alone.	
Kellner et al. (1975)	6	Outpatients diagnosed by DSM-II criteria; selected for complaints of anxiety and apparent response to CDZP in open trial.	CDZP 150–300 mg/d vs. PBO added to neuroleptic; multiple crossovers between PBO and CDZP; 1–2 wks in each treatment period, 10–12 wks total.	SRT; a global self-rating scale; HAM-A; BPRS.	2 patients had dramatic improvement, 1 moderate, 3 no change.	Patients with highest symptom ratings responded best. Hallucinations and thought disorder were reduced as well as anxiety.
Lingjaerde et al. (1979)	23	Clinical diagnosis of chronic schizophrenia; prominent positive symptoms despite neuroleptics.	Crossover study: 15 mg/d DZP vs. PBO added to neuroleptic for 3–4 wks.	BPRS; NOSIE; global clinical impression.	DZP produced small reduction of total BPRS and significantly reduced suspiciousness and unusual thought content subscales.	Drowsiness, dysarthria, and ataxia frequently encountered.
Ruskin et al. (1979)	8	Clinical diagnosis of chronic schizophrenia; "severely ill with positive and negative symptoms" despite neuroleptics.	Crossover study: First, 40 mg/d DZP for 1 wk, then 80 mg/d for 2 wks vs. PBO added to neuroleptic.	BPRS.	DZP no better than PBO in the group data.	1 patient with "considerable motor tension" improved.
Lingjaerde (1982)	58	Patients with chronic auditory hallucinations; 52 of 58 given clinical diagnosis of schizophrenia; symptoms refractory to neuroleptics.	Crossover study: 6 mg/d estozolam vs. PBO, added to neuroleptic, 3 wks in each phase.	CPRS; CGI.	Estozolam superior to PBO on global ratings and on auditory and visual hallucinations and "compulsive thoughts."	

Study	N	Sample	Design	Scales	Results	Side effects/Comments
Jimerson et al. (1982)	6	Diagnosed by RDC; 5 with schizophrenia, 1 schizoaffective, 4 with poor response to neuroleptics.	Crossover study: DZP (max. dose 60–300 mg/d) vs. PBO added to neuroleptic for 1–2 wks each phase.	15-point global scale; blind clinical observations.	2 of 6 patients showed clinically significant symptom reduction with DZP relative to PBO.	Sedation, ataxia, and dysarthria frequent, especially above 50 mg/d.
Karson et al. (1982)	13	RDC diagnoses of chronic schizophrenia.	Crossover study: clonazepam (max. dose 1–5 mg/d) for 4 wks vs. PBO, added to neuroleptic.	BPRS.	No benefit; 4 patients developed aggressive behavior.	
Nestoros et al. (1982)	12	Acute admissions meeting DSM-III criteria for chronic schizophrenia, paranoid type.	First, 70–400 mg/d DZP vs. PBO for 1 wk, then vs. 30 mg/d HPL for 6 wks.	BPRS; CGI; SS-PSE; SANRS.	Marked benefit from DZP in first wk, few data given about subsequent wks.	Troublesome sedation occurred only after psychotic symptoms decreased.
Wolkowitz et al. (1986)	2	Met RDC and DSM-III criteria for chronic schizophrenia, paranoid type; symptoms only partially responsive to neuroleptics.	Crossover study: alprazolam (max. dose 3.5–4.0 mg/d) for 6–8 wks vs. PBO, added to neuroleptic.	BPRS; B-H GPR; A-T RSEB.	Significant clinical improvement in both patients.	In 1 patient, withdrawal of alprazolam exacerbated symptoms to greater than baseline levels.
Csernansky et al. (1988)	55	Outpatients with RDC diagnosis of schizophrenia and at least mild negative symptoms.	Alprazolam (avg. dose 3.6–4.2 mg/d) vs. DZP (avg. dose 39–44 mg/d) vs. PBO added to neuroleptic for 4 wks.	BPRS; SANS; CGI.	No persistent benefit seen with alprazolam or DZP.	Used stable outpatients; focused on negative symptoms.
Wolkowitz et al. (1988)	12	Inpatients meeting RDC and DSM-III criteria for schizophrenia, 10 with mild, 1 with severe psychotic symptoms.	Crossover design: alprazolam (avg. dose 2.9 mg/d) for 2–4 wks, then PBO for 2 wks, added to neuroleptic.	BHGRS; BPRS; A-T RSEB.	Significant but "modest" decreases in global psychosis and positive symptoms with alprazolam; 5 of 12 patients were definite responders.	Patients with higher baseline anxiety and psychosis ratings showed largest symptom reductions.

Abbreviations.—CDZP = chlordiazepoxide; CPZ = chlorpromazine; PBO = placebo; DZP = diazepam; HPL = haloperidol.

Scales.—IMPS (Lorr and Klett 1966); BPRS = Brief Psychiatric Rating Scale (Overall and Gorham 1962); SRT = Symptom Rating Test (Kellner and Sheffield 1973); HAM-A = Hamilton Anxiety Rating Scale (Hamilton 1959); NOSIE = Nurses Observation Scale for Inpatient Evaluation (Honigfeld et al. 1966); CGI = Clinical Global Impressions (Guy 1976); RDC = Research Diagnostic Criteria (Spitzer et al. 1978); CPRS = Comprehensive Psychopathological Rating Scale (Åsberg et al. 1978); SS-PSE = Schizophrenia Subscale of the Present State Exam (Wing et al. 1974); SANRS = Simpson-Angus Neurological Rating Scale (Simpson and Angus 1970); B-H GPR = Bunney-Hamburg Global Psychosis Rating Scale (Bunney and Hamburg 1963); A-T RSEB = Abrams-Taylor Rating Scale for Emotional Blunting (Abrams and Taylor 1978); SANS = Scale for the Assessment of Negative Symptoms (Andreasen 1983); BHGRS = Bunney-Hamburg Global Rating Scales (Bunney and Hamburg 1963).

It is interesting that the response described with benzodiazepines is more than simple reduction in anxiety or agitation. Patients who respond are described as improving globally, with reductions of hallucinations and delusions (Kellner et al. 1975; Lingjaerde et al. 1979; Jimerson et al. 1982; Nestoros et al. 1982; Wolkowitz et al. 1986, 1988), tension (Kellner et al. 1975), hostility (Jimerson et al. 1982), and excitement (Kellner et al. 1975), and with notable increases in spontaneous, appropriate, warm social engagement (Jimerson et al. 1982; Wolkowitz et al. 1986).

As a whole, these data suggest that a (probably small) subgroup of patients with chronic schizophrenia receives significant benefit from an adjunctive benzodiazepine compared with PBO. Patients who respond poorly to traditional neuroleptics appear to be among those who may respond. Four of these 11 double-blind studies specifically investigated neuroleptic-resistant patients (Holden et al. 1968; Lingjaerde et al. 1979; Ruskin et al. 1979; Wolkowitz et al. 1986). All used a crossover design; each patient at one point had a benzodiazepine, and at another point a PBO, added to his or her neuroleptic. Two of these four studies describe significant improvement from the benzodiazepine compared with PBO (Ruskin et al. 1979; Wolkowitz et al. 1986). Also relevant to the use of an adjunctive benzodiazepine in neuroleptic-resistant patients is a double-blind trial of estazolam (a triazolobenzodiazepine available in Europe) in 58 patients with chronic hallucinations refractory to neuroleptics (52 patients were diagnosed with schizophrenia). Significant global improvement was found (Lingjaerde 1982).

Benzodiazepine trials must be carried out carefully in patients with schizophrenia because of the potential for abuse and, if the treatment is stopped abruptly, withdrawal symptoms and seizures. Other significant side effects include social disinhibition (Bechmann and Haas 1980); aggression (Karson et al. 1982); sedation, ataxia, and dysarthria (Jimerson et al. 1982); and parkinsonism (Suranyi-Cadotte et al. 1985). Studies reporting positive results suggest that responders can be identified by the second or third week of a benzodiazepine trial, and two groups have noted that responders could often be distinguished within the first few days of the trial (Kellner et al. 1975; Lingjaerde 1982). Therefore, if after 2 to 3 weeks no obvious target symptom has been reduced, the trial should be discontinued and the patient tapered off the drug.

Whether certain benzodiazepines are more likely to produce benefit than others in patients with schizophrenia remains unclear. Of the benzodiazepines available in the United States, benefit has been reported in double-blind studies with alprazolam (Wolkowitz et al. 1986, 1988), diazepam (Lingjaerde et al. 1979; Jimerson et al. 1982), and chlordiazepoxide (Kellner et al. 1975). In many cases, diazepam and chlordiazepoxide might be preferable to alprazolam, because their longer half-lives provide greater protection against withdrawal problems resulting from patients abruptly stopping the drug on their own. Also, withdrawal of alprazolam has, in some patients, been associated with the appearance of psychotic symptoms more severe than those present before the trial (Wolkowitz et al. 1986, 1988).

Dosage is also unclear. In double-blind studies reporting benefit, daily doses of diazepam as low as 15 mg

(Lingjaerde et al. 1979) and as high as 300 mg (Jimerson et al. 1982) have been used, with no clear indication that very high doses offer significant therapeutic advantages. Because the risk of side effects, abuse, and withdrawal difficulties increases as the dose increases, high doses cannot be recommended without further evidence from controlled studies that clearly document their superiority over low or moderate doses.

Electroconvulsive Therapy (ECT).
ECT, one of the first useful treatments of schizophrenia, continues to have a place in the management of some patients. The literature on ECT use in schizophrenia is large, but much of it has serious methodologic flaws (Salzman 1980; Small 1985). Because fairly recent reviews by Salzman (1980), Fink (1985), and Small (1985) have covered this area well, we simply summarize the salient clinical points here.

The patients with schizophrenia who are most likely to benefit from ECT are those with catatonia, prominent affective symptoms, or a very short duration of illness (Salzman 1980; Fink 1985; Small 1985). For patients with chronic psychotic symptoms, the role of ECT is less clear and an important distinction appears to be whether ECT is used alone or in combination with neuroleptics. Clinicians with considerable experience maintain that ECT alone only rarely produces significant lasting benefit in patients with schizophrenia (Salzman 1980; Fink 1985). This clinical impression is supported by the relatively few well-controlled studies available. A landmark study by May and Tuma (1965) of treatments of schizophrenia found ECT alone superior to psychotherapy, but inferior to even low doses of neuroleptic. Other controlled studies have

found ECT alone to be inferior to neuroleptics in chronic schizophrenia (Baker et al. 1958; May et al. 1976), or no better than sham ECT (Miller et al. 1953; King 1960) or PBO (Brill et al. 1959). Combining ECT with neuroleptics appears to produce better results. The majority of controlled studies addressing the use of the combination have found it more effective than neuroleptics alone (Brill et al. 1959; Smith et al. 1967; Taylor and Fleminger 1980; Brandon et al. 1985), although this difference has been found to disappear after 4 to 6 months (Smith et al. 1967; Taylor and Fleminger 1980; Brandon et al. 1985).

Although these data point overall to ECT having some efficacy in schizophrenia, the relevance of these studies to the use of ECT in chronic, neuroleptic-resistant patients is debatable. In many of the studies, most or all of the patients either were in acute exacerbation or had been ill less than 2 years (Brill et al. 1959; Smith et al. 1967; Taylor and Fleminger 1980; Brandon et al. 1985). No controlled study has specifically examined patients chosen for neuroleptic nonresponsiveness. Some data do exist from uncontrolled studies in which ECT has been added to the neuroleptic regimens of treatment-resistant patients. From a review of these data and his own investigations, Friedel (1986) concluded that some of these patients received definite additional benefit from ECT. The combination of the controlled data from studies of unselected patients plus these uncontrolled results in neuroleptic-resistant patients appears to justify cautious use of adjunctive ECT as a second- or third-line treatment in neuroleptic-resistant schizophrenia. However, controlled studies of the adjunctive use of ECT in neuroleptic-resistant patients are

clearly needed to assess definitively the efficacy of ECT for this indication.

The presence of significant affective symptoms may make response to ECT more likely (Folstein et al. 1973), but it is not required for a response to be obtained in patients with schizophrenia. In a well-controlled study using sham ECT, all the patients with schizophrenia who received real ECT improved, despite only half of them having clinically significant depressive symptoms (Taylor and Fleminger 1980).

The symptoms that were found to improve more rapidly in patients who received combined therapy versus neuroleptics alone included delusions, hallucinations, agitation, and hostility as well as depression (Smith et al. 1967; Taylor and Fleminger 1980; Brandon et al. 1985). Although it has been stated that often at least 20 ECT treatments are required to alleviate psychotic symptoms (Fink 1985), this requirement is not true for all patients. Three carefully controlled studies found definite improvement after 12 treatments or fewer (May and Tuma 1965; Smith et al. 1967; Taylor and Fleminger 1980). Even with neuroleptic-resistant patients, Friedel (1986) found that the mean number of treatments required to produce a full response was 13.6. Like using ECT for depression, placing unilateral electrodes over the nondominant hemisphere is recommended, because it has been found to be as effective as bilateral placement in schizophrenia (Small 1985) and produces fewer cognitive side effects (Fink 1985).

Finally, the legal and political issues that have emerged regarding ECT cannot be ignored. They should not, however, be allowed to obscure the clinical utility that this treatment may have for some patients. As with

all treatments, the clinician considering ECT must be careful to assess, discuss, and document risks and benefits and attend to issues of appropriate consent (National Institutes of Health 1985).

Reserpine. Reserpine (table 4) was the first medication found to be effective for treating psychotic symptoms, and it was widely used just before neuroleptics were introduced in the mid-1950's. Evidence for its efficacy was based on numerous trials that were undertaken when the diagnosis of schizophrenia was applied in the United States to a broader range of psychopathology than now, and when standardized diagnostic criteria were not available. Many trials were done with diagnostically heterogeneous patient groups, and many did not employ controlled, double-blind methods. Most of these reports lack detailed descriptions of specific symptoms, but the chronicity of the illness is usually described. So that we could interpret findings regarding reserpine more accurately in relation to DSM–III–R criteria, (American Psychiatric Association 1987) for schizophrenia, which stress chronic impairment, we limited our consideration to double-blind investigations involving only patients with a diagnosis of schizophrenia of many months' or years' duration. We found eight such studies (Finn et al. 1955; Gardner et al. 1955; Hollister et al. 1955b, 1956; Naidoo 1956; Penman and Dredge 1956; Gore et al. 1957; Shawver et al. 1959); all examined chronically hospitalized patients, and four specifically selected patients with severe behavioral problems (Finn et al. 1955; Hollister et al. 1955b; Naidoo 1956; Gore et al. 1957).

Clear clinical improvement in the majority of patients treated with re-

Table 4. Double-blind studies of reserpine in patients with chronic schizophrenia

Study	Number of patients	Patient description	Study design	Outcome measures	Results	Comments
Finn et al. (1955)	22	Most disturbed schizophrenic patients on max. security ward; ill average of 13.5 yrs, 20 of 22 ill more than 5 yrs.	Reserpine vs. PBO, crossover; max. dose 7.3–12.2 mg/d; 12 wks on reserpine, 8 wks on PBO.	MSRPP; neuropsychological tests.	18 improved clinically on reserpine, 9 markedly; statistically significant improvement on total MSRPP and subscales.	Increased dose gradually.
Gardner et al. (1955)	30	Locked ward inpatients with chronic "schizophrenic psychosis"; average duration of illness 8 yrs.	Reserpine vs. CPZ vs. PBO for 14 wks; reserpine dose 2–5 mg/d.	MSRPP; neuropsychological tests; global clinical assessment.	Some improvement seen in 6 of 10 reserpine patients, 8 of 9 CPZ patients, and 2 of 10 PBO patients.	Vague criteria for global improvement.
Hollister et al. (1956)	40	Inpatients with "chronic schizophrenia reactions," ill at least 2 yrs.	Reserpine vs. PBO: 3 mg p.o. + 1 mg IM for 7 d, then 3 mg p.o. for 10 d.	Global clinical impressions.	13 of 20 improved on reserpine, 5 markedly vs. 3 of 20 on PBO.	No quantitative ratings, no statistical analysis, no description of what symptoms improved.
Hollister et al. (1955b)	38	Inpatients with "chronic schizophrenic reactions," ill at least 6 mos; selected for severe symptoms of withdrawal, anxiety, hostility, or frequent need of seclusion.	Reserpine vs. PBO, 2 mg p.o. for 50 d.	Global clinical impressions.	6 of 19 reserpine patients showed "unequivocal though not marked" improvement vs. 2 of 20 on PBO.	Rather low dose, no quantitative ratings or statistical analysis, no description of what symptoms in these patients improved.
Naidoo (1956)	80	Hospitalized "chronic schizophrenics" with severely disturbed behavior, ill at least 2 yrs.	4 groups: reserpine, PBO, reserpine + ECT, PBO + ECT; max. 10 mg reserpine/d, 1 ECT per wk for 12 wks.	5-point global assessment scale.	Reserpine and reserpine + ECT groups much more improved than ECT alone or PBO.	No statistical analysis; max. benefit reached by 5–7 wks; obvious reserpine side effects may have compromised blind.
Penman & Dredge (1956)	80	Chronic inpatients with "schizophrenic reactions", mean length of hospitalization in the experimental groups 9.3–12.5 yrs.	Reserpine vs. PBO vs. no medication, 90-d study, max. dose 8 mg/d.	L-M FFBRS.	Reserpine no better than PBO or no medication.	21 patients dropped out of study.

Study	N			Scales		
Gore et al. (1957)	20	Hospitalized females with "chronic and intractable schizophrenia" selected for being exceptionally difficult nursing problems; hospitalized at least 2 yrs.	Reserpine vs. PBO, crossover; max. dose 4 mg/d, 3 wks each phase.	Global clinical impression; JHHBC.	4 of 20 showed "slight but definite improvement" on reserpine compared to PBO.	No statistical analysis; brief duration of trial may have minimized observed benefit.
Shawver et al. (1959)	120	Chronic inpatients with schizophrenia who had received CPZ for at least 6 mos.	Reserpine 2 mg/d vs. 200 mg/d CPZ vs. PBO for 6 mos.	MSRPP plus their own psychiatric behavior rating scale.	On overall ratings, reserpine superior to PBO at 3 mos but not 6 mos; CPZ superior to PBO at 3 and 6 mos.	Conclusions difficult because low doses were used.

Abbreviations.—CPZ = chlorpromazine; PBO = placebo; IM = intramuscular; ECT = electroconvulsive therapy.

Scales.—MSRPP = Multidimensional Scale for Rating Psychiatric Patients (Lorr et al. 1953); L-M FFBRS = L-M Fergus Falls Behavior Rating Scale (Mayer and Lucero 1953); JHHBC = Johns Hopkins Hospital Behavior Chart (Muncie 1939).

serpine was reported in three of these studies (Finn et al. 1955; Hollister et al. 1956; Naidoo 1956). Four found only modest benefit or improvement in a minority of patients (Gardner et al. 1955; Hollister et al. 1955b; Penman and Dredge 1956; Shawver et al. 1959), and one study found no advantage to reserpine over PBO (Penman and Dredge 1956). The variability of results may be related to a dose effect, because two (Finn et al. 1955; Naidoo 1956) of three studies employing doses greater than 7 mg/day (Finn et al. 1955; Naidoo 1956; Penman and Dredge 1956) reported definite improvement in most patients, whereas similar results were found by only one (Hollister et al. 1956) of five investigations that used lower doses (Gardner et al. 1955; Hollister et al. 1955b, 1956; Gore et al. 1957; Shawver et al. 1959). Although these studies are far from perfect by modern standards, as a group they document some efficacy for reserpine in schizophrenia. Decreases in motor activity, agitation, and assaultiveness were the most commonly noted improvements (Finn et al. 1955; Naidoo 1956; Gore et al. 1957; Shawver et al. 1959). More detailed accounts also described reductions in hallucinations, delusions, and disorientation (Finn et al. 1955) and improvement in cooperation, hygiene, and interpersonal responsiveness (Naidoo 1956; Gore et al. 1957).

Because both neuroleptics and reserpine appear to act by decreasing effective dopaminergic transmission, patients who do not respond to neuroleptics would also be expected to respond poorly to reserpine. This supposition has not been tested with a controlled trial of reserpine in neuroleptic-resistant patients. There is anecdotal and uncontrolled evidence, however, that some patients

who respond poorly to neuroleptics improve with reserpine (Braun 1960; Bacher and Lewis 1985; Berlant 1986). Such evidence is tentative, but it does raise the possibility that the factors involved in response to these agents are complex and that empirical trials of reserpine may be warranted in some neuroleptic-resistant patients.

Reserpine can have serious side effects, including severe depression (Goodwin and Bunney 1971); significant hypotension, exacerbation of asthma, peptic ulceration and hemorrhage (Weiner 1985); and extrapyramidal side effects (EPS) (Hollister et al. 1955a). Whether the potential benefits of reserpine outweigh its potential risks in patients with refractory schizophrenia is thus unclear. Until careful double-blind studies are performed to clarify this issue, it seems best to use reserpine cautiously and only after other reasonable alternatives have failed.

The reserpine dose used in double-blind studies varied from 2 to 12 mg/day. The greatest benefit was seen with daily amounts of 8 to 12 mg (Finn et al. 1955; Naidoo 1956). There is evidence that a gradual increase to a full dose reduces some side effects. Patients started on 8 mg/day were described as having a "turbulent phase"—an early transient increase in agitation and psychotic symptoms (Naidoo 1956). This effect generally was not seen when the starting daily dose was 5 mg or less (Naidoo 1956). If reserpine is added to a neuroleptic, some evidence suggests that less reserpine (1 to 5 mg/day) is needed to achieve an adequate effect (Tuteur and Lepson 1957). The combination can produce increased side effects, however, especially EPS (Hollister et al. 1955a). Reserpine reaches maximal benefit more slowly than neuroleptics, and

the better-designed studies suggest that at least 5 to 7 weeks are required for an adequate trial (Finn et al. 1955; Naidoo 1956).

Carbamazepine (CBZ). The use of CBZ (table 5) in treating schizophrenia is relatively new. Anecdotal reports and uncontrolled studies have reported benefit in neuroleptic-resistant patients with schizophrenia (Hakola and Laulumma 1982; Ballenger and Post 1984; Luchins 1984), particularly those manifesting aggression (Hakola and Laulumma 1982; Luchins 1984).

We found five double-blind trials of CBZ in patients with schizophrenia (Neppe 1983; Klein et al. 1984; Kidron et al. 1985; Dose et al. 1987; Okuma et al. 1989). All added either CBZ or PBO to the neuroleptic regimen of the patients. Two of these studies examined patients selected only for schizophrenia (Kidron et al. 1985; Dose et al. 1987). In both, no difference was noted between CBZ and PBO in symptom improvement, but one study found that significantly lower levels of neuroleptic were used in the patients receiving CBZ (Dose et al. 1987).

The other three double-blind studies examined more select patient groups. Two groups of investigators studied treatment-refractory patients with schizophrenia plus symptoms of mania, excitement, or overactivity (Klein et al. 1984; Okuma et al. 1989). In a large multicenter trial, Okuma et al. (1989) found small but statistically significant differences favoring CBZ in the reduction of excitement, manic-type symptoms, and suspiciousness. Patients with prominent violence, aggression, or paranoia were more likely to respond. The overall effect of CBZ was not impressive, however; only one of three global response scales demon-

strated a significant benefit of the drug compared with PBO. Klein et al. (1984) also found that CBZ produced a modest reduction in excitement, tension, and unusual thought content compared with PBO. This benefit was still present when patients with diagnoses of schizophrenia or schizoaffective illness (mainly schizophrenia) were analyzed separately.

Finally, Neppe (1983) compared CBZ with PBO in a diagnostically heterogeneous group of 13 nonepileptic, chronically hospitalized patients selected for temporal lobe electroencephalogram (EEG) abnormalities, seven of whom were diagnosed as having schizophrenia by *DSM-III* (American Psychiatric Association 1980) criteria. CBZ reduced ratings of psychiatric symptoms significantly more than PBO. Although not analyzed separately, the data for the patients who were diagnosed with schizophrenia closely paralleled the results for the whole group. The number of patients was too small for statistically significant change to be found in individual symptom clusters, but the author's impression was that the bulk of the observed improvement related to a reduction of aggressive acts and improved self-control in interpersonal situations. Because there was no control group with normal EEG readings, it cannot be ascertained from this study whether the presence of temporal lobe EEG abnormalities predicts a higher likelihood of response to CBZ. EEG abnormalities are not required to obtain a response; aggressive behavior has also been found to be reduced in an open study of CBZ in violent patients with schizophrenia and normal EEG readings (Luchins 1984).

Although further studies are needed for firm conclusions, these

Table 5. Double-blind studies of carbamazepine in schizophrenia

Study	Number of patients	Patient description	Study design	Outcome measures	Results	Comments
Neppe (1983)	13	Nonepileptic patients with temporal lobe EEG abnormalities, hospitalized continuously for at least 6 mos; 7 given hospital diagnosis of schizophrenia.	Crossover study: 600 mg/d CBZ vs. PBO added to neuroleptic.	BPRS; their own global rating scale.	CBZ superior to PBO; main improvement was reduced aggression.	Results in schizophrenic patients paralleled results for whole group.
Klein et al. (1984)	43	New admissions with "excited psychosis": RDC mania and SA diagnoses plus schizophrenics with overactivity or pressured speech.	CBZ, adjusted to 8–12 mcg/mL vs. PBO added to neuroleptic for 5 wks.	BPRS; CGI.	CBZ significantly better than PBO on total BPRS, but not CGI.	Benefit more noticeable in the more schizophrenic patients.
Kidron et al. (1985)	11	RDC diagnosis of schizophrenia, significant positive symptoms despite neuroleptics.	Crossover study: 5–18 mcg/mL CBZ vs. PBO, added to neuroleptic, 5 wks each phase.	BPRS.	No patient showed greater benefit with CBZ than with PBO.	
Dose et al. (1987)	22	Inpatients meeting ICD-9 criteria for acute schizophrenic, schizophrenic, or SA (nonmanic) psychosis.	PBO vs. CBZ (8–12 mcg/mL) added to variable HPL dose for 4 wks.	IMPS; BPRS; CGI; SANRS.	PBO and CBZ produced some degree of improvement; CBZ patients needed significantly less HPL.	
Okuma et al. (1989)	162	Patients with *DSM-III* schizophrenia (n = 127) or SA disorder (n = 35); all neuroleptic resistant, with "excited psychotic states."	CBZ (mean dose 586 mg/d) vs. PBO added to neuroleptic for 4 wks.	BPRS; CPRG mania scale; their own global rating scale and own scale rating "excited states."	Global: CPZ > PBO on own scale, no difference on CPRG global scale or total BPRS. Symptoms: CPZ > PBO for several manic symptoms and BPRS symptoms of uncooperativeness, suspiciousness, and excitement.	Overall, CBZ-PBO differences small; patients with prominent violence, aggression, or paranoia more likely to respond.

Abbreviations.—SA = schizoaffective; CBZ = carbamazepine; EEG = electroencephalogram; PBO = placebo; HPL = haloperidol.

Scales.—BPRS = Brief Psychiatric Rating Scale (Overall and Gorham 1962); RDC = Research Diagnostic Criteria (Spitzer et al. 1978); CGI = Clinical Global Impressions (Guy 1976); ICD-9 = Manual of the International Statistical Classification of Diseases (World Health Organization 1978); IMPS = Inpatient Multidimensional Psychiatric Scale (Lorr and Klett 1966); SANRS = Simpson-Angus Neurologic Rating Scale (Simpson and Angus 1970); *DSM-III* = Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association 1980); CPRG = Clinical Psychopharmacology Research Group of Japan (Takahashi et al. 1975).

five studies suggest that any antipsychotic action of CBZ is quite modest and perhaps more likely to be seen in patients with psychomotor overactivity or concomitant manic symptoms. The most impressive clinical benefit noted in these reports seemed to relate instead to a reduction of excitement, impulsivity, and aggression (Neppe 1983; Klein et al. 1984; Okuma et al. 1989), a finding also noted in uncontrolled trials (Hakola and Laulumma 1982; Luchins 1984). It thus appears that the main benefits of CBZ in patients with treatment-refractory schizophrenia may be reduced aggression and improved control in interpersonal situations.

The doses used in most of these studies were sufficient to produce levels considered therapeutic for anticonvulsant activity with trial durations of 4 to 6 weeks (Klein et al. 1984; Kidron et al. 1985; Dose et al. 1987). Because CBZ has been found to lower HPL blood concentrations (Kidron et al. 1985), HPL levels should also be followed when these two drugs are used together.

Propranolol (PPL). The initial open trials of the beta-adrenergic receptor antagonist, PPL (table 6), in patients with schizophrenia produced considerable enthusiasm. Patients with chronic neuroleptic-resistant symptoms appeared to improve markedly (Donaldson et al. 1986). In the first double-blind, PBO-controlled investigation of PPL in schizophrenia, Yorkston et al. (1977) found clear clinical improvement on global patient ratings after 8 to 12 weeks of adding PPL to the neuroleptic regimen of patients with treatment-resistant schizophrenia. Eight double-blind trials of PPL in schizophrenia have been reported since then, generally with much less encouraging results (Bigelow et al. 1978; King et al.

1980; Lindstrom and Persson 1980; Myers et al. 1981; Peet et al. 1981; Yorkston et al. 1981; Pugh et al. 1983; Manchanda and Hirsch 1986). Only one (Lindstrom and Persson 1980) found similar global benefit. Four reported modest benefit (Bigelow et al. 1978; Pugh et al. 1983) or questionable benefit (Yorkston et al. 1981; Manchanda and Hirsch 1986); three found no differences between PPL and PBO treatment (King et al. 1980; Myers et al. 1981; Peet et al. 1981).

The variability of results is difficult to explain. That treatment-resistant patients had been selected in four trials that reported poor results (Bigelow et al. 1978; King et al. 1980; Myers et al. 1981; Pugh et al. 1983) does not explain the negative findings because treatment-resistant patients had also been selected in the two investigations with the best results (Yorkston et al. 1977; Lindstrom and Persson 1980). Insufficient dose and inadequate trial duration do not explain the negative results, because only one (Lindstrom and Persson 1980) of five studies using higher doses (greater than 1,000 mg/d) (Bigelow et al. 1978; King et al. 1980; Lindstrom and Persson 1980; Myers et al. 1981; Manchanda and Hirsch 1986) and one (Yorkston et al. 1977) of five investigations with trial durations greater than 4 weeks reported definite global benefit (Yorkston et al. 1977; Myers et al. 1981; Peet et al. 1981; Yorkston et al. 1981; Pugh et al. 1983; Manchanda and Hirsch 1986).

Both of the investigations (Yorkston et al. 1977; Lindstrom and Persson 1980) that reported clear-cut benefit from PPL used it in conjunction with neuroleptics. This point suggests that PPL may be ineffective alone, but that when used adjunctively it might enhance or complement neuro-

leptic effects. PPL has been found to increase the plasma level of CPZ (Peet 1981) and thioridazine (Greendyke and Kanter 1987), but not HPL (Greendyke and Kanter 1987). Some researchers have proposed that the improvement seen is due simply to elevation of plasma neuroleptic levels (Peet 1981), but others have noted studies showing that patients who respond to PPL do not always respond to an increased neuroleptic dose (Donaldson et al. 1986). Perhaps more likely is the suggestion that any improvement may be largely due to a reduction by PPL of neuroleptic-induced akathisia (Donaldson et al. 1986). However, beneficial effects of adjunctive PPL appear to be small or rare, because several double-blind investigations of the addition of PPL to neuroleptics found either slight or no benefit (Bigelow et al. 1978; King et al. 1980; Myers et al. 1981; Pugh et al. 1983; Manchanda and Hirsch 1986).

In summary, any antipsychotic activity possessed by PPL is, at best, slight, infrequent, or both, is seen more reliably when PPL is used in addition to neuroleptics, and may be related to beneficial pharmacokinetic interactions or a reduction of akathisia. The limited potential for antipsychotic benefit combined with the risk of serious cardiovascular and pulmonary side effects (Greenblatt and Shader 1972; Donaldson et al. 1986) makes PPL a much less viable alternative for most patients with neuroleptic-resistant schizophrenia.

L-Dopa. Although L-dopa (table 7) may worsen psychotic symptoms and increase agitation and hostility in some patients with chronic schizophrenia (Yaryura-Tobias et al. 1970; Angrist et al. 1973; Calil et al. 1977), three double-blind, PBO-controlled studies (Gerlach and Luhdorf 1975;

Table 6. Double-blind studies of propranolol in schizophrenia

Study	Number of patients	Patient description	Study design	Outcome measures	Results	Comments
Yorkston et al. (1977)	14	Chronic schizophrenics diagnosed by PSE, with "florid" symptoms despite neuroleptics.	PPL vs. PBO added to neuroleptic; average max. PPL dose 450 mg/d for 12 wks.	BPRS; doctors' global rating scale; 24-item nursing rating scale.	Significantly reduced psychotic symptoms on BPRS; global ratings significantly better than PBO at 8 and 12 wks.	2 patients who had not responded to PPL at 12 wks responded at 16.
Bigelow et al. (1978)	7	RDC diagnosis of schizophrenia, chronically hospitalized despite neuroleptics.	Crossover study: PPL (max. dose 1600 mg or 1920 mg/d) for 4 wks vs. PBO (4 wks) added to neuroleptic.	BPRS.	2 patients improved modestly, 1 worse, 1 without change.	Only 4 patients completed trial.
Lindstrom & Persson (1980)	12	Chronic inpatients with hospital diagnosis of schizophrenia, ill 5–16 yrs.	Crossover study: PPL (1280–1980 mg) for 2 wks vs. PBO (2 wks) added to neuroleptic.	CPRS.	Significant decrease in CPRS total score and thought disturbance subscale; 6 patients appeared improved.	Patients stabilized on open PPL before entering double-blind phase.
King et al. (1980)	5	Chronic inpatients with Feighner criteria of schizophrenia, "extremely ill with florid symptoms."	Crossover study: PPL 1000 mg/d vs. PBO added to neuroleptic; 3 wks each phase.	Modified BPRS; WWBS; their own nurses' psychosis rating scale.	No benefit from PPL found.	Patients entered double-blind phase after 12 wks on 1000 mg/d PPL; small number of patients.
Myers et al. (1981)	20	Neuroleptic refractory inpatients with diagnosis based on presence of at least one Schneiderian first-rank symptom.	PPL (max. dose 1920 mg/d) vs. PBO added to neuroleptic for 12 wks.	BPRS and their own rating scale.	PPL no better than PBO.	Very broad diagnostic criteria.
Peet et al. (1981)	53	Inpatients diagnosed with schizophrenia by Feighner criteria.	PPL (640 mg/d) vs. CPZ (400 mg/d) vs. PBO for 12 wks.	Modified BPRS; NOSIE; their own 7-point global rating of severity.	Neither PPL nor CPZ produced greater benefit than PBO.	Relatively low dose of CPZ used; 1 PPL patient had cardiovascular collapse.
Yorkston et al. (1981)	46	Newly admitted to hospital, PSE diagnosis of chronic schizophrenia "with florid symptoms."	PPL (max. dose 670 mg/d) vs. CPZ (max. dose 300 mg/d) for 12 wks.	Modified BPRS, their own severity of illness scale.	PPL equal in efficacy to CPZ; effect of either treatment quite modest.	9 patients on PPL and 10 on CPZ dropped out; no PBO group used.
Pugh et al. (1983)	41	Inpatients diagnosed by Feighner criteria; "florid symptoms" despite neuroleptics.	PPL (max. dose 640 mg/d) vs. PBO added to neuroleptic for 12 wks.	BPRS; CPRS; NOSIE; analog scales of global change.	PPL superior on NOSIE, but no different from PBO on BPRS, CPRS, and global scales.	

Table 6. Double-blind studies of propranolol in schizophrenia—Continued

Study	Number of patients	Patient description	Study design	Outcome measures	Results	Comments
Manchanda & Hirsch (1986)	36	Acutely admitted patients diagnosed with schizophrenia by PSE.	PPL (max. dose 1760 mg/d) vs. PBO; added to neuroleptic for 1 wk, then alone for 2-3 wks.	BPRS; Manchester Scale.	In the period after neuroleptic withdrawal, PPL protected better against relapse, but ratings across the entire study showed no global benefit from PPL.	

Abbreviations.—PPL = propranolol; PBO = placebo; CPZ = chlorpromazine.

Scales.—PSE = Present State Examination (Wing et al. 1974); BPRS = Brief Psychiatric Rating Scale (Overall and Gorham 1962); RDC = Research Diagnostic Criteria (Spitzer et al. 1978); CPRS = Comprehensive Psychopathological Rating Scale (Åsberg et al. 1978); Feighner Criteria (Feighner et al. 1972); Modified BPRS = Modified Brief Psychiatric Rating Scale (Yorkston et al. 1974); WWBS = Wing Ward Behavior Scale (Wing 1961); NOSIE = Nurses Observation Scale for Inpatient Evaluation (Honigfeld et al. 1966); Manchester Scale (Krawiecka et al. 1977).

Inanaga et al. 1975; Brambilla et al. 1979) and one double-blind, single-case, crossover trial (Kay and Opler 1985) have reported some benefit relative to PBO in schizophrenic patients who were selected for a predominance of negative symptoms such as apathy, withdrawal, and emotional flatness. These patients lacked psychomotor excitement, agitation, and prominent hallucinations (although some of them had experienced these symptoms in the past), and most were chronically hospitalized and refractory to neuroleptics. Clinically meaningful change occurred in 10 percent (Inanaga et al. 1975) to one-third (Brambilla et al. 1979) of L-dopa-treated patients. Exacerbation of psychosis and hostility was not seen. The patients who responded were reported to be more active and alert (Gerlach and Luhdorf 1975; Inanaga et al. 1975; Brambilla et al. 1979; Kay and Opler 1985), more motivated to work (Inanaga et al. 1975), and more interested in social contacts (Gerlach and Luhdorf 1975; Inanaga et al. 1975; Brambilla et al. 1979; Kay and Opler 1985). The degree of improvement observed in most of these investigations was small, however (Buchanan et al. 1975; Gerlach and Luhdorf 1975; Inanaga et al. 1975).

It is of some concern that the majority of the positive reports regarding L-dopa were published between 1975 and 1979 and that little has been published since then. Perhaps subsequent studies were less encouraging and were never carried through to publication. The positive results that have been reported, however, do seem to justify careful trials of L-dopa in refractory schizophrenic patients in whom negative symptoms predominate and produce serious social impairment, as long as the relatively low frequency of response is

Table 7. Double-blind studies of L-dopa in schizophrenic patients with mainly negative symptoms

Study	Number of patients	Patient description	Study design	Outcome measures	Results	Comments
Gerlach & Luhdorf (1975)	18	Outpatients with "simple schizophrenia": apathy, poor relationships and motivation, rare brief positive symptoms.	Crossover study: L-dopa vs. PBO added to neuroleptic, max. L-dopa dose 900 mg/d plus 225 mg/d benserazid, 12 wks each phase.	BPRS, plus their own global assessment scale.	Significant activation and total BPRS reduction (slight); no significant change in global ratings.	No exacerbation of psychosis seen.
Inanaga et al. (1975)	104	Inpatients with clinical diagnosis of schizophrenia, with abulia, apathy, impaired relationships, and no positive symptoms.	L-dopa 300–600 mg/d vs. PBO added to neuroleptic; 8-wk trial.	Their own symptom rating scale.	Significantly more L-dopa patients rated as "excellent" responders; no difference in the number considered "good" or "fair" responders.	Significant differences between L-dopa patients and PBO more consistently seen in patients ill less than 5 years.
Brambilla et al. (1979)	6	ICD-9 (WHO) diagnostic criteria used, plus selected for poor prognosis, prominent negative symptoms, and thought disorder without hallucinations or delusions.	Crossover design: carbidopa/L-dopa combination alone (max. dose 200 mg/2 g daily) vs. PBO, 4 wks each phase.	A general symptom rating scale plus neuropsychological tests.	2 patients reported to be much improved.	No statistical analysis of data presented.
Kay & Opler (1985)	1	Patient with *DSM-III* chronic schizophrenia and prominent withdrawal, amotivation, anergy, and blunted affect.	Single case study with A–B–A design: PBO vs. carbidopa/L-dopa combination (max. dose 75/750 mg/d); active treatment for 8 wks.	BPRS; PRS; Span of Attention Test.	Significant improvement in negative but not positive symptoms with carbidopa/L-dopa combination.	

Abbreviations.—PBO = placebo.

Scales.—BPRS = Brief Psychiatric Rating Scale (Overall and Gorham 1962); ICD-9 = Manual of the International Statistical Classification of Diseases (World Health Organization 1978); *DSM-III* = Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association 1980); PRS = Psychopathology Rating Scale (Singh and Kay 1975); Span of Attention Test (Kay 1982).

discussed with the patient and family before the trial.

The effect of duration of illness on responsiveness to L–dopa is unclear. In the largest double-blind study, 86 percent of the L-dopa-treated patients who had been ill for fewer than 5 years showed some improvement versus 29 percent of those treated with PBO, yet no difference between L-dopa and PBO was noted for patients who had been ill for more than 5 years (Inanaga et al. 1975). However, a controlled trial of L-dopa in patients selected not for negative symptoms but for long duration of illness (10–35 years) (Buchanan et al. 1975) reported small but statistically significant improvement in vitality and activation without worsening of psychotic symptoms. The place of dopamine (DA) agonists in treating later stages of chronic schizophrenia is particularly pertinent because negative symptoms often become more prominent as the illness progresses (Pfohl and Winokur 1982). This area is an important one for further investigation.

The daily dose of L-dopa used in these studies varied widely, from 300 mg (Inanaga et al. 1975) to 2 g (Brambilla et al. 1979). Combining a peripheral dopa decarboxylase inhibitor (i.e., carbidopa) with L-dopa would be expected to reduce side effects and the total dose needed for therapeutic benefit (Bianchine 1985). Improvement in studies using L-dopa generally became statistically significant by 7 to 8 weeks, suggesting that an adequate trial may need to last up to 2 months.

Most investigators have given L-dopa in combination with neuroleptics (Gerlach and Luhdorf 1975; Inanaga et al. 1975; Kay and Opler 1985). A significant clinical response to L-dopa, however, raises the question of whether continued adminis-

Table 8. Other treatments investigated in schizophrenia

Antidepressants (Siris et al. 1978)

Apomorphine (Tamminga et al. 1986)

Baclofen (Gulmann et al. 1976)

Beta-endorphin (Berger and Barchas 1983)

Bromocriptine (Brambilla et al. 1983)

Cholecystokinin (Mattes et al. 1986)

Clonidine (Freedman et al. 1982)

(Des-tyr)-γ-endorphin (Meltzer et al. 1982)

Megavitamins (Ban et al. 1977)

Naloxone (Naber et al. 1983)

Naltrexone (Gitlin et al. 1981)

Thyrotropin-releasing hormone (Inanaga et al. 1978)

Valproic acid (Linnoila et al. 1976; Ko et al. 1985)

Vasopressin (Iager et al. 1986)

Verapamil (Pickar et al. 1987)

tration of a DA receptor antagonist is needed or may even be detrimental. This point has not been systematically studied, but one of the double-blind studies reported good results in two of six patients with predominantly negative symptoms using L-dopa plus carbidopa alone (Brambilla et al. 1979). Currently, it seems best to try L-dopa in combination with a neuroleptic at first (a relatively specific DA D_2 receptor antagonist such as molindone or HPL might interfere less with the L-dopa effect), and then to consider gradually withdrawing the neuroleptic in the few patients who show a significant improvement.

Other Drugs

Many treatments other than those discussed here have been tried in patients with schizophrenia. Table 8 lists some that have received attention in recent years but did not meet our criteria for inclusion in this re-

view. For some (including baclofen, calcium channel blockers, cholecysto-kininlike agents, large vitamin and mineral doses, and apomorphine), the majority of controlled studies have not documented sustained efficacy (Gulmann et al. 1976; Ban et al. 1977; Mattes et al. 1986; Tamminga et al. 1986; Pickar et al. 1987). For the others, such as valproate (Linnoila et al. 1976; Ko et al. 1985), the double-blind data are too limited for even preliminary conclusions. This list is by no means exhaustive. New agents are continually being explored as a better understanding of the neurotransmitters and neuromodulators that may be relevant to schizophrenia emerges.

Choosing Among the Treatment Alternatives

Many clinicians working with treatment-resistant schizophrenic patients are already using one or more of the treatment alternatives

reviewed here. It is not so clear, however, that they are always doing so with well-formulated strategies for choosing among the alternatives. For many of the treatments reviewed, the data are insufficient for final conclusions to be made regarding their place in the treatment of these patients. It is possible, however, to obtain a sense of where the available data are strongest and weakest and use this knowledge to form some treatment guidelines. The guidelines are preliminary, however, and will likely change as new data come to light.

These treatment guidelines are given to help organize thinking about the use of these agents in refractory schizophrenia and to provide foci for further discussion and research. They are not meant to encourage a "cookbook" approach to treating these diverse and often complicated patients. Decisions regarding empirical trials must take into account the nuances of the clinical situation. Considerations regarding side effects, in particular, vary among patients. Decisions to proceed to higher risk or lower yield alternatives must involve careful weighing of the full range of risks (which is beyond the scope of this review) against the overall severity of the patient's condition.

We agree with Kane (1989) that candidates for alternative or adjunctive treatments are those patients with active, chronic symptoms and significant impairment in functioning despite two or three trials of at least 4 weeks' duration of different classes of neuroleptics, in whom both higher and lower doses (daily minimum of 400 mg CPZ equivalence) have been tried, and in whom possible organic factors have been ruled out. In most cases, the alternative treatment will be given in addition to the patient's

neuroleptic medication. Lithium, benzodiazepines, and ECT appear to offer the most consistent benefit when used adjunctively. Indiscriminate multiple drug treatment, which has been used in some psychiatric patients to their detriment, is unjustifiable and is not what we are advocating. Trials of combinations of medications must be based on the best available evidence concerning possible usefulness and carried out in a manner that allows for clear conclusions concerning benefit. Only one change in a patient's regimen should be made at a time, and a trial of sufficient dose and duration should be given before another change is made. As a rule, adding the alternative medication slowly is advisable, and care should be taken about additive or synergistic side effects. Specific target symptoms should be identified and the drug should not be continued beyond the length of the trial unless clinically significant improvement in those symptoms is seen. If adding an alternative medication does produce significant benefit, a tapering of the neuroleptic could then be considered after a period of clinical stability to see if the second medication, either alone or with a reduced dose of neuroleptic, controls the symptoms.

Many of the treatments discussed here do not have schizophrenia as an approved indication. Before any alternative treatment is tried, the rationale and the risks versus potential benefits must be carefully explained to the patient and to others concerned about him or her and documented in the chart.

We first present a general approach, applicable to that majority of patients who have predominantly positive symptoms (e.g., hallucinations, delusions, disordered thought, agitation) or positive symptoms

mixed with negative symptoms (e.g., apathy, social withdrawal, blunted affect). Then we discuss some modifications of that approach for two subgroups: patients with predominantly negative symptoms, and patients with concomitant impulsive aggression.

General Approach. For patients with significant refractory positive symptoms, or both positive and negative symptoms, CLOZ, adjunctive lithium, and adjunctive benzodiazepines have the best documented benefit. The treatment that appears capable of the most dramatic benefit for neuroleptic-resistant patients is clearly CLOZ (Kane et al. 1988); CLOZ should be tried first in most patients. If CLOZ proves either ineffective or impractical, a trial of adjunctive lithium is recommended next, because the evidence for its efficacy is more extensive and more consistent than the evidence for adjunctive benzodiazepines (Small et al. 1975; Carmen et al. 1981). If lithium produces little improvement, a trial of adjunctive benzodiazepine in moderate dosage is a good next choice for many patients, particularly those who are not substance abusers and who are quite psychotic or agitated. The evidence that symptoms of a small subgroup of patients respond to a benzodiazepine is relatively good (Holden et al. 1968; Kellner et al. 1975; Lingjaerde et al. 1979; Ruskin et al. 1979; Jimerson et al. 1982; Lingjaerde 1982; Wolkowitz et al. 1988).

The primary options remaining after CLOZ, lithium, and benzodiazepines include ECT, reserpine, and CBZ, all of which have weaker evidence for efficacy in neuroleptic-resistant patients. Nonetheless, we feel this evidence is sufficient to justify trials of some of these treatments

in those patients who continue to have severe, disabling, refractory symptoms. The data available provide only hints, nothing conclusive, regarding which of these treatments to try first. Concomitant affective symptoms increase the likelihood of response to ECT (Smith et al. 1967; Salzman 1980; Taylor and Fleminger 1980; Brandon et al. 1985; Fink 1985; Small 1985) and possibly to CBZ (Klein et al. 1984). For patients without significant affective symptoms, ECT or reserpine may be the best choices because, of the four treatments, they have the best documented efficacy in general populations of patients with schizophrenia (Finn et al. 1955; Gardner et al. 1955; Hollister et al. 1955b, 1956; Naidoo 1956; Gore et al. 1957; Shawver et al. 1959; May and Tuma 1965; Smith et al. 1967; Folstein et al. 1973; May et al. 1976; Salzman 1980; Taylor and Fleminger 1980; Brandon et al. 1985; Fink 1985; Small 1985; Friedel 1986). Finally, if ECT, reserpine, and CBZ are not helpful, a trial of adjunctive PPL could be considered.

Patients in Whom Negative Symptoms Predominate. Many patients have prominent symptoms of both the positive and negative type, and for these patients we recommend the treatment approach outlined in the preceding paragraphs. Negative symptoms have been reported to improve along with positive symptoms in trials of CLOZ (Kane et al. 1988), lithium (Small et al. 1975; Carmen et al. 1981), and alprazolam (Wolkowitz et al. 1986, 1988). Controlled studies have yet to be done, however, to assess the value of these agents in patients with marked negative symptoms and few, if any, positive symptoms. Such studies are needed.

For patients whose symptoms of schizophrenia are predominantly negative, L-dopa is the only treatment that is suggested to be beneficial by even a few double-blind studies (Gerlach and Luhdorf 1975; Inanaga et al. 1975; Brambilla et al. 1979; Kay and Opler 1985). L-dopa is thus worth trying in such patients, especially those with disabling withdrawal and apathy; the evidence is limited, however, and benefit may be infrequent.

Patients With Concomitant Impulsive Aggression. Impulsive outbursts of hostility and aggression are at times present in patients with schizophrenia and can be refractory to neuroleptics. When such outbursts are clearly in response to overt psychotic phenomena such as delusions and hallucinations, managing them varies little from the approach outlined previously. In such cases, the only modification we recommend is to be more careful with the use of benzodiazepines. Although benzodiazepines are often helpful in reducing agitation and outbursts, they can at times increase aggression by disinhibiting behavior (Karson et al. 1982).

There are some patients, however, with refractory impulsive aggression that is relatively autonomous from their more overtly psychotic symptoms. In these patients, the impulsive aggression should be considered a separate target for treatment.

Various adjunctive agents may reduce impulsive aggression. CBZ has been reported helpful in uncontrolled trials (Hakola and Laulumma 1982; Luchins 1984) and one controlled trial (Neppe 1983). It is intriguing that L-tryptophan significantly reduced aggressive ward incidents in a double-blind PBO-controlled study in patients with schizophrenia who had committed violent, person-related

crimes and who continued to be violent despite being treated with neuroleptics (Morand et al. 1983). L-tryptophan, probably from a contaminated source, has been linked to a severe eosinophilia-myalgia syndrome (Hertzman et al. 1990) and is currently unavailable. The data, however, are consistent with a growing body of evidence linking serotonergic functions to aggression or impulsive behaviors across diagnostic categories (Brown et al. 1982). Other serotonin-augmenting strategies such as the use of serotonin reuptake inhibitors might also prove useful but have not been studied in a controlled fashion in impulsively aggressive patients with schizophrenia.

Other treatments that may also be considered for impulsive aggression include beta-blockers and lithium. Double-blind PPL trials in schizophrenia generally do not comment specifically about aggressive symptoms, but an open trial of the beta-blockers nadolol and PPL (Sorgi et al. 1986) reported these agents to be helpful in reducing aggressive outbursts in patients with schizophrenia. Although this finding must be seen as tentative pending controlled investigation, it is consistent with reports of antiaggressive effects of beta-blockers in other disorders (Yudofsky et al. 1981). Lithium has also been reported helpful with aggression in other patient populations (Watanabe and Ishino 1980), but it has not been studied specifically in aggressive patients with schizophrenia.

Conclusions

One cannot help being struck by how relatively small the literature is on adjunctive and alternative somatic treatments in neuroleptic-resistant patients with schizophrenia, given

the magnitude of the problem. More research needs to be done, with special attention to rigorously controlled study designs and well-defined patient selection. When potential new schizophrenia treatments are identified and studied, some of the investigations should target patients selected for clearly documented neuroleptic resistance. Not only do these patients have the greatest need, but whatever is contributing to their neuroleptic nonresponsiveness may also lead to unusual responsiveness to other agents. The CLOZ trial by Kane et al. (1988) provides an excellent model of criteria and methods for selecting neuroleptic-resistant patients. The few studies to date investigating DA agonists for negative symptoms and L-tryptophan for impulsive aggression encourage further attempts to examine subgroups of patients with specific and enduring constellations of symptoms that are hypothesized to have a different pattern of drug responsiveness.

For all the treatments discussed here and those still in more preliminary stages, much work remains. Further studies are needed to identify predictors of response, determine optimal dose and duration of trials, and investigate mechanisms of therapeutic benefit. Intriguing questions remain for all of these treatments. CLOZ is different from traditional neuroleptics in a number of ways (Fisher-Cornelssen and Ferner 1976; Richelson 1984; Povlsen et al. 1985). Which, if any, of these differences is key to its unusual efficacy? Does lithium reduce frequency of subsequent exacerbations in those patients whose symptoms respond to it acutely? Are specific benzodiazepines—perhaps based on differing structures or receptor subtype affinities—better than others for treating chronic symptoms and are they different from those that may be helpful in acute exacerbations (Nestoros et al. 1982)? Would trials of DA agonists that act directly on the postsynaptic receptors show a benefit in patients specifically selected for marked negative symptoms—a benefit that has not been seen in trials of these agents in unselected patients (Brambilla et al. 1983)? Would specific D_1 receptor agonists reduce negative symptoms with less risk of exacerbation of positive symptoms? What is the most effective method of serotonergic augmentation for reducing impulsive aggression in patients with chronic schizophrenia? Might the best treatment strategies be different for older patients than for patients in earlier stages of the illness? Many other questions could be added to this short list.

Treating a patient with schizophrenia whose symptoms are incompletely responsive to neuroleptics can be difficult and frustrating; one is tempted to try anything that is reported to help. We have presented an approach to choosing among the available alternative somatic treatments based on results of controlled studies. Because so few controlled data are available for some of these treatments, the question of how closely this literature reflects clinical reality remains open. Future double-blind studies should, and probably will, significantly alter the recommended approach to such patients. Also, it is important to remember that somatic treatments are only one part of the approach to these patients. Adjunctive psychosocial therapies have demonstrated impressive benefits (Liberman and Mueser 1989) and should be used in parallel with somatic therapies.

A word about fiscal realities is necessary. The majority of patients with chronic treatment-resistant schizophrenia cannot afford private care and therefore receive their treatment in public clinics and hospitals. Psychosocial therapies and careful trials of alternative somatic treatments require significant clinical resources that are not adequate in many communities. In addition to providing the best care possible given current resources, the need is clear for increases in funds for public mental health facilities and programs.

In considering somatic alternatives to neuroleptics, the choices are still few. The fact remains that many patients will not obtain significant symptom relief from any of these treatments. Yet, refractory schizophrenia often has devastating lifelong morbidity. We therefore urge the clinician to resist therapeutic pessimism and to carefully pursue trials of the available alternatives. The impact on the lives of individual patients who do respond can be profound.

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