One More Look at Propranolol for the Treatment of Refractory Schizophrenia

by Jeffrey L. Berlant

Abstract

Propranolol, a β-adrenergic blocking agent, has been proposed previously as potentially useful in the treatment of certain otherwise treatment-unresponsive psychotic patients. This article reviews the published clinical trials of the efficacy of propranolol in schizophrenia to characterize those patients in whom it might be helpful and for whom future clinical trials should be designed. Despite a large number of inconsistent reports, the evidence to date favors its potential value as an adjunct to neuroleptic therapy in neuroleptic-resistant chronic schizophrenic patients. Several recommendations are made to improve the methodology of future clinical trials with this agent for the treatment of schizophrenia.

Propranolol, a β-adrenergic blocking agent used predominantly for the treatment of hypertension, cardiac arrhythmias, coronary artery disease, thyrotoxicosis, migraine headache, and a number of other conditions, has also been proposed as potentially useful in the treatment of certain psychiatric conditions. These have included acute porphyria (Atsmon and Blum 1970), schizophrenia (Atsmon et al. 1971), mania (Atsmon et al. 1971; Moller et al. 1979), aggressive organic brain syndromes (Elliott 1977; Yudofsky et al. 1981), chronic anxiety (Kathol et al. 1980), and compulsive water drinking (Shevitz et al. 1980).

The potential utility of propranolol as a treatment for schizophrenia has received attention in a number of clinical trials. In broad, critical reviews of clinical trials of unconventional antipsychotic medications for the treatment of schizophrenia, Donaldson et al. (1983), as well as Hayes and Schulz (1983), concluded that propranolol did not appear to be an effective antipsychotic medication for schizophrenia in general but might be helpful in selected schizophrenic subtypes. Since then, there have been a small number of additions to the clinical research literature. It is timely to review the available studies, to question again whether pursuing investigation with propranolol further is worthwhile and, if so, to identify methodological issues that may have confounded earlier research efforts.

Following the anecdotal observations of Atsmon and Blum (1970) and Atsmon et al. (1971) of positive responses to treatment with very high doses of propranolol in patients with acute psychoses, Yorkston et al. (1974) administered propranolol to 14 chronically refractory, noneuphoric schizophrenic patients characterized as "hebephrenic patients," most of whom had failed to respond to large doses of neuroleptics over months and years (up to 17 years). After the open addition of propranolol 240–3,000 mg q.d. to existing neuroleptics, 6 of 14 patients reportedly lost schizophrenic symptoms completely. Yorkston et al. claimed that "their affective reactions were appropriately modulated and were indistinguishable from normal. Several found the change hard to believe" (p. 633). Of the patients who improved, most improved within a week and maintained this improvement as long as they remained on propranolol. Upon stopping it, they relapsed.

Yorkston et al. (1976a) expanded the study of propranolol in psy-
chotic patients, selecting 55 patients who had “florid schizophrenic symptoms” without evidence of mania, depression, or confusional states for open trials of high doses of propranolol. Twenty-six reportedly underwent a complete remission of symptoms, regardless of the previous duration of psychosis. Of the total number of patients in the study, 38 had been ill for longer than 1 year and included “some of the most chronically and severely ill schizophrenics in large hospitals who usually failed to respond to many treatments” (p. 179). Eleven of the 38 remitted completely, and 6 of the 11 were given propranolol without a neuroleptic. Reportedly, “when psychosis remitted, the patients felt and looked well. They were lucid, alert, and lacked the apathetic unreactive appearance of many patients who are stabilized on phenothiazine drugs” (p. 179). Psychosis scores on the Brief Psychiatric Rating Scale fell to zero. Reduction of psychotic symptoms was maintained as long as propranolol was administered, reportedly for periods of time varying from 10 days to 18 months.

To overcome methodological shortcomings of open trials, Yorkston et al. (1977a) later undertook a double-blind, placebo-controlled, 12-week clinical trial of propranolol versus placebo in 14 floridly psychotic patients receiving chlorpromazine who had previously not responded well to neuroleptics. Five of seven patients in the combined treatment group responded within the 12-week treatment period, and two of the initial nonresponders improved following an additional month of exposure to propranolol (i.e., 100 percent response in the treatment group). By week 12 of treatment, there was significant mean improvement in the propranolol group compared to the placebo group. Furthermore, significant improvement had occurred in the propranolol group, but there had been no significant change in the placebo group. Five patients in the placebo control group who had subsequently crossed over to propranolol for a period of 4 months also improved. At followup, 7 of 12 patients receiving propranolol had “lost all their schizophrenic symptoms.” Yorkston et al. claimed that this finding was “statistically highly significant” (p. 577).

The average dose of propranolol used in the controlled, randomized clinical trial of Yorkston et al., < 500 mg/day, was comparatively low in contrast to previous trials, certain of which used daily propranolol doses in the several-gram range (e.g., Atsmon et al. 1971, 1972; Gardos et al. 1973). The finding of a positive response in this moderate range appeared encouraging because of the possibility that therapeutic responses might be attainable without the marked adverse side effects of seizures and cardiovascular instability occasionally seen with propranolol at higher doses (Yorkston et al. 1976b). From a wider perspective, however, this finding only contributed to the ambiguity over the dosage range putatively therapeutic for propranolol in schizophrenia (see table 1). That is, an optimally therapeutic and safe dosage for propranolol remained—and still remains—unknown.

The controlled study of Yorkston et al. (1976a) was an object of methodological criticism. Tyrer (1977) noted that the adequacy of the double-blind condition in that study was questionable, since close monitoring of vital signs and medication side effects might well have affected clinical ratings because of characteristic physiological responses to propranolol, such as bradycardia and relative hypotension. Yorkston et al. (1977b) responded with evidence demonstrating no significant difference between propranolol and placebo with respect to effect on heart rate, systolic blood pressure, or diastolic blood pressure. A second objection to this study was the use of unusually high neuroleptic doses (modal dosage of 954 mg of chlorpromazine equivalents daily) in chronic schizophrenic patients. Tyrer (1977) proposed that propranolol might reduce toxic neuroleptic activity, so that patients demonstrated improvement on the basis of reduction of excessive neuroleptic effect rather than true antipsychotic response. In the same vein, Tyrer proposed that possible amelioration by propranolol of some of the peripheral side effects that neuroleptics can produce might also account for some appearance of improvement. Finally, the duration of illness for patients in the placebo group was longer than for the patients in the treatment group, and duration of illness may correlate with refractoriness to treatment.

Reports by other investigators did not consistently find the dramatic results reported by Yorkston et al. Gardos et al. (1973) had previously found no improvement with propranolol therapy in an uncontrolled study of eight refractory chronic schizophrenic patients. Lindstrom and Persson (1980), however, found in a crossover study of propranolol and placebo that nearly 50 percent of patients on neuroleptics responded better during the propranolol phase.

Most studies using propranolol, however, have been open uncontrolled studies; this situation has constituted a major methodological weakness of the cumulative evidence to date. By 1981, the score-
Table 1. Clinical trials of propranolol in schizophrenia

<table>
<thead>
<tr>
<th>Year</th>
<th>Author</th>
<th>Design</th>
<th>n</th>
<th>Chronicity</th>
<th>Diagnostic criteria</th>
<th>Propranolol regimen</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1971</td>
<td>Atsmon et al.</td>
<td>Open</td>
<td>9</td>
<td>?</td>
<td>Unspecified</td>
<td>?–5800 mg/d x ? duration</td>
<td>3/5 “complete remission”</td>
</tr>
<tr>
<td>1973</td>
<td>Gardos et al.</td>
<td>Serial</td>
<td>8</td>
<td>Chronic</td>
<td>Unspecified</td>
<td>120–2880 mg/d x 6–10 wk</td>
<td>No improvement</td>
</tr>
<tr>
<td>1977</td>
<td>Ridges et al.</td>
<td>Open</td>
<td>10</td>
<td>Chronic</td>
<td>Unspecified</td>
<td>320–640 mg/d x 38 d</td>
<td>4/10 improved</td>
</tr>
<tr>
<td>1979</td>
<td>Belmaker et al.</td>
<td>Open</td>
<td>10</td>
<td>Chronic</td>
<td>Unspecified</td>
<td>1000 mg/d x 3 wk</td>
<td>3 improved; 2 worse</td>
</tr>
<tr>
<td>1979</td>
<td>Elizur et al.</td>
<td>Serial</td>
<td>10</td>
<td>Chronic</td>
<td>DSM–II + FRSs</td>
<td>160–640 mg/d x 12 wk</td>
<td>Prop &gt; PBO</td>
</tr>
<tr>
<td>1980</td>
<td>Hanssen et al.</td>
<td>Serial</td>
<td>5</td>
<td>?</td>
<td>FRSs</td>
<td>1440 mg/d x 2–4 wk</td>
<td>3/5 improved</td>
</tr>
<tr>
<td>1981</td>
<td>Peet et al.</td>
<td>Random DB</td>
<td>53</td>
<td>Chronic</td>
<td>Feighner</td>
<td>640 mg/d x 12 wk</td>
<td>Prop = 1 CPZ = PBO</td>
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<tr>
<td>1983</td>
<td>King et al.</td>
<td>Open</td>
<td>12</td>
<td>Chronic</td>
<td>Feighner</td>
<td>CPZ 400 mg/d x 12 wk</td>
<td>No improvement</td>
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<td></td>
<td><strong>II. Trials of propranolol alone in patients with unspecified prior neuroleptic response</strong></td>
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</tr>
<tr>
<td>1972</td>
<td>Atsmon et al.</td>
<td>Open</td>
<td>5</td>
<td>Chronic</td>
<td>Unspecified</td>
<td>400–4280 mg/d x ? duration</td>
<td>0/5 improved</td>
</tr>
<tr>
<td>1981</td>
<td>Yorkston et al.</td>
<td>Random DB</td>
<td>46</td>
<td>Acute</td>
<td>PSE</td>
<td>300–670 mg/d x 12 wk</td>
<td>CPZ &gt; prop at 12 wk</td>
</tr>
<tr>
<td>1981</td>
<td>Hirsch et al.</td>
<td>Open</td>
<td>9</td>
<td>Chronic</td>
<td>PSE</td>
<td>Mean 1329 mg/d x 3.1 wk</td>
<td>7/9 improved</td>
</tr>
<tr>
<td>1983</td>
<td>Sethi &amp; Dube</td>
<td>Open</td>
<td>15</td>
<td>?</td>
<td>ICD-9</td>
<td>1920 mg/d x 28 d</td>
<td>Improved at wk 2–4</td>
</tr>
<tr>
<td>1984</td>
<td>Scheinin et al.</td>
<td>Serial</td>
<td>8</td>
<td>Chronic</td>
<td>RDC/DSM–III</td>
<td>120–3200 mg/d x 7–63 d</td>
<td>No improvement</td>
</tr>
<tr>
<td></td>
<td><strong>III. Trials of propranolol with neuroleptics in neuroleptic-refractory nonchronic patients</strong></td>
<td></td>
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<tr>
<td>1979</td>
<td>Sheppard</td>
<td>Open</td>
<td>8</td>
<td>?</td>
<td>FRSs</td>
<td>360–600 mg/d x 3 wk</td>
<td>7/8 improved</td>
</tr>
<tr>
<td>1980</td>
<td>Hanssen et al.</td>
<td>Serial</td>
<td>6</td>
<td>?</td>
<td>FRSs</td>
<td>1440 mg/d x 2–4 wk</td>
<td>5/6 improved</td>
</tr>
<tr>
<td>1981</td>
<td>Myers et al.</td>
<td>Random DB</td>
<td>20</td>
<td>?</td>
<td>PSE</td>
<td>1920 mg/d x 12 wk</td>
<td>Prop = PBO</td>
</tr>
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<td></td>
<td><strong>IV. Trials of propranolol with neuroleptics in neuroleptic-refractory chronic patient</strong></td>
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<tr>
<td>1977a</td>
<td>Yorkston et al.</td>
<td>Random DB</td>
<td>14</td>
<td>Chronic</td>
<td>PSE</td>
<td>&lt; 500 mg/d x 12 wk</td>
<td>Prop &gt; PBO at wk 12</td>
</tr>
<tr>
<td>1978</td>
<td>Bigelow et al.</td>
<td>Crossover</td>
<td>4</td>
<td>Chronic</td>
<td>RDC</td>
<td>1600–1920 mg/d x 4 wk</td>
<td>Prop not markedly better</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>than PBO</td>
</tr>
<tr>
<td>1980</td>
<td>King et al.</td>
<td>Serial</td>
<td>5</td>
<td>Chronic</td>
<td>CATEGO/PSE</td>
<td>1000 mg/d x 6 wk</td>
<td>Prop = prop + neuroleptic</td>
</tr>
<tr>
<td>1980</td>
<td>Lindstrom &amp;</td>
<td>Crossover</td>
<td>12</td>
<td>Chronic</td>
<td>Unspecified</td>
<td>1280–1920 mg/d x 2 wk</td>
<td>6 improved; 3 worse</td>
</tr>
<tr>
<td>Persson</td>
<td></td>
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</tr>
<tr>
<td>1983</td>
<td>Pugh et al.</td>
<td>Random DB</td>
<td>41</td>
<td>Chronic</td>
<td>Feighner</td>
<td>160–640 mg/d x 12 wk</td>
<td>Prop &gt; PBO</td>
</tr>
</tbody>
</table>

card for open trials read as follows: studies that obtained positive results were based on a total of 108 subjects. Studies bearing a negative outcome were based on a total of only 22 patients (Yorkston et al. 1981). So the preponderance of evidence from the open data pointed toward substantial potential clinical utility of propranolol.

The few well-designed, randomized, double-blind clinical trials using propranolol have not particularly resolved the issue of the possible efficacy of this agent in schizophrenia. There are, for example, only two studies that have conducted randomized clinical trials of propranolol alone versus placebo (King et al. 1980; Peet et al. 1981).

The first double-blind crossover study examining this agent in neuroleptic-refractory chronic schizophrenic patients (King et al. 1980) found propranolol equal to placebo. But the small sample size in this study (n = 5) raises a high likelihood of a type II error, i.e., discarding a true positive finding because of an insufficiently large sample.

Another study comparing propranolol to placebo (Peet et al. 1981) appears to be the best-designed negative study in the literature. Random allocation of 53 patients stated to be resistant to neuroleptics to three treatment groups—propranolol, 640 mg q.d.; chlorpromazine, 400 mg q.d.; and placebo—revealed no between-group differences for any agent. Perhaps the absence of a positive response to chlorpromazine provides some substantiation of the claimed lack of impact of neuroleptics in this patient population. They concluded that there was no convincing evidence that propranolol is effective in treating schizophrenia of the original refractory subtype described by Yorkston et al.

The study by Peet et al. also introduced laboratory evidence that propranolol can raise circulating levels of chlorpromazine and its active metabolites. The author interpreted this finding as an alternative explanation for the earlier findings of Yorkston et al. of a positive adjunctive role for propranolol through the induction of an antipsychotic effect by elevating neuroleptic levels into an effective range. This argument, one might note, seems contradictory to Tyrer's (1971) suggestion that propranolol might reduce the effects of excessive doses of neuroleptics into a more beneficial range, as well as the assumption that patients in the earlier studies were truly resistant to the action of neuroleptics.

More recently, there have been two additional randomized studies of propranolol and placebo, both in patients receiving neuroleptics. One (n = 20) found no difference in outcome (Myers et al. 1981). Another (n = 41) found that propranolol, 640 mg q.d., is significantly more effective, particularly for irritable patients (Pugh et al. 1983). This report is similar to other reports of the effectiveness of propranolol in patients with violent organic psychoses (Elliott 1977; Yudofsky et al. 1981). Perhaps the more violence-prone, irritable subgroup of chronic schizophrenic patients may be prime clinical candidates for further research with this agent.

Summary of Clinical Findings

Because of uncertainties about the potential differences between acute and chronic psychoses and neuroleptic-responsive and neuroleptic-resistant psychoses, it is important to separate medication effects according to chronicity and neuroleptic responsivity to discriminate improvements that can be ascribed to medication instead of to nonspecific effects such as spontaneous remission. It is unclear whether acute psychoses are mere brief variants of their chronic counterparts or have biologically different substrates; similarly, patients who respond differentially to neuroleptics may have different underlying biological disturbances.

Review of studies of the efficacy of propranolol (table 1, part II) reveals predominantly negative findings in trials selecting patients who were not previously identified as resistant to neuroleptics. Two of three uncontrolled trials of racemic propranolol in chronic schizophrenic patients showed no advantage to propranolol (Atsmon et al. 1972; Sethi and Dube 1983; Scheinin et al. 1984); a single small trial of d-propranolol was, however, favorable (Hirsch et al. 1981). A randomized trial of propranolol and chlorpromazine in 46 acutely ill patients with schizophrenic symptoms indicated no difference at 6 weeks and a significant difference favoring chlorpromazine at 12 weeks (Yorkston et al. 1981).

Review of the studies in table 1, part I suggests that propranolol alone may be no better than placebo or neuroleptics in the treatment of either acute or chronic treatment-resistant schizophrenic patients. Although in seven uncontrolled trials of propranolol in drug-free, neuroleptic-refractory schizophrenic patients, five suggested a positive effect (Atsmon et al. 1972; Ridges et al. 1977; Belsma et al. 1979; Elizur et al. 1979; Hanssen et al. 1980), the single randomized trial of propranolol alone in this population was negative (Peet et al. 1981).

Nonetheless, the combined use of propranolol plus neuroleptics may be effective in certain as yet poorly
In neuroleptic-refractory patients with schizophrenic symptoms selected without respect to chronicity (table 1, part III), there was improvement observed in two small uncontrolled studies (Sheppard 1979; Hanssen et al. 1980) but not in a double-blind, randomized study of 20 patients (Myers et al. 1981). In studies restricted to chronic schizophrenic patients refractory to neuroleptics treated with combined neuroleptics and propranolol (table 1, part IV), one uncontrolled study of five patients (King et al. 1980) and one double-blind crossover study of four patients (Bigelow et al. 1978) were negative, but one double-blind crossover study examining 12 patients (Lindstrom and Persson 1980) and two double-blind randomized clinical trials using 14 and 41 patients, respectively (Yorkston et al. 1977a; Pugh et al. 1983), were positive. It is in this last clinical subgroup in which propranolol is used as an adjunct to neuroleptics that the case for its role as an antipsychotic is strongest.

Discussion

A number of crucial methodological issues recur throughout the clinical trials of propranolol. Perhaps the most frequent source of ambiguity has been wide variability in the definition of key terminology relevant to the selection and comparison of patient groups. Before the question of efficacy of this medication can be resolved, greater attention needs to be paid to at least the following issues:

1. The definition of schizophrenia. Diagnoses of schizophrenia used in the studies examined in this article have been based on a wide assortment of definitions of schizophrenia. Early studies cited no explicit diagnostic criteria for schizophrenia, and subsequent studies drew upon a variety of diagnostic systems for schizophrenia, including the presence of Schneiderian first-rank symptoms (Schneider 1959), CATEGO/Present State Examination (Wing et al. 1974), Feighner criteria (Feighner et al. 1972), Research Diagnostic Criteria (Spitzer et al. 1978), and both DSM-II (American Psychiatric Association 1968) and DSM-III (American Psychiatric Association 1980). In view of the lack of diagnostic specificity of Schneiderian first-rank symptoms (which have been reported to occur with appreciable frequency in both organic and affective psychoses (Silverstein and Harrow 1981), use of definitions that rely extensively on these symptoms, including the Present State Examination and CATEGO, may result in studying an aggregate which is excessively heterogeneous to produce meaningful and reproducible results.

A more discerning strategy may be to restrict the use of the term "schizophrenia" to a residual category of psychotic disorders narrowly defined as those conditions remaining following exclusion of known causes of "schizophrenic symptoms." Certain existing diagnostic systems, including Feighner criteria, Research Diagnostic Criteria, and DSM-III, which incorporate this approach, have superior predictive validity (Strauss and Gift 1977; Kendell et al. 1979) and should be preferred in future studies.

2. Adequate exclusion of other psychiatric disorders. Because organic and affective psychoses can produce "schizophrenia"-like symptoms with significant frequency, care needs to be taken to exclude such conditions. To do otherwise may compromise the ability to identify specific biological and pharmacological properties of homogeneous groupings by allowing excessive diagnostic heterogeneity in inclusion criteria (Pope and Lipinski 1978).

Certainly, drug-induced or toxic psychoses and epileptic psychoses should be excluded, as well as the wide range of variants of bipolar illness. In addition to excluding classical forms of manic-depressive illness meeting modern criteria for bipolar disorder, variants with predominantly psychotic rather than affective symptomatology yet responsive to lithium should be excluded. To do so may require a lithium carbonate trial to exclude this group.

For patients with schizoaffective disorders who respond well to lithium carbonate, there may be limited clinical need to uncover new therapeutic agents. There may be reason, however, to study the effects of propranolol on some forms of mainly schizophrenic schizoaffective disorder which are only partially responsive to lithium. Comparisons of lithium versus propranolol augmentation for these subgroupings would be of great interest.

Strategically, it is prudent to keep open the possibility that propranolol may be an effective treatment for some conditions for which there already exists conventional therapy. As a first step, however, because review of the literature suggests that neuroleptic-refractory, chronically psychotic patients may be helped by the adjunctive use of propranolol with neuroleptics and because this clinical group desperately needs an effective treatment, studying a narrowly defined group of neuroleptic-resistant, lithium-resistant chronic psychotics would seem to be a logi-
nal place to start. Subsequent studies of the potential utility of propranolol in other diagnostic categories, such as toxic or epileptic psychoses, could be undertaken with the expectation that results may be more reliable and reproducible in studies conducted with "pure cultures."

3. Stratification of chronicity. None of the studies specified the duration of continuous psychosis necessary to qualify for chronic status. Minimally, there is a need to adopt a standard operationalized value such as the 2-year duration cited in DSM-III. Future studies need to control for variation in response rates to medication which might be linked to duration of illness.

4. Definition of refractoriness. None of the studies provided an operational definition of "refractoriness to medications" (either neuroleptics or lithium carbonate). In light of reports of a possible therapeutic window for certain neuroleptics (Magliozzi et al. 1981; Kucharski et al. 1984), documentation should be provided of response at different dose ranges, perhaps refined by the use of circulating neuroleptic levels. A definition should also include an adequate duration of neuroleptic exposure. Furthermore, an adequate definition should include a standardized, quantitative method of documenting residual psychotic symptomatology, such as the Brief Psychiatric Rating Scale (Overall and Gorham 1962) or the Comprehensive Psychopathological Rating Scale. Finally, sufficient information should be provided to evaluate the validity of the reports of lack of response to medication.

5. Operational criteria for responsiveness. A statistically significant difference in improvement between a treatment group and control group may not be clinically significant.

Studies which report a statistically significant improvement when propranolol is compared to conventional treatment do not adequately address the issue of whether the extent of improvement is clinically important for the overall management and performance of patients. There is a need in the planning and design of clinical trials to preset a threshold of improvement in psychotic symptomatology which must be attained to be deemed clinically significant. Practical criteria might be either a raw difference in total BPRS score of 20 or a percentage reduction, such as 50 percent, which must be reached before it is concluded that an individual subject or group of subjects is clinically improved.

6. Adequate sample size. Among studies of propranolol alleging to demonstrate a negative effect on schizophrenic symptoms, although the data may have failed to show a statistically significant difference in outcome, the sample sizes of these studies were all insufficiently large to prevent the possibility of a type II error. Studies that use small sample sizes are prone to the risk of falsely rejecting a true difference between groups. To guard against this possibility, the conventional rule is to design studies with a power ≥ 0.80 (Cohen 1977).

Power analysis of the important negative studies reviewed raises significant questions about the adequacy of safeguards against a type II error. For example, when the negative study of King et al. (1980) with an n of 5 was subjected to power analysis using the method of Cohen (1977), it achieved a power < .15. The negative study of Bigelow et al. (1978) with an n of 4 reached a power < .31. Thus, neither of the negative clinical trials for patients treated with combined propranolol and neuroleptic therapy for neuroleptic-refractory chronic schizophrenia is sufficiently large to reject the possibility of efficacy of this treatment.

Similarly, the study of propranolol and neuroleptics in unspecified neuroleptic-refractory schizophrenics by Myers et al. (1981) with an n of 20 (10 in each comparison group) could achieve a power level at best of .39, even assuming that the effect size under study was large.

Among those negative studies of the effect of propranolol alone in neuroleptic-refractory schizophrenia, the study by Gardos et al. (1973) with an n of 8 at best could attain a power level < .31; the study of King et al. (1983) of 12 patients could reach a power level of .46; and the study of Peet et al. (1981) of 53 patients in three sample groups—believed by some to be a strong refutation of earlier positive findings—reaches a power of .73 only if the true effect were a large one. Were there, in fact, a medium-sized effect to be detected, the study of Peet et al. would have a power of only .34. Thus, even studies that at first glance appear to have large sample sizes have still borne substantial risks of type II errors.

7. Controlling for effects on neuroleptic side effects. Cohen and Lipinski's (1986) observation that positive effects of propranolol on psychotic symptoms may be limited to those patients who have neuroleptic-induced akathisia suggests that future studies control for neuroleptic effects which may aggravate psychosis. Reports by Van Putten et al. (1975) and Van Putten (1975) suggest that akathisia may indeed worsen psychosis. These observations have led some investigators to explore the utility of propranolol (Lipinski et al. 1984) and other β-blockers (Zubenko et al. 1984) as treatment for neuroleptic-induced
akathisia. Sufficient evidence exists at present to treat akathisia at least as a potentially confounding variable.

8. Sequencing of medications. Most studies of combination effects have been based on observations of response to the addition of propranolol to neuroleptics. The failure to find a significant improvement in the negative-outcome study of Myers et al. (1981) may, among other possibilities, have been due to the order in which medications were introduced. The practice of addition of neuroleptics to baseline treatment with propranolol alone in this study may have introduced a difference in sequencing of the addition of medications as a confounding factor in analyzing combination effects.

9. Targeting subsets of patients responsive to specific agents. Passing references in the research literature to hebephrenic patients, aggressive patients, and floridly psychotic patients are not very helpful because of the lack of specific, tightly operationalized research criteria for these conditions. Some of the more common clinical distinctions in the schizophrenia research literature between predominantly positive and negative symptoms of schizophrenia (Crow's [1980] types I and II) may not have been adequately taken into account in the above clinical trials. Such refinements need to be included in future work with these agents. In the current state of affairs, the reader cannot quite discern the nature of the disorders treated in these studies.

Conclusion

One reason for the preparation of this review has been to reassess the scientific basis for the current relative lack of enthusiasm in the research community for conducting clinical trials necessary to clarify the actual value of propranolol for patients for whom the field of psychiatry presently has no effective treatment. Perhaps workers in the field have been prematurely ready to reject what seem like predominantly encouraging findings even in the absence of an adequate number of large or well-designed negative studies. There may be a danger in the course of adopting a skeptical posture toward claims of dramatic new treatments for desperately ill, treatment-resistant patients that a cluster of small negative studies can discourage appropriate future inquiry. One solution may be to maintain an equally skeptical posture about the significance of negative as well as positive small studies and the use of moderate-sized samples for the next generation of clinical trials of propranolol.

Another factor that requires attention is the tendency of psychopharmacological studies to rely on single-drug therapies rather than combination treatments. To be sure, methodological issues are much more complicated with combination therapies. These obstacles and challenges need to be placed in the larger context of the successes attained in another field—cancer chemotherapy—by the development of studies and methodologies for systematically testing the effects of combination chemotherapy. This approach has produced major breakthroughs in the treatment of a number of tumors (DeVita et al. 1985). Perhaps psychiatry would also benefit by adopting more refined methodological strategies for handling the possibility of interactive synergistic effects in treating the more treatment-resistant psychiatric disorders.

As discussed above, most of the negative studies in this review have been at risk of making type II errors. If the questions raised by these clinical trials are ever to be put to rest, clinical trials with adequately large samples are necessary. In the instances discussed in this article, there are enough provocative studies and the number of patients involved in the negative studies is so small that there is a scientific need to go on to larger studies to lay uncertainty to rest. To facilitate obtaining rapid answers to these questions, multicenter drug trials are needed to gather adequate sample sizes in a short period of time.

Although the few methodologically sound studies in the existing literature provide virtually no support of the antipsychotic effects of propranolol when used alone in chronic schizophrenia, the least ambiguous demonstration of the presence of synergism can be accomplished through three-way trials which compare trial medication alone to neuroleptic alone and to trial medication combined with neuroleptic. Particularly in view of the as yet poorly clarified risks of treatment with a very active cardiovascular agent, it is important to continue to control for possible placebo effects before recommending its widespread clinical use. Such trials require substantial numbers of patients, and medium-sized samples or even large, multicenter studies might be required to resolve the questions at hand.

A note of caution should be introduced about the interpretation of past and future positive findings. Not only may clinical improvement accompanying the use of propranolol be due to indirect antipsychotic effects of propranolol such as the possible reduction of neuroleptic-associated akathisia, as discussed above, but even if propranolol has direct antipsychotic properties, the
mechanism may not be mediated through $\beta$-adrenergic blockade. The $d$-stereoisomer of propranolol is practically devoid of $\beta$-blocking activity yet exhibits antimanic properties (Emrich et al. 1979). This observation prompts the need to consider other, nonadrenergic neuronal effects of propranolol before attributing any observed antipsychotic effects to only one of many properties of this medication.

Future studies need to take particularly careful note of the issue of refractoriness to neuroleptics. The term “schizophrenia” is still so broadly drawn as probably to encompass a wide range of clinical conditions. The subpopulation of patients who are resistant to neuroleptics may have different disorders from ordinary, neuroleptic-responsive psychoses. The problem may be analogous to the argument by Lerer (1985) that carbamazepine, which has been demonstrated to be effective in the treatment of lithium-unresponsive mania, still requires demonstration of efficacy in a “typical” population of lithium-responsive bipolar patients.

A potential—and perhaps common—fallacy is to test agents that appear promising in patients poorly responsive to neuroleptics in a different population, i.e., schizophrenic patients responsive to neuroleptics. Such a procedure runs the risk of rejecting the agent in toto when it fails to work in the more general psychotic population. Screening out neuroleptic responders should be part of standard investigation with unconventional antipsychotic medications. In the event that propranolol does prove effective in neuroleptic-refractory patients, investigation into the underlying biological abnormalities of these patients might yield new theories and insights into the biological nature of psychosis.

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