The Pharmacologic Treatment of Schizophrenia: A Progress Report

by Susan R. Donaldson, Alan J. Gelenberg, and Ross J. Baldessarini

Abstract

Pharmacologic agents currently used or being studied for the treatment of schizophrenia are reviewed. Neuroleptic medications are still the mainstay of treatment, but recent studies suggest new approaches to dosage and to the treatment of acute psychosis. Lithium is beneficial in psychotic illnesses with acute onset and a remitting course, regardless of the acute psychotic symptoms. Antidepressant agents may ameliorate depression in psychotic patients, but do not improve psychotic symptoms or social withdrawal. Propranolol's reported antipsychotic action has not been confirmed by controlled studies, but the drug may have a role in treating organic psychoses. The benzodiazepines, clonidine, and carbamazepine all merit more investigation as possible treatments for psychosis. The implications of differential treatment response among schizophrenic patients are discussed.

Schizophrenia is heterogeneous. Consequently, the pharmacologic treatment of schizophrenia is likely to be diverse. It is unreasonable to expect any one agent to treat all patients diagnosed as schizophrenic. Several treatments are currently used or are under investigation for use in schizophrenia. Each has been successful in treating some schizophrenic patients and has failed in treating others. Presumably, a given agent may most successfully treat some subgroup of schizophrenic patients who are homogeneous with respect to etiology or pathophysiology. Only recently, however, has the attempt to delineate such subgroups become a part of research in this area.

This article discusses several medications currently being evaluated in the treatment of patients diagnosed as schizophrenic, and so is limited by our present understanding of that diagnostic category. The discussion is directed primarily toward the practicing clinician with an interest in innovative treatment, and so is limited to medications that are currently available. Both commonly used and more innovative treatments are reviewed, and evidence for the efficacy of each approach is highlighted. However, data available for several agents encourage the attempt to define a subgroup of patients for whom that treatment seems particularly successful. While such suggestions are necessarily speculative, they may serve to guide future research and may have implications for clinical practice.

The difficulty of defining homogeneous patient populations poses some problems for research. Perhaps the most prevalent are errors in which an effect pertaining to a small part of a population is obscured by the larger part of the population to whom it does not apply, leading to a false negative conclusion. Thus, a particular agent might be successful in treating a subgroup comprising 5 percent of unselected patients with a diagnosis of schizophrenia, but the proof of this effectiveness would require the independent identification of the subgroup and its separate evaluation.

Other problems plague this area of research as well. The complex nature...

Reprint requests should be sent to Dr. S.R. Donaldson, St. Elizabeth's Hospital, 750 Cambridge St., Brighton, MA 02135.
of outcome measurements makes the evaluation of treatment effects uncertain. Studies using different outcome measures are difficult to compare. Spontaneous fluctuations in the course of the illness may obscure treatment effects. Finally, the ubiquitous placebo effect makes the evaluation of uncontrolled studies hazardous, if not impossible, especially given the unavoidably subjective nature of outcome ratings and the responsiveness of psychotic patients to environmental changes. Because of these uncertainties, the criteria for final acceptance or rejection of a given treatment must be unusually rigorous. At the same time, the devastating nature of schizophrenic illnesses and the inadequacy of current treatments justify an open-minded and adventurous spirit in approaching and evaluating innovative treatments.

The first section of this article describes recent attempts to refine the use of currently available antipsychotic agents. Subsequent sections deal with the use of other medications still considered experimental in treating schizophrenic patients.

**Conventional Antipsychotic Agents**

The present mainstay of treatment in schizophrenia is the group of drugs now known as antipsychotic or neuroleptic agents. They encompass several chemical classes, of which the most familiar are the phenothiazines, thioxanthenes, and butyrophenones, as well as the indolones and dibenzazepines (such as molindone and loxapine, respectively). Experimental agents that may be close to general availability include diphenylbutylpiperidines (pimozide, penfluridol), newer dibenzazepines (clozapine and congeners), and substituted benzamides (sulpiride, metaclopramide). With a decisiveness that is rare in psychopharmacology, these agents have all been demonstrated to be superior to placebo in the vast majority of trials (Baldessarini, in press). Consequently, current questions focus not so much on whether to use available neuroleptics as on how to use them to achieve maximum benefit with minimum toxicity.

**Pharmacology.** A brief consideration of the pharmacology of antipsychotic agents can help to guide their best use. Some antipsychotic drugs, in particular chlorpromazine, are absorbed rather erratically after oral administration, and blood levels following a given dose vary widely among individuals (Garattini and Morselli 1978). Genetic factors may account for much of this variation (Hansult and Fuller 1978). Furthermore, attempts to correlate plasma concentrations of antipsychotic agents or their metabolites with clinical response have usually not been successful (Cooper, Simpson, and Lee 1976; Baldessarini 1979). The apparent therapeutic range for chlorpromazine levels, for example, extends from 20 ng/ml (below which clinical response is unlikely) to 750 ng/ml (above which toxic effects are probable). Since this range is almost 40-fold, it provides little clinical guidance. Newer approaches to plasma-level monitoring may offer some hope. These include improved assay methods and control of critical variables such as dose and patient selection (Cohen et al. 1980). The usefulness of plasma drug assays to guide treatment in chronic psychosis remains unproved.

Oral administration of antipsychotic agents is further complicated by their decreased absorption in the presence of food or colloidal antacids. Although it has been suggested that concomitant use of antiparkinsonism medication might also decrease absorption of antipsychotic agents (Rivera-Calimlin et al. 1976), this impression has not been supported by recent, better designed evaluation (Simpson et al. 1980).

A final unpredictable element in the pharmacokinetics of antipsychotic agents is their uneven elimination from the body. Plasma elimination half-life typically ranges from 10 to 30 hours; however, metabolites of some antipsychotics have been detected in the urine for several months after drug discontinuation (Breyer and Gaertner 1974). The half-life of elimination from human brain is unknown. In animal studies, behavioral effects of antipsychotic agents persist after brain levels are no longer detectable by even very sensitive assays (Campbell et al. 1980). This observation suggests that the drugs may dissociate slowly from a small critical pool in central nervous system (CNS) tissue which may include brain receptor sites. The slow removal of drug may contribute to the typical delay between the time that antipsychotic medication is stopped and the occurrence of a clinical relapse. The delay between drug discontinuation and relapse, along with the complex contribution of natural history and environmental factors, makes it difficult to assess clinically the need for continuing neuroleptic treatment.

**Strategies for the Use of Antipsychotic Agents.** Virtually all of the currently available antipsychotic agents are remarkably similar in their...
main pharmacologic action and overall antipsychotic efficacy (Appleton and Davis 1980). Controlled studies of several drugs do not support the possibility of selecting a class of agents, much less a particular drug, for a specific type of psychotic patient (Baldessarini, in press). Thus, at present, a particular medication can reasonably be selected on the basis of predicted adverse effects, prior treatment response, or possibly a family history of medication response.

Strategies for the short-term treatment of acute psychoses or acute exacerbations of schizophrenia and for long-term management should be considered separately.

Treatment of acute psychosis. The acutely psychotic patient, whether visibly agitated or not, may potentially be a threat to himself or others, and the goal of treatment must be the rapid resolution of psychotic symptoms. However, there is substantial disagreement about the best way to achieve such a resolution. In contrast to prior impressions, it may even be that daily doses of an antipsychotic agent lower than the equivalent of 300 mg of chlorpromazine (CPZ) are effective for many acutely psychotic patients (Cohen et al. 1980). Daily doses in the range of 100–300 mg CPZ produce improvement in many acutely psychotic patients over several days or weeks. Whether a similar response is likely in exacerbations of chronic psychosis is less certain. Doses higher than the equivalent of 500 mg CPZ are unlikely to add much benefit, and side effects increase (Cole 1982). Beyond this general impression, however, the dose-response curve for acute antipsychotic effects remains undefined, even after 30 years of experience.

Attempts to speed improvement in acute psychosis, or to resolve psychosis in a higher percentage of patients, have produced some controversial strategies. Some clinicians, attempting to hasten the resolution of psychosis, have advocated the use of rapidly repeated doses of high potency antipsychotic agents, sometimes up to 30–60 mg of haloperidol or fluphenazine over 4–6 hours (Donlon et al. 1980). While initial uncontrolled studies indicated many acutely psychotic patients improved rapidly on such treatment, later partially controlled studies have questioned whether these high doses produce any better results than more modest doses, even in the early hours of treatment (Ericksen et al. 1978). It may be that much of the benefit of high-dose treatment represents sedation rather than a specific antipsychotic effect. In support of this idea, one study found intravenous (i.v.) diazepam to be as effective as i.v. haloperidol in reducing acute psychotic symptoms within a 24-hour period (Lerner et al. 1979). (This study also raises the question of possible antipsychotic properties of diazepam, as reviewed below.)

One of the implications of these studies is that more is not necessarily better where antipsychotic medications are concerned. This observation throws into question not only the practice of rapid high dose treatment, but also the time-honored practice of giving "as needed" doses to acutely agitated patients. In the absence of a demonstrated dose-response relationship, there is no reason to assume that an additional dose will improve the situation (except perhaps by sedation). While high dose treatment may be the strategy of choice for some psychotic patients, these patients are as yet clinically indistinguishable from those who will respond to a lower dose. Even such a limited claim, however, has yet to be supported empirically. Meanwhile, large doses of high potency antipsychotic agents may carry some additional risk of adverse effects (most commonly, dystonias and akathisia: rarely, neuroleptic malignant syndrome or cardiovascular or respiratory compromise) (Mehta et al. 1979; Gelenberg et al. 1983) and should be used with caution.

Patients whose psychosis does not respond to antipsychotic medications even after several weeks or months of treatment pose a special problem. Some investigators have tried using extremely high doses of potent antipsychotic agents over several weeks—sometimes as much as several hundred milligrams per day of fluphenazine or haloperidol (Quitkin et al. 1975). Controlled studies indicate that such doses probably do not increase the overall rate of response, especially if comparisons are made to vigorous ordinary-dose treatment (tens of milligrams) after 2 to 3 months (Quitkin, Rifkin, and Klein 1975). Very high doses are not innocuous, and CNS side effects including dystonias, akathisia, akinesia, and sedation are common (Quitkin, Rifkin, and Klein 1975).

Any psychotic person certainly deserves an adequate trial of an antipsychotic agent. However, some patients apparently do not benefit from neuroleptic agents, and attention is increasingly turning to the prediction of antipsychotic responsiveness. At present, clinical predictors for acute response parallel the predictors of overall good prognosis: acute onset and good premorbid functioning are favorable omens (Baldessarini, Finklestein, and Arana 1983). In addition, biological markers are being sought that would
give a more objective prediction of response. One group has identified changes in electroencephalographic (EEG) patterns that appear to distinguish responders from nonresponders following a test dose of antipsychotic medication (Itil et al. 1981). At present, however, a clinical trial of antipsychotic medication is generally indicated.

Maintenance Treatment. For patients who have benefited from the short-term use of an antipsychotic agent (up to 3 months), long-term treatment is usually considered. The goal of maintenance treatment is sustained control of symptoms in the chronically psychotic patient. Such maintenance treatment is not benign, posing as it does the risk of irreversible neurologic damage in the form of tardive dyskinesia. The burden of proof thus rests with the clinician who recommends long-term treatment to establish its value in each patient.

A few controlled studies suggest that chronically impaired schizophrenic patients who are maintained on a placebo following a psychotic exacerbation will experience relapses at the rate of approximately 5 to 10 percent per month (Hogarty et al. 1974; Baldessarini et al. 1980). Antipsychotic medications can reduce this risk by a factor of two or three (Baldessarini et al. 1980). Thus, prophylactic medication for this period is generally justified, although responses of individual patients must be considered. After the first year of followup, data are sparse (Baldessarini et al. 1980), and individual judgments must be made. Whether prevention of relapses in remitting psychoses, such as bipolar illness, also can be effected by long-term neuroleptic treatment, remarkably, remains unknown (Baldessarini and Davis 1980; Baldessarini et al. 1980).

Given that a decision is made for continuous medication, what dose is recommended? In a recent analysis of nearly 30 placebo-controlled, prospective studies representing most of the available literature (Baldessarini and Davis 1980), maintenance doses ranged from 125 to 2,000 mg/day of CPZ. The percentage of patients who appeared to benefit from medication in the different studies ranged from about 10 to 75 percent. Nevertheless, the correlation between dose and efficacy in the combined data was almost nil ($r = 0.07$), suggesting that higher doses are not necessarily more effective than low doses in preventing relapse in the range of doses tested. Inadequate study design may contribute to this observation; another explanation is that even the lower doses used may exceed the requirements of some patients, obscuring a possible dose-response curve that might emerge below 100 mg of CPZ equivalent per day. In support of this idea, preliminary results of studies by Kane et al. (1979, in press) and by Branchey, Branchey, and Richardson (1981) suggest that some schizophrenic patients may be adequately maintained for up to a year at daily doses less than the equivalent of 100 mg of CPZ daily. These patients are at somewhat higher risk for exacerbations, but seem to function adequately socially and may be more satisfied with treatment than patients on higher doses (see Kane, this issue). These early findings suggest that gradually diminishing doses should be considered in any long-range management program.

The risk of tardive dyskinesia as a complication of prolonged antipsychotic therapy is well known (Baldessarini et al. 1980; Jeste and Wyatt 1982). Recently, a parallel concern has been raised by Chouinard and Jones (1980): the possibility of a "supersensitivity psychosis" which, hypothetically, reflects sensitization of dopamine receptors in the mesolimbic system. This syndrome is of some theoretical as well as clinical interest, and some case studies have been published that are consistent with the hypothesis. However, interpretation is confounded by the similarity of the putative "tardive psychosis" to reemergence of the underlying psychotic process being treated. Supersensitivity psychosis is said to parallel tardive dyskinesia in its course and to be associated with tardive dyskinesia and with a high prolactin level. It is said to be characterized by florid psychotic symptoms (hallucinations, delusions) and by a late-appearing increasing medication requirement. Thus far, most cases reported have involved patients treated for 3 to 4 years with depot fluphenazine esters (Chouinard and Jones 1980), but the association with this agent may be coincidental. Whether or not it can be proved that a "new" element of psychosis is involved in this phenomenon, a prudent interpretation is that some patients may develop tolerance to antipsychotic medications over several years of continuous treatment.

**Lithium in Schizophrenia**

There is a growing consensus that lithium carbonate may play a useful role in the treatment of some patients who meet current diagnostic criteria for schizophrenia or schizophreniform psychosis. This idea contradicts traditional wisdom, which suggests that lithium is only effective in affective disorders and, at best, may ameliorate affective symptoms in schizoaffective patients.
(Jefferson and Greist 1977; Fieve 1980). Indeed, some authors have suggested that lithium might be preferentially toxic to schizophrenic patients and is, therefore, contraindicated (Shopsin, Johnson, and Gershon 1970; Prakash, Kelwala, and Ban 1982)—an idea not supported by other studies. In contrast, a recent review by Delva and Letemendia (1982), which provides detailed summaries of the major controlled and uncontrolled studies in this area, concludes that “between one-third and one-half of patients with schizophrenia will benefit from lithium” (p. 391).

Obviously the question of diagnosis is crucial. Lithium is an effective treatment for mania, bipolar disorders, and perhaps other affective disorders (Baldessarini, in press), and one might accordingly assume that all that responds to lithium must be affective illness. In fact, many schizophrenic patients who respond to lithium appear to have many clinical features in common with affectively ill patients, and it has been suggested that these patients (DSM-III “schizophreniform,” “schizoaffective,” or “atypical psychosis”) may be inseparable from affective patients (Pope and Lipinski 1978; Fogelson, Cohen, and Pope 1982). However, several studies also suggest that some patients who clearly meet current criteria for a diagnosis of chronic schizophrenia may benefit from lithium.

The following sections examine, in the light of current literature, several hypotheses that have been advanced about patient characteristics that might predict a beneficial response to lithium.

Predictive Value of Current Symptoms. The Research Diagnostic Criteria (RDC) of Spitzer, Endicott, and Robins (1975) provide a useful test of the value of affective symptoms alone in predicting lithium response. According to RDC, schizophrenic patients are distinguished from schizoaffective patients solely by the presence or absence of affective symptoms at the time of evaluation. Three studies allow the separate assessment of RDC schizophrenics versus schizoaffectives in their response to lithium, either alone or combined with an antipsychotic agent (Alexander, van Kammen, and Bunney 1979; Hirschowitz et al. 1980; Carman, Bigelow, and Wyatt 1981). A statistical combination of these three studies finds no significant difference in response to lithium between the two diagnostic groups. Thus, patients without affective symptoms responded approximately as often as patients who displayed such symptoms. A more recent study (Braden et al. 1982), while not giving exact numbers of patients improved, also found that RDC diagnosis (as well as other symptom-oriented as opposed to course-oriented criteria) did not predict outcome, nor did it distinguish response to lithium from response to CPZ. Thus, it appears that affective symptoms are neither necessary nor sufficient to predict a beneficial response to lithium treatment.

Other reviews have suggested that specific psychotic symptoms, including the first-rank symptoms of Schneider (1959), also do not predict lithium responsiveness (Pope and Lipinski 1978; Delva and Letemendia 1982).

Predictive Value of Prognostic Category. A more useful division may be the distinction between good- and poor-prognosis schizophrenia (McCabe et al. 1971). The former is characterized by good premorbid history, acute onset, remitting course, and good recovery of function between psychotic episodes. Poor-prognosis schizophrenia has a more insidious onset, with poor premorbid history and a deteriorating course without return to previous level of functioning between exacerbations; this pattern accords with recent conceptualizations of schizophrenia as a chronic, idiopathic psychotic illness. DSM-III (1980) has recognized this distinction in the separation of “schizophrenia” from “schizophreniform disorder.”

Table 1 summarizes 10 recent studies of the use of lithium to treat schizophrenic patients (diagnosed using the broader definition). Where possible, patient descriptions have been included that allow some characterization of their illness and prognosis. Although conclusions are by no means clear-cut, the following impressions can be drawn:

- In poor-prognosis or chronic schizophrenia, acute exacerbations respond poorly to lithium alone; CPZ may or may not produce a more favorable response. For maintenance treatment, lithium alone appears not to be of value. Surprisingly, however, several studies using specific contemporary diagnostic criteria found that the addition of lithium to an antipsychotic agent benefited about half of chronic, poor-prognosis patients (Small et al. 1975; Biederman, Lerner, and Belmaker 1979; Carman, Bigelow, and Wyatt 1981).

- In good-prognosis schizophrenia, for acute exacerbations, lithium and CPZ appear to be equally effective. Maintenance with lithium has not been studied in good-prognosis schizophrenics, but
<table>
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<tr>
<th>Study</th>
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<th>Diagnosis/description</th>
<th>Study design</th>
<th>Results</th>
<th>Comments</th>
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<tr>
<td>Johnson (1970)</td>
<td>11</td>
<td>Schizoaffective with insidious onset, residual personality impairment, poor function between psychotic episodes</td>
<td>Lithium vs. CPZ, double-blind</td>
<td>6/11 worsened, apparently due to neurotoxicity</td>
<td>Manic patients on same protocol improved. Lithium levels as high as 2.55 mEq/l</td>
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<td>Shopsin, Kim, &amp; Gershon (1971)</td>
<td>21</td>
<td>Newly hospitalized acute schizophrenic, including chronic undifferentiated, paranoid, schizoaffective. 14/21 had affective symptoms</td>
<td>Lithium vs. CPZ, double-blind</td>
<td>6/11 treated with lithium neurotoxic</td>
<td>Lithium levels .65–1.28 mEq/l</td>
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<td>Prien, Caffey, &amp; Klett (1972)</td>
<td>83</td>
<td>Schizoaffective by DSM-II</td>
<td>Lithium = CPZ for &quot;mildly active,&quot; CPZ &gt; lithium for &quot;highly active&quot;</td>
<td>2/83 became toxic; high dropout rate in high activity/lithium group may account for findings. Lithium works more slowly</td>
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<td>Small et al. (1975)</td>
<td>22</td>
<td>“Very chronically ill” schizophrenic (14) or schizoaffective (8) by Feighner criteria: insidious onset, poor functioning</td>
<td>Neuroleptic + lithium or placebo</td>
<td>10 patients improved and continued on lithium after study. Cognitive symptoms and excitement improved</td>
<td>1/22 toxic; no good predictors of improvement were found, including diagnostic subtype</td>
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<td>Biederman, Lerner, &amp; Belmaker (1979)</td>
<td>36</td>
<td>Schizoaffective by RDC. Subdivided into affective (good inter-episode function) and schizophrenic (chronic impairment)</td>
<td>Neuroleptic + lithium or placebo</td>
<td>Lithium benefited both groups. Affective group showed more improvement, but lithium accounted for more of improvement in schizophrenic group. Both cognitive and affective symptoms improved</td>
<td>1/36 toxic</td>
</tr>
<tr>
<td>Alexander, van Kammen, &amp; Bunney (1979)</td>
<td>13</td>
<td>By DSM-II: 10 schizophrenic, 3 schizoaffective. By RDC: 5 schizophrenic, 8 schizoaffective. Also rated for prognosis</td>
<td>Lithium vs. placebo</td>
<td>7 responders of whom only 4 relapsed off lithium; 4 nonresponders. Of 6 good-prognosis patients, 4 were responders</td>
<td>Data given did not allow clear assessment of correlation of lithium response (including relapse status) with prognostic category.</td>
</tr>
<tr>
<td>Study</td>
<td>n</td>
<td>Diagnosis/description</td>
<td>Study design</td>
<td>Results</td>
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<td>Growe et al. (1979)</td>
<td>8</td>
<td>RDC: 6 schizophrenic, 2 schizoaffective. &quot;Chronic, treatment-resistant&quot;</td>
<td>Neuroleptic + lithium or placebo</td>
<td>Of 8 scales used, only &quot;psychotic excitement&quot; showed significant decrease on lithium. No change in thought disorder. Trend for improvement on 2 other scales</td>
<td>No toxicity seen. Small n makes lack of significance hard to assess</td>
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<td>Hirschowitz et al. (1980)</td>
<td>31</td>
<td>RDC schizophrenic or schizoaffective. By DSM-III: 9 schizophreniform, 15 schizoaffective, 7 others. Also rated for prognosis</td>
<td>Uncontrolled; lithium alone</td>
<td>Among schizophreniform patients: 7/9 improve, mean 50% improvement. Among DSM-III schizophrenics, 1 improved, mean 0.6% improvement. Among other patients, prognosis predicted lithium response</td>
<td>Schizophrenic vs. schizophreniform distinction also divided good from poor prognosis patients. No toxicity seen</td>
</tr>
<tr>
<td>Carman, Bigelow, &amp; Wyatt (1981)</td>
<td>18</td>
<td>RDC schizophrenic or schizoaffective. Chronic, poor premorbid or intermorbid function, insidious onset</td>
<td>Neuroleptic + lithium or placebo</td>
<td>Approximately 50% benefited, mostly on &quot;arousal&quot; scale (of 3 scales). 3/4 relapsed on lithium alone</td>
<td>Good premorbid history, episodic course, and affective symptoms were predictors of lithium response, but 3 patients with none of these showed clear improvement</td>
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<tr>
<td>Braden et al. (1982)</td>
<td>78</td>
<td>New admissions with 2 or more symptoms of mania. By RDC: 12 schizophrenic, 30 affective, 31 schizoaffective, 5 other. By DSM-III: 11 schizophrenic, 53 affective, 14 other</td>
<td>Lithium vs. CPZ</td>
<td>No diagnostic system predicted differential drug response: in general, good-prognosis had better outcome than poor-prognosis patients. Patients with higher activity levels did better on CPZ</td>
<td>4 patients became &quot;more confused&quot; on lithium at therapeutic levels: 2 manic, 2 schizoaffective. No evidence that effect of lithium was confined to affective symptoms</td>
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However, none of diagnostic groupings used predicted lithium response vs. nonresponse.

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schizoaffective patients with a good prognosis appear to do better on lithium maintenance than on a placebo (Angst et al. 1970; Pope and Lipinski 1978).

Predictive Value of Level of Activity. A distinction not noted in the table separates highly active from less active psychotic patients. In two studies, highly active patients appeared to do better with CPZ than with lithium during the acute phase of illness (Prien, Caffey, and Klett 1972; Braden et al. 1982). It is unclear to what extent this difference merely represents lithium’s slower onset of action, and the clinical difficulty of managing an “active” patient until lithium takes effect.

Predictive Value of Biological Markers. Several recent studies have attempted to correlate lithium responsiveness with biochemical measurements to complement clinical observations. The following studies predicted lithium response at a statistically significant level using biological measures, although none has been replicated:

- Hirschowitz, Zemlan, and Garver (1982) studied 31 patients diagnosed by DSM-III (1980) criteria as schizophrenic (25) or schizoaffective (6). DSM-III diagnoses predicted lithium response for all but one patient in each diagnostic group (“schizoaffective” patients improved, while “schizophrenic” patients did not). However, response was even more accurately predicted by observations of the in vitro erythrocyte ratio of intracellular to extracellular lithium combined with assessment of plasma growth hormone level increases in response to apomorphine.
- Edelstein et al. (1981) tested 11 patients with RDC diagnoses of schizophrenia or schizoaffective illness, using i.v. physostigmine. Four of the 11 patients showed a transient reduction in psychotic thinking after physostigmine treatment, while the other seven did not; the same four later improved on lithium treatment, while the remaining patients did not improve.
- Alexander, van Kammen, and Bunney (1979) studied 13 patients with RDC diagnoses of schizophrenia or schizoaffective illness. Six of their patients were classified as good-prognosis schizophrenics. They attempted to confirm in this population the findings of Carman et al. (1974), which suggested that a high pretreatment serum Ca/Mg ratio predicted a good response to lithium in affectively ill patients. The findings of Alexander, van Kammen, and Bunney (1979) were consistent with the hypothesis of Carman et al., but did not reach statistical significance.

All of these studies used lithium alone as the treatment, and none included a placebo control. While it is not possible to construct a coherent biomedical theory incorporating all of the above findings, it does appear that biochemical studies may usefully supplement clinical observations in predicting response to lithium. The cautious reader, however, will recall the difficulties of past investigators in replicating biochemical studies in the idiopathic psychoses, and will await further data.

Specific Effects of Lithium in Schizophrenic Patients. Clinical lore has suggested that lithium can effectively treat affective symptoms in psychotic patients regardless of diagnosis, but does not affect the presumed core symptoms of schizophrenia (withdrawal, illogical thought, mood-incongruent delusions) (Fieve 1980). As table 1 shows, some studies support this notion. However, three carefully documented studies found lithium to have a beneficial effect on symptoms of cognitive disorganization in schizophrenic patients (Small et al. 1975; Biederman, Lerner, and Belmaker 1979; Braden et al. 1982).

A small number of studies have suggested that lithium may be contraindicated in schizophrenic patients because of a supposedly increased risk of neurotoxicity at “therapeutic” blood levels (Shopsin, Johnson, and Gershon 1970; Prakash, Kelwala, and Ban 1982). While such cases have been reported, there is no controlled evidence that such toxicity occurs more frequently in schizophrenic patients than in manic-depressive patients. Furthermore, as can be seen in table 1, a majority of studies have found lithium to be well tolerated by schizophrenic patients.

Summary. It appears that lithium may benefit some patients diagnosed as schizophrenic even by contemporary research criteria. Affective symptoms do not predict lithium response, nor do Schneiderian symptoms preclude it. Good-prognosis (or schizoaffective) patients may be treated acutely with lithium unless their activity level requires rapid control with an antipsychotic or sedative agent. Good-prognosis patients who are diagnosed “schizoaffective” may benefit from lithium prophylaxis between episodes. Chronically psychotic schizophrenic patients whose response to antipsychotics is incomplete may sometimes benefit from the addition of lithium to an antipsychotic agent, although this
group is less likely to respond than others. The fact that lithium is of value in these patients does not necessarily demand a rediagnosis, as treatment responses in psychiatry are not highly specific and may or may not serve as a useful part of the definition of a diagnostic category. However, it may well be that lithium-responsive patients diagnosed as schizophrenic using a broader definition constitute a biologically distinct subgroup. Our prediction is that they may prove to be more closely related to patients with affective disorder than to chronic poor-prognosis schizophrenic patients.

**Antidepressants in Schizophrenia**

Schizophrenic patients are sometimes clinically depressed. Some clinicians consider depressive episodes to be a common component of chronic psychotic illness; others see depression as an appropriate response to a devastating illness. In addition, some characteristic schizophrenic symptoms—energy, anhedonia, and flatness of affect—give the appearance of depression even in the absence of overt reports of depressed mood, and so, rightly or wrongly, may prompt treatment with an antidepressant. On such clinical grounds, many schizophrenic patients have been treated with antidepressants over the past three decades. However, a review of the literature suggests that this practice may be on shaky ground, not only theoretically, but empirically as well.

**Review of Studies.** In 1978, Siris, van Kammen, and Docherty (1978) compiled a comprehensive review of controlled studies of antidepressants in schizophrenia. The following discussion is taken largely from their article, as more recent studies have not produced substantially different findings (Prusoff et al. 1979; Brenner and Shopsin 1980; Editorial 1980; Waehrens and Gerlach 1980).

The limitations of the individual studies in this review are a primary concern. Of the 42 studies reviewed in 1978 by Siris, van Kammen, and Docherty, only 11 were published in the 1970s. This fact in itself bespeaks a waning enthusiasm for the use of antidepressants in schizophrenia. More importantly, it means that only a small number of studies used diagnostic criteria that can be accurately translated into current practice. For example, one study assured the reader that subjects were drawn from "the hard core of long-stay schizophrenics"; no other description is given (Collins and Dundas 1967). In addition, measures of clinical change are often idiosyncratic and difficult to evaluate: for example, an increase in the level of motor activity and speech was noted in several studies, but was interpreted as improvement in some, as worsening in others.

An added complexity is that, for the most part, the studies reviewed did not treat depressed schizophrenics specifically, nor did they confine their outcome measures to depressive symptomatology. Rather, they usually sought improvement in the "core" symptoms of schizophrenia. However, some of the studies suggested that precisely those schizophrenic patients with a superimposed major depression benefited from antidepressants. Unfortunately, this group has not been studied specifically, and most studies do not state clearly whether their subjects were clinically depressed or not.

Despite these limitations, Siris et al. (1978) extracted the following impressions from their review:

- **Antidepressant agents alone.** There is little evidence that antidepressants given without an antipsychotic agent have beneficial effects in schizophrenic patients. This impression applies to both tricyclic antidepressants and monoamine oxidase (MAO) inhibitors. An exception to this generalization was one study (Pishkin 1972) in which patients were specifically selected for depressive symptoms; these patients showed modest improvements in their cognitive functioning when treated with imipramine.

- **Tricyclic antidepressants with antipsychotic agents.** Ten of 12 studies found an antipsychotic agent alone to be as effective in reducing schizophrenic symptoms as the combination of a tricyclic and an antipsychotic agent; the antidepressant agent conveyed no extra benefit. Again, exceptions were two studies (Michaux, Kurland, and Agallianos 1966; Hanlon, Ota, and Kurland 1970) in which patients with depressive symptoms were assessed as separate group; the depressed groups seemed to benefit more from the combination.

- **MAO inhibitors with antipsychotic agents.** Many of the studies of this combination dealt with long-term hospitalized patients, and sought to improve their characteristic apathy and anhedonia. There was no definite evidence of benefit, but several controlled studies showed trends for some withdrawn schizophrenic patients to improve when an MAO inhibitor was added. The improvement usually took the form of an increase in activity level or interest in the surroundings, rather than a reduction in psychotic symptoms. Uncontrolled studies also reported optimistic findings; but, not surprisingly, a separate review of 14 studies of MAO inhibitors in schizophrenia (Brenner and Shopsin 1980) found that open studies reported...
improvement significantly more often than did controlled trials.

Although a wide range of antidepressants is not represented in the studies reviewed by Siris, van Kammen, and Docherty (1978) (which favored the combinations of amitriptyline-perphenazine and tranylcypromine-trifluoperazine), there was no indication that one member of a class was more effective than another.

Siris, van Kammen, and Docherty (1978) also considered different categories of patients. Their impressions suggested that schizophrenic patients without superimposed depression were unlikely to benefit from antidepressants, either alone or in combination with an antipsychotic, while some patients with a typical depressive picture in addition to schizophrenic illness might benefit. They also cited the clinical impression that current that agitated schizophrenic patients may develop exacerbations of their psychosis if given an antidepressant. They noted Klein’s (1972) impression that schizophrenic patients with a history of childhood asociality may show a biphasic course on antidepressants, with initial improvement but subsequent deterioration.

Pharmacologic Considerations. The pharmacology of antidepressant treatment in schizophrenia is of interest. Any specific effect on depression may involve the same mode of action postulated for antidepressant therapy in affective disorders. At the pharmacokinetic level, tricyclic antidepressants may, through competitive inhibition of hepatic enzymes, increase blood levels of simultaneously administered antipsychotic agents (Loga, Curry, and Lader 1981). Any improvement during addition of an antidepressant agent may, therefore, reflect only a greater bioavailability of the antipsychotic agent. Alternatively, the anticholinergic action associated with tricyclic antidepressant agents may counteract antipsychotic-induced extrapyramidal symptoms, many of which may mimic depression. This effect could produce a spurious impression of specific antidepressant effect. In general, however, antidepressants appear to have little use in schizophrenia unless a depressive syndrome also is present; specifically, tricyclic antidepressants and MAO inhibitors have not been shown to ameliorate the passive withdrawal of chronic schizophrenics, while their addition probably does increase the risk of toxic reactions.

Propranolol

Review of Studies. A recent tantalizing entry into the field of putative antipsychotic medications has been propranolol, along with other β-adrenergic receptor blockers. In the early 1970s, several reports claimed dramatic improvements in both acute and chronic psychosis following treatment with high doses of propranolol (Atsmon et al. 1972; Gardos et al. 1973; Yorkston et al. 1974, 1976a; Atsmon 1976; von Zerssen 1976; Sheppard 1979). Although early reports cited mixed groups of patients, including some with mania, organic psychosis, or puerperal psychosis, attention quickly focused on the startling remissions seen in some chronically ill patients diagnosed as schizophrenic who had been refractory to treatment with antipsychotic agents. In these early uncontrolled studies, very high doses of propranolol were typically used—up to 3 or 4 g/day in some series (Atsmon et al. 1972; Yorkston et al. 1974, 1976a; von Zerssen 1976). In some cases propranolol replaced an antipsychotic agent, while in others the two treatments were combined; successes were reported in both conditions. (See table 2 for a review of representative reports on β-blockers.)

Three points are worth noting in reviewing these reports. One is the ubiquitous lack of clear diagnostic criteria. A second point is the inconsistency in the length of time required for a therapeutic effect. While some authors found improvement within a week of beginning treatment, others maintained that several weeks or even months were needed to observe changes (Yorkston et al. 1977; Sheppard 1979). Sheppard reported clinical improvement within 10 days in seven out of eight patients, but six of these patients deteriorated again as the trial continued. Finally, the nature of the improvement varied. Some investigators documented a decrease in positive symptoms such as aggression and thought disorder, while others noted improvement in negative symptoms of withdrawal and apathy. Despite these inconsistencies, it appeared that propranolol might be a useful addition to the therapeutic armamentarium.

Since 1977, however, a series of controlled studies have given a less optimistic picture. The following points should be noted (table 2):

- One double-blind study (Yorkston et al. 1981) of propranolol alone found propranolol to be only slightly less effective than CPZ in treating acute exacerbations of psychosis; however, improvement was minimal in both the propranolol and CPZ groups. Three other controlled studies of propranolol alone compared to CPZ or to placebo failed to find any therapeutic effect of propranolol, or found it to be less
<table>
<thead>
<tr>
<th>Study</th>
<th>Type of study</th>
<th>No. of patients completing trial</th>
<th>Dosage of propranolol (mg/day)</th>
<th>Concomitant neuroleptic medication</th>
<th>Results</th>
<th>Adverse reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atsmon et al.</td>
<td>Open</td>
<td>12 (6 males, 6 females); 7 acute, 5 chronic</td>
<td>400–4280, average 1400</td>
<td>N.A.</td>
<td>5 of 7 acute showed much improvement. 3 of 5 chronic showed some improvement</td>
<td>Hypertension, ataxia</td>
</tr>
<tr>
<td>(1972)</td>
<td></td>
<td></td>
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<tr>
<td>Gardos et al.</td>
<td>Open</td>
<td>8 (6 males, 2 females)</td>
<td>120–720, 1 patient up to 2560; 1 patient up to 2880</td>
<td>None</td>
<td>No antipsychotic effect</td>
<td>Hypotensive episode, insomnia, fatigue, 1 fatal bleeding ulcer on 2880 mg</td>
</tr>
<tr>
<td>(1973)</td>
<td></td>
<td></td>
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<tr>
<td>Yorkston et al.</td>
<td>Open</td>
<td>14 (9 males, 5 females); not responding to phenothiazines</td>
<td>500–3000</td>
<td>Phenothiazines</td>
<td>6 complete remission of symptoms; 5 improved; 2 minimal or transient improvement; 1 unchanged with severe toxic reaction</td>
<td>Ataxia, confusional states, visual hallucinations</td>
</tr>
<tr>
<td>(1974)</td>
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<tr>
<td>Atsmon</td>
<td>Open</td>
<td>44; 11 acute schizophrenics; 15 chronic schizophrenics; 8 postpartum psychosis; 5 manic psychosis; 5 psychosis due to organic brain syndrome</td>
<td>≤ 2600</td>
<td>None</td>
<td>18 markedly improved 7/11 3/15 5/8 3/5 0/5</td>
<td>Acute hypertension, vomiting and diarrhea, fatigue, vivid dreams, impaired coordination, slurred speech, 1 patient premature ventricular contractions, 1 mild congestive heart failure</td>
</tr>
<tr>
<td>(1976)</td>
<td></td>
<td></td>
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<tr>
<td>Yorkston et al.</td>
<td>Open</td>
<td>55</td>
<td>160–3000 (median 1125)</td>
<td>Phenothiazines, butyrophenones</td>
<td>28 complete remission of symptoms, 17 with propranolol alone and 11 with propranolol + a phenothiazine</td>
<td>Ataxia, dysarthria, visual hallucinations, confusional state, congestive heart failure, hypertension, angina</td>
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<tr>
<td>(1976a)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Study/Reference</td>
<td>Design</td>
<td>Participants</td>
<td>Dose</td>
<td>Treatment</td>
<td>Outcome</td>
<td></td>
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<tr>
<td>von Zerssen (1976)</td>
<td>Open</td>
<td>17, including 6 manic, 2 porphyria, 3 schizophrenic, 6 schizoaffective</td>
<td>&lt; 3780 Oxprenolol: 1480–4720</td>
<td>None</td>
<td>2 organic psychoses—marked improvement; 6 manic—2 improved, 4 did not; 3 schizophrenics—no improvement; 6 schizoaffective psychosis—slight improvement</td>
<td></td>
</tr>
<tr>
<td>Yorkston et al. (1977)</td>
<td>Propranolol vs. placebo</td>
<td>14 (5 males, 9 females); not improved by major tranquilizers; CPZ average 1634 mg</td>
<td>Average dose 954</td>
<td>Phenothiazines, butyrophenones</td>
<td>“Both groups improved, but the propranolol group improved significantly more.” 12-week trial: first change noted at 8 weeks</td>
<td></td>
</tr>
<tr>
<td>Bigelow, Zalcman, &amp; Kleinman (1978)</td>
<td>Double-blind, crossover, random assignment</td>
<td>11</td>
<td>1920</td>
<td>None</td>
<td>2/11 improved but not when repeated</td>
<td></td>
</tr>
<tr>
<td>Sheppard (1979)</td>
<td>Open</td>
<td>8 male (Schneider’s criteria), acute; partial response to antipsychotics</td>
<td>≤ 2400</td>
<td>Phenothiazines, butyrophenones</td>
<td>7 patients showed significant clinical evidence of psychiatric improvement (3-week trial), but 8/7 deteriorated later in trial</td>
<td></td>
</tr>
<tr>
<td>Belmaker et al. (1979)</td>
<td>Open (to determine biological effect)</td>
<td>10</td>
<td>1000</td>
<td>None</td>
<td>None did as well as on neuroleptics; 3 had some effect (3 weeks)</td>
<td></td>
</tr>
</tbody>
</table>

Toxic psychoses, epileptic seizures (2 patients), gastrointestinal hemorrhage (latter on other meds as well)
<table>
<thead>
<tr>
<th>Study</th>
<th>Type of study</th>
<th>No. of patients completing trial</th>
<th>Dosage of propranolol (mg/day)</th>
<th>Concomitant neuroleptic medication</th>
<th>Results</th>
<th>Adverse reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elizur et al. (1979)</td>
<td>Single-blind</td>
<td>10 (5 males, 5 females)</td>
<td>Up to 3000/day</td>
<td>No other</td>
<td>3/10 marked improvement; 1/10 partial; 6/10 no improvement or deterioration</td>
<td>Hypertensive encephalopathy</td>
</tr>
<tr>
<td>Lindstrom &amp; Persson (1980)</td>
<td>Double-blind, crossover</td>
<td>12 (10 males, 2 females); incomplete response to antipsychotics</td>
<td>1280-1920</td>
<td>Flupenthixol</td>
<td>6 improved (2 weeks); 3 unchanged; 3 deteriorated</td>
<td>Hypotension, ataxia</td>
</tr>
<tr>
<td>Hanssen et al. (1980)</td>
<td>Open</td>
<td>6 (2 males, 4 females); Schneider's criteria; &quot;refractory&quot; to phenothiazines</td>
<td>1440</td>
<td>Antipsychotics (not added until after propranolol given 2-4 weeks) and benzodiazepines as needed</td>
<td>3/6 improved (2-4 weeks)</td>
<td>Bradycardia, hypotension, sleep disturbance</td>
</tr>
<tr>
<td>King et al. (1980)</td>
<td>Open, then double-blind</td>
<td>8 patients, all male, results on 5; Feighner criteria</td>
<td>1000</td>
<td>Trifluoperazine added in one section</td>
<td>No statistically significant improvement. Some improvement when antipsychotic added (3 weeks)</td>
<td>1/5 seizures (history of seizures before study)</td>
</tr>
<tr>
<td>Yorkston et al. (1981)</td>
<td>Double-blind, random assignment</td>
<td>35; Schizophrenia Research Project criteria &quot;acute&quot;</td>
<td>670</td>
<td>Rare, as needed</td>
<td>Propranolol equally effective as CPZ, but neither very effective (3-month trial)</td>
<td>Ataxia, dizziness</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Sample Size</td>
<td>Methodology</td>
<td>Results</td>
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<tr>
<td>Peet et al. 1981</td>
<td>Double-blind, randomized comparison of propranolol, CPZ, placebo</td>
<td>53 (19 on propranolol); Feighner criteria, long-term hospitalization</td>
<td>640</td>
<td>None</td>
<td>Neither propranolol nor CPZ different from placebo (3-month trial) 1 patient had cardiovascular collapse</td>
<td></td>
</tr>
<tr>
<td>Myers 1981</td>
<td>Double-blind, random assignment</td>
<td>20 (10 on propranolol); &quot;treatment resistant&quot;</td>
<td>1920</td>
<td>Depot antipsychotics throughout</td>
<td>No difference between propranolol and placebo</td>
<td>Hallucinations, syncope (1), drowsiness, ataxia</td>
</tr>
</tbody>
</table>
effective than CPZ (Bigelow, Zalcman, and Kleinman 1978; King et al. 1980; Peet et al. 1981). All of these studies used doses of propranolol comparable to those used in earlier open studies reporting therapeutic success, and all allowed sufficient time to detect improvement (at least 12 weeks). One might argue that the populations used were particularly refractory to treatment, since CPZ also failed to produce substantial effects in most cases. However, the earlier studies had suggested that propranolol could treat such patients, and in fact had proposed that propranolol might be particularly effective in patients with psychosis that was resistant to vigorous neuroleptic treatment.

- Two controlled studies of propranolol or placebo added to a neuroleptic agent found propranolol to be a more effective adjunct than placebo (Yorkston et al. 1977; Lindstrom and Persson 1980). A third such study failed to show any advantage of propranolol over a neuroleptic alone (Myers et al. 1981). The doses of propranolol used and the duration of the study do not explain this difference in findings.

It is difficult to know how to interpret such diverse findings. There is certainly considerable smoke in the form of reported efficacy in some patients, but the fire of statistical significance is elusive. The possibility of a type II error must be borne in mind—that is, that a clinically useful effect may be missed for lack of overall statistical significance. Such errors are possible, in view of the small sample sizes and heterogeneous populations typical of these studies. It is clear that propranolol does not have the broad efficacy of the conventional antipsychotic agents. It may, however, be effective in some small, as yet undefined, subgroup of psychotic patients.

**Adverse Effects.** Although many psychotic patients have tolerated propranolol well, even at very high doses, unwanted effects have been reported. Dizziness, ataxia, hypotension, sleep disturbances, and delirium are not uncommon. Cardiovascular collapse has been reported (Peet et al. 1981). Paradoxically, hypertensive responses also have been described, with accompanying angina or encephalopathy (Atsmon et al. 1972; Atsmon 1976; Yorkston et al. 1976a; Elizur et al. 1979). Three patients are reported to have experienced grand mal seizures at high doses of propranolol (one during withdrawal); only one patient had a previous history of seizures (von Zerssen 1976; King et al. 1980). Yorkston et al. (1976b) suggest that most of these serious adverse effects can be avoided by using a twice daily dosage schedule, raising the dose not more than 40–80 mg/day, and monitoring patients carefully.

Two fatalities have been reported during high-dose propranolol treatment of psychosis. One patient bled to death from an unsuspected gastric ulcer while taking 2,880 mg of propranolol (Gardos et al. 1973). A second unexplained and apparently sudden death occurred in a healthy 18-year-old outpatient who was taking 1,280 mg/day of propranolol for treatment of psychosis (S.C. Schulz, personal communication, 1982). The patient was found dead at home, and autopsy revealed no physical abnormality or evidence of overdose.

Despite such sobering reports, propranolol is well tolerated by the majority of schizophrenic patients when doses are raised gradually. It may, however, carry the potential for unpredictable, severe, or even fatal reactions, and empirical trials should be limited to patients who fail to respond to vigorous application of more conventional treatments.

**Theoretical Implications.** Speculations as to why β-adrenergic blockers might have antipsychotic activity have been offered by several investigators. Peet, Middlemiss, and Yates (1981b) demonstrated that adding propranolol to a constant dose of chlorpromazine markedly increased chlorpromazine blood levels. This is not an entirely satisfactory explanation. At least one study (Sheppard 1979) noted that patients who improved with propranolol had previously failed to improve at substantially higher doses of CPZ than were given with the propranolol (blood levels were not reported). In addition, the assumption that “more is better” in antipsychotic therapy must be questioned. Gruzelier et al. (1979) found that propranolol corrected apparent abnormalities in habituation of alerting responses in schizophrenic patients, and suggested that this response might be related to an antipsychotic effect.

With respect to the dramatic successes described with propranolol treatment in early trials, another observation is in order. At least some of the initial successes reported were not in schizophrenic patients, but rather in patients with mania or with organic mental syndromes such as acute intermittent porphyria (Atsmon 1976; von Zerssen 1976). It is apparent from examination of table 2 that propranolol’s apparent efficacy in schizophrenia wanes as diagnostic rigor increases. Included in the studies cited are three case histories of schizophrenic patients who responded well to treatment with propranolol (Yorkston et al. 1974; Hanssen et al. 1980). Of the three,
two patients had histories highly suggestive of temporal lobe epilepsy (one developed a chronic psychosis following a parietal skull fracture and had an abnormal electroencephalogram; the other complained of olfactory hallucinations and sudden attacks of agitation, both of which suggest temporal lobe dysfunction). It is possible, then, that propranolol has a specific antipsychotic effect in patients with coarse brain dysfunction, independent of any possible antischizophrenic effect. While not used as an anticonvulsant in humans, propranolol has anticonvulsant activity in animals (Yeoh and Wolf 1968), and so might suppress temporal lobe dysrhythmias. Several recent reports also suggest that patients with brain damage who show violent or aggressive behavior may become calmer and more manageable after treatment with propranolol (Elliott 1977; Yudofsky, Williams, and Gorman 1981). The mechanism of this action is not known.

Schizophrenia, as a heterogeneous clinical syndrome, undoubtedly includes patients with various kinds of brain dysfunction. It may be that propranolol’s success in treating some schizophrenic patients—particularly in studies lacking rigorous diagnostic criteria—in fact represents treatment of coarse brain dysfunction.

**Benzodiazepines in Schizophrenia**

Benzodiazepines have been used in the treatment of schizophrenia and other psychotic disorders for several reasons. Many schizophrenic patients suffer from anxiety, and the use of anxiolytics seems clinically reasonable. This is particularly the case when the anxiety appears to be secondary to external stress or deficient coping skills rather than to the underlying psychosis (Schatzberg and Cole 1981). Curiously, this use of benzodiazepines has not been adequately studied in its own right. However, the studies cited below provide enough data to suggest that even an antianxiety effect of benzodiazepines is not established in schizophrenic patients. Benzodiazepines are also used as hypnotics in psychotic patients, but again, efficacy remains to be established (Jus et al. 1979). Benzodiazepines are given, with variable efficacy, to relieve the akathisia associated with antipsychotic medications. They also have an accepted place in the management of some hallucinogen-induced psychoses, and in the management of acute psychotic agitation in mania (Baldessarini, in press). But benzodiazepines also have themselves been used as primary antipsychotic agents, and have been given in various doses in hopes of ameliorating symptoms such as disordered thinking and hallucinations.

A plausible theoretical justification for using benzodiazepines as antipsychotic agents has been offered by van Kammen (1977). Benzodiazepines facilitate γ-aminobutyric acid (GABA) neurotransmission. GABA, which functions as an inhibitory neurotransmitter, may modulate the activity of dopamine; specifically, it probably mediates an inhibitory striatonigral feedback loop and may also inhibit activity in mesolimbic dopamine projections. Evidence that schizophrenic patients have decreased central GABA activity, which might contribute to a hypothesized dopamine excess associated with psychosis, is suggestive (Bird et al. 1977) but not firm (Cross, Crow, and Owen 1979). While benzodiazepines might indirectly decrease dopamine activity, they do not have obvious antidopamine activity as do neuroleptic agents.

The data are even less elegant than the theory. Nestoros (1980) summarized the controlled studies then available. He argued that benzodiazepines had been wrongly maligned as ineffective antischizophrenic agents. He pointed to three studies in which a benzodiazepine was superior to placebo in treating psychosis, and three others in which a benzodiazepine outperformed an antipsychotic. In the remaining 11 comparisons, however, benzodiazepines were at best as effective as placebo, and sometimes less effective. Nestoros cites doses used and points out that many studies in which benzodiazepines were ineffective used relatively low doses (e.g., 30 mg of chlordiazepoxide), but several of the favorable studies used similar doses. To add to the confusion, several of the comparison antipsychotic agents also were given in relatively low doses (e.g., CPZ 150 mg; trifluoperazine 2–8 mg). In summary, little can be concluded from these studies.

The few additional studies since Nestoros’ review yield equally mixed results (table 3). No clear pattern is discernible correlating efficacy with dose or with the concomitant use of antipsychotic medication. Despite the lack of definitive data, however, some interesting points emerge. One is the repeated finding that in a given group of patients, some prove to be completely unresponsive, while others improve markedly. Several investigators have remarked on this variance, but have been unable to find clinical predictors of response (Beckmann and Haas 1980; Jimerson et al. 1982). Three authors have proposed that schizophrenic and schizoaffective patients may respond differentially (Beckmann and Haas 1980; Lechin and van der Dijs 1981; Jimerson et al. 1982), but their
<table>
<thead>
<tr>
<th>Study</th>
<th>Patient description</th>
<th>n</th>
<th>Study design</th>
<th>Drug &amp; dose</th>
<th>Concomitant antipsychotic?</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kellner et al. (1975)</td>
<td>Anxious schizophrenic, selected for good response in open trial</td>
<td>6</td>
<td>Double-blind</td>
<td>Chlordiazepoxide, 300 mg</td>
<td>Yes</td>
<td>2 patients improved &quot;substantially,&quot; including hallucinations and thought disorder; 1 showed moderate improvement; 3 showed no change</td>
</tr>
<tr>
<td>Ruskin et al. (1979)</td>
<td>Unselected chronic schizophrenic</td>
<td>8</td>
<td>Open</td>
<td>Diazepam, 40-80 mg</td>
<td>?</td>
<td>No clinical benefit, including measures of anxiety and tension</td>
</tr>
<tr>
<td>Lingjaerde et al. (1979)</td>
<td>&quot;Chronic schizophrenic or chronic psychotic reaction&quot;</td>
<td>23</td>
<td>Double-blind</td>
<td>Diazepam, 15 mg</td>
<td>Yes</td>
<td>Small but statistically significant decrease in BPRS score on diazepam, including symptoms of thought disorder, but not &quot;anxiety&quot;</td>
</tr>
<tr>
<td>Lingjaerde (1982)</td>
<td>Mostly &quot;chronic schizophrenic&quot; with auditory hallucinations, poorly responsive to antipsychotics</td>
<td>58</td>
<td>Double-blind</td>
<td>Estazolam, 6 mg</td>
<td>Yes</td>
<td>Estazolam superior to placebo in reducing auditory and visual hallucinations and compulsive thoughts, also on global rating</td>
</tr>
<tr>
<td>Karson et al. (1982)</td>
<td>RDC: chronic schizophrenic</td>
<td>13</td>
<td>Double-blind</td>
<td>Clonazepam, ? 1-5 mg</td>
<td>Yes</td>
<td>No significant improvement for any symptom; trend toward decreased anxiety; 3 patients demonstrated unaccustomed violent behavior</td>
</tr>
<tr>
<td>High dose treatment</td>
<td>Beckmann &amp; Haas (1980)</td>
<td>RDC: schizophrenic (9) and schizoaffective (5)</td>
<td>15</td>
<td>Open</td>
<td>Diazepam, 400 mg maximum</td>
<td>No</td>
</tr>
<tr>
<td>Jimerson et al. (1982)</td>
<td>RDC: schizophrenic (5) and schizoaffective (1)</td>
<td>6</td>
<td>Double-blind, cross-over</td>
<td>Diazepam, 300 mg maximum</td>
<td>No</td>
<td>Only 3/6 patients tolerated high dose; others were ataxic, sedated; 1 schizoaffective improved substantially and relapsed when tapered; 1 other had mild improvement; 1 was unchanged</td>
</tr>
</tbody>
</table>
hypotheses as to which diagnostic group will improve with benzodiazepines are mutually contradictory.

Despite the consistent anxiolytic effect of benzodiazepines in patients who are not psychotic, many nonresponding psychotic patients in these studies failed even to show decreased anxiety (Lingjaerde et al. 1979; Ruskin et al. 1979). Conversely, schizophrenic patients who did respond to benzodiazepines not only became less anxious, but most also showed a decrease in psychotic symptoms. Hallucinations in particular appeared to be sensitive to benzodiazepines, while delusions and disordered thinking were less responsive (Kellner et al. 1975; Beckmann and Haas 1980; Lingjaerde 1982).

It is as yet unclear whether such antipsychotic effects represent a nonspecific response to decreased anxiety or whether the effect is specific. For example, one study found intravenously administered diazepam to reduce acute psychotic symptoms as well as haloperidol over the first 24 hours of treatment (Lerner et al. 1979). The authors concluded that haloperidol’s primary action during the first hours of treatment was probably sedation rather than a specific antipsychotic action. They acknowledged, however, the possibility the diazepam might have antipsychotic action—an interpretation supported by the dramatic decrease in measures of thought disorder.

A few investigators have treated patients with high daily doses of benzodiazepines (up to 400 mg of diazepam) (Beckmann and Haas 1980; Jimerson et al. 1982). These “megadoses” have been suggested by animal studies which demonstrated reversal of the stimulatory behavioral effects of amphetamine (van Kammen 1977). While some efficacy has been claimed for this treatment, the studies are so few, and the results sufficiently mixed, that it is not clear whether high doses of benzodiazepines will better the uneven performance of low to moderate doses. Jimerson et al. (1982) noted that the patients who improved on a high dose of diazepam had previously responded well to neuroleptic medication, and they suggested that this specific subgroup had a dopamine-mediated psychosis.

**Adverse Effects.** Few serious adverse effects have been reported with the use of benzodiazepines in schizophrenic patients. Sedation and ataxia could be controlled by lowering the dose. However, there are some suggestions that even low or moderate doses of benzodiazepines may “disinhibit” patients sufficiently to increase inappropriate sexual or aggressive activity. This effect may reflect more than nonspecific intoxication, and has sometimes been dramatic at high doses (Beckmann and Haas 1980; Karson et al. 1982). Significant withdrawal reactions were not reported in any of the studies cited. Addiction and drug-seeking behavior also were not reported in these studies, but certainly are not unknown to clinicians using benzodiazepines for other disorders.

**Summary.** Of the five recent double-blind studies cited, all but one have found benzodiazepines to outperform placebo in some, but not all, schizophrenic patients. Surprisingly, psychotic symptoms as well as anxiety were found to improve in those patients who responded favorably. Given the presumed heterogeneity of schizophrenic patients, a treatment that consistently benefits even a small proportion of such patients deserves further investigation. However, clinical use of benzodiazepines as antipsychotic agents should await clearer definition of their efficacy and safety.

**Clonidine in Schizophrenia**

Clonidine, currently approved as an antihypertensive agent, stimulates α-2 (presynaptic) and, to a lesser extent, α-1 (postsynaptic) adrenergic receptors. By stimulating inhibitory presynaptic sites, clonidine decreases norepinephrine release. Because the noradrenergic system may be implicated in psychosis, a few investigators have treated psychotic patients experimentally with clonidine. One presumptive advantage of clonidine is that, like propranolol, it should be free of adverse neurologic effects associated with dopamine-blocking agents.

At least six studies describe the treatment of schizophrenic patients with clonidine. Of these, only one was performed double blind, and that study described only eight patients (Freedman et al. 1982). Only two studies found clonidine to have an apparent antipsychotic effect; one of these reports comes from the small double-blind study already mentioned. The other comes from an intriguing but uncontrolled study in which 41 patients were assigned to either clonidine or clonazepam on the basis of the response of distal colon motility to the same agents (Lechin and van der Dij 1981). These treatments, so assigned, appeared remarkably successful. The authors note, without documenting the statement, that patients assigned to each treatment deteriorated when given the alternative treatment. If this finding were reproduced in a double-blind study, it would be of considerable interest.
Four other studies of clonidine in schizophrenic patients all report uniformly discouraging results, with two groups noting that patients became more hostile and aggressive when given clonidine (Sugarman 1967; Simpson, Kunz-Bartholini, and Watts 1967; Elizur et al. 1980; Jimerson et al. 1980). Some authors speculated that such deterioration might result from a postsynaptic $\alpha$-adrenergic action of clonidine. Other adverse effects of clonidine included hypotension, which limited dosage in many patients, and some sedation. Most investigators also noted a high incidence of psychotic exacerbations on withdrawal from clonidine, often to a level worse than the original psychosis.

Patients who responded well to clonidine tended to have responded previously to neuroleptic agents. Both of the positive studies specifically chose patients with a history of good response to conventional antipsychotics (Lechin and van der Dijs 1981; Freedman et al. 1982). Most other reports did not mention previous treatment response, but one did note that both patients studied had previously been unsuccessfully treated with neuroleptics (Elizur et al. 1980). Two other investigators (Simpson, Kunz-Bartholini, and Watts 1967; Sugarman 1967) appeared to have chosen their subjects from chronically hospitalized patients who presumably did not respond adequately to previous treatment. The clinical usefulness of clonidine in psychosis may therefore be limited, especially in view of its adverse cardiovascular and sedative effects, to those patients who develop unacceptable side effects on available antipsychotic agents. In this context, it is of interest that in two studies clonidine appeared to diminish the abnormal movements of tardive dyskinesia (Lechin and van der Dijs 1981; Freedman et al. 1982).

**Carbamazepine in Schizophrenia**

Carbamazepine, currently used as an anticonvulsant and in the treatment of central pain syndromes, is finding increasing use in the treatment of affective disorders (Ballenger and Post 1980). There are only rare reports on the use of carbamazepine in the treatment of schizophrenia. One is an uncontrolled pilot study of eight violent schizophrenic patients (no criteria were given for diagnosis, but patients were chronically hospitalized in a maximum-security hospital) (Hakola and Laulumaa 1982). All eight had nonspecific electroencephalographic (EEG) abnormalities, but none had a clinical diagnosis of epilepsy. After treatment with carbamazepine, "violent behavior disappeared almost completely in all eight patients," and six of the eight could be transferred or discharged. A second, controlled trial compared carbamazepine and placebo in 11 diverse psychotic patients, all of whom had temporal lobe EEG abnormalities and were unresponsive to conventional antipsychotic agents (Neppe 1982). Eight carried the diagnosis of schizophrenia, but criteria were not stated. Carbamazepine was said to be significantly better than placebo, but specific details of improvement were not given.

It is possible that some of these patients were, in fact, suffering from temporal lobe dysfunction. However, all were diagnosed as schizophrenic, despite questionable findings on EEG recordings. Limbic dysrhythmias have been reported in schizophrenic (pre-DSM-III) patients (Heath 1962; Monroe 1970), but the implications for diagnosis or treatment are unclear. More rigorous studies of anticonvulsant drugs in schizophrenia remain to be done.

For the present, one may conclude either that carbamazepine may be an effective treatment for schizophrenic patients with EEG abnormalities, or that some patients with temporal lobe disorders may be misdiagnosed as schizophrenic.

**General Conclusions**

None of the experimental treatments reviewed have outperformed available neuroleptics in treating schizophrenia. In that sense, little has been learned that is clinically applicable, and even that is predominantly negative (e.g., the failure of antidepressants or high dose antipsychotic schedules to better the performance of conventional antipsychotic treatment). For most of the treatments reviewed, the conflicting data make clinical recommendations premature, although further evaluation seems worthwhile.

Nonetheless, such studies may make a useful contribution to the definition of schizophrenic illnesses. Lehmann (1971) suggested that "therapeutic responsiveness to particular psychotropic drugs may serve as external criteria for new diagnostic categories." In the past, psychotropic medications have been regarded as primarily symptom-specific rather than disease-specific. But currently, as in the studies reviewed here, patients whose symptoms are clinically similar seem to respond differently to medication. Borrowing a model from internal

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1 As yet, the combination of clonidine and a neuroleptic as a treatment for psychosis has not been described in the literature. One could speculate that a combined dopaminergic and adrenergic blockade might be of value in some patients.
medicine, two patients with clinical evidence of pneumonia may have similar syndromes, but respond to different antibiotic treatments because the bacterial etiology differs. Psychiatry lacks the equivalent of a bacteriologic laboratory, but need not therefore ignore clues that may arise out of differential treatment response: patients who respond to different treatments may have different illnesses.

Lithium carbonate appears to be an effective treatment for patients with schizophreniform, schizo-affective, and perhaps other atypical psychoses, but not for patients with chronic, poor-prognosis schizophrenia. This differential treatment response supports a distinction that can be made on clinical grounds, albeit not by acute symptoms. Whether schizophreniform or schizo-affective disorders can be usefully distinguished from affective illness is an important question that requires further study. The unexpected evidence that lithium added to an antipsychotic agent may also benefit about half of patients who seem to meet DSM-III criteria for schizophrenia supports the notion that even this relatively rigorously defined category is probably heterogeneous.

Carbamazepine and propranolol are both reported to be successful in treating some chronically psychotic patients, but may be especially useful in patients with evidence of temporal lobe or other definable brain dysfunction. The DSM-III (1980) diagnosis of schizophrenia requires that psychotic symptoms not be due to an organic disorder. However, patients with soft neurologic signs, such as nonspecific EEG abnormalities, are seldom excluded from the diagnosis. If the hint of selective treatment responses in past studies is supported by more evidence, these patients may deserve a separate diagnosis, or at least separate consideration in future investigations. Clinical research in psychiatry is always complex, and conflicting data emerge from the best of studies. Future research should recognize the heterogeneous nature of schizophrenic patient populations, and should use response variance to generate nosologic or pathophysiologic hypotheses instead of dismissing data as useless merely because they are inconclusive.

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The Authors

Susan R. Donaldson, M.D., is Instructor in Psychiatry, and Alan J. Gelenberg, M.D., is Associate Professor of Psychiatry, Harvard Medical School. In addition, Dr. Donaldson is Staff Psychiatrist, and Dr. Gelenberg is Associate Chief, Special Studies Clinic, Massachusetts General Hospital and Erich Lindemann Mental Health Center, Boston, MA. Ross J. Baldessarini, M.D., is Professor of Psychiatry, Harvard Medical School. Dr. Baldessarini is also Associate Director, Laboratories for Psychiatric Research, Mailman Research Center, McLean Hospital, Belmont, MA.