Lithium Combined with Haloperidol in Schizophrenic Patients

YAACOV LERNER, YAACOV MINTZER and MIGUEL SCHESTATZKY

Previously, the addition of lithium to haloperidol has been reported to be of modest benefit to schizoaffective patients. To test this treatment on a different sample, 36 mainly schizophrenic patients were subdivided on the basis of the median of their initial depression score on the BPRS into depressive and non-depressive schizophrenic subjects. Each group randomly received haloperidol plus placebo or haloperidol plus lithium for 8 weeks. The schizophrenic patients who were on the depressive side of the median BPRS depression score were found to be the most resistant to neuroleptic treatment alone, and benefited from the addition of lithium.

For the last 10 years, data have been accumulating indicating that, contrary to former evidence, lithium may play a useful role in the treatment of certain schizophrenic patients. Delva & Letemendia (1982), after reviewing major controlled and uncontrolled studies in this area, concluded that "between one-third and one-half of patients with schizophrenia will benefit from lithium".

In two of the controlled studies, lithium alone was shown to be better than placebo (Alexander et al., 1979), or to compare favourably with chlorpromazine (Braden et al., 1982). In four other controlled studies (Small et al., 1975; Growe et al., 1979; Carman et al., 1981; Delva et al., 1981), the combination of lithium with neuroleptics showed an additional therapeutic benefit compared with neuroleptics plus placebo. Biederman et al. (1979), who included schizoaffective patients in their controlled study, found that the subgroup of 'schizophrenic schizoaffective' (36% of their patients) showed considerably less total improvement than the subgroup of affective schizoaffective patients. However, the beneficial effect of lithium carbonate added to haloperidol was at least as apparent in this group as in the depressive subgroup. Regarding symptom specificity, Growe et al. (1979) and Carman et al. (1981) found that lithium affected mainly excitement and arousal (affective components). Other studies (Small et al., 1975; Biederman et al., 1979; Delva et al., 1981; Braden et al., 1982; Zemlan et al., 1984) found lithium also had a beneficial effect on symptoms of thought disorder in schizophrenic patients.

Reanalysing the Brief Psychiatric Rating Scale (BPRS) data of Biederman et al's (1979) study by using non-parametric statistical techniques for multi-dimensional evaluation of ratings, Shalif et al. (1981) showed that the beneficial effect of the lithium supplementation was most apparent in those schizophrenic patients who were on the depressive side of the median (as rated by the anxiety–depressive items of the BPRS). That group responded poorly to neuroleptics alone. In order to demonstrate that respondents to lithium supplementation did not in fact represent the affective pole of the schizoaffective patients (as detected by the BPRS items), we decided to replicate the design of our former study (Biederman et al., 1979), but to include this time only true schizophrenic, or clearly schizophrenic schizoaffective patients.

Method

All psychotic patients admitted to Eitanim Psychiatric Hospital, Jerusalem, who met the RDC criteria for schizophrenic and schizoaffective disorder – mainly schizophrenic (Spitzer et al., 1978) were referred to the study. Patients outside the age range 18–55, or suffering from any cardiovascular systemic or organomental disease, were excluded. All patients had given informed consent. Patients who received, during the 2 weeks prior to admission, neuroleptics for more than 2 days, or a depot injection of neuroleptics, were excluded. The study was of a double-blind design. Haloperidol treatment was begun on the day of admission and continued until the end of the study, with dosages prescribed by the ward psychiatrist as required by the clinical status of the patients. Anti-Parkinson treatment (trihexyphenidyl) was given routinely. After 2 weeks, each patient began receiving an additional four capsules of lithium carbonate (300 mg per day), or identical capsules of placebo. Patients were assigned to treatment by lithium or placebo in a random order. The study continued for 8 weeks. Serum lithium levels were monitored by the control psychiatrist (YL). Placebo patients' blood samples were assigned dummy results.

Response to the study treatment was assessed by using the BPRS. All patients were assessed independently by the two ward psychiatrists (YL and MS) who were unaware of the lithium–placebo schedule. Scores were assigned by consensus between the two raters. Every patient was rated on admission to the study project, and then on weeks 2, 4, 6, and 8.
Of the 41 patients who entered the study, five were excluded due to lack of co-operation in taking drug treatment. Of these, three patients were dropped after 3 weeks, and two after 4 weeks. They included two in the lithium group and three in the placebo group. The characteristics of the five patients in the drop-out group did not differ from those in the study group (Table I). The remaining 36 patients were divided into two subgroups according to the median of their initial depressive-anxiety core on the BPRS. The relevant items to this score are: somatic concern, anxiety, guilt feelings, and depression (Guy et al, 1976). Eighteen patients scored less than 4 on the depression factor ('non-depressed schizophrenics'), and 18 scored 4 or more ('depressed schizophrenics'). This terminology will be used on the basis of their relative depression score, even if clinically their depression was mild. Of the 18 depressed patients, nine received the haloperidol and lithium treatment and nine received haloperidol and placebo. The same was true of the 18 non-depressed patients (Table I). The BMDP Statistical Software Package (Dixon, 1985) was used for statistical analyses (computer program 2 V, analysis of variance and co-variance with repeated measures, 3 D and 9 D for comparison and multiway description of groups).

The two grouping factors were 'treatment' (lithium or placebo) and 'state of patients' (depressed vs non-depressed). The dependent variable, BPRS, was measured repeatedly five different times on weeks 0, 2, 4, 6, and 8. No interaction between the repeated measure variable, time, and treatment (lithium—no lithium) was found. Also, no interaction between the repeated measures and the state of the patient (depressive—non-depressive) was found. When the two grouping factors were combined in the analysis (creating four different groups), the interaction between the repeated BPRS scores, the 'treatment', and the 'state', was a
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Figure 1 shows the mean BPRS scores during the 8 weeks of the study for the four groups: the lithium plus haloperidol depressed group; the lithium plus haloperidol non-depressed group; the placebo plus haloperidol depressed group; and the placebo plus haloperidol non-depressed group. The Scheffe (1959) multiple-comparison test statistic was used to compare the average repeated measures over the 8-week study period between the four groups. The BPRS value for the placebo-depressed group was found to be significantly higher than the other averages \( k=4, (k-1) F=10.9, d.f. = 3, 33, P<0.05 \).

To examine the possibility that the beneficial effect of lithium is not only on the affective aspect of the BPRS, preventing perhaps further increase of the depressive symptoms, as hinted at by Biederman et al (1979), we analysed separately the thought-disturbance items of the BPRS: conceptual disorganisation; grandiosity; hallucinatory behaviour; unusual thought content (Guy et al., 1976). Analysis of variance with repeated measures was used for these items but only two time points were tested — baseline and week eight. Interaction between ‘treatment’ (lithium vs. placebo) and ‘state of patient’ (depressed vs. non-depressed) turned out to be significant \( F=4.41; d.f. = 1, 32; P<0.05 \). This means that when combined treatment (lithium plus haloperidol) was given to depressed schizophrenic patients, their scores on thought disorder decreased more than those of non-depressed schizophrenic patients receiving haloperidol plus placebo.

Since haloperidol was not prescribed in this study on a fixed-dosage schedule, but on the basis of the clinical decision of the ward psychiatrist, a separate analysis was done to study possible differences in the dosages given to the four groups of patients. It was found that from week 6, the average prescribed dosage of haloperidol was gradually reduced in the two lithium groups. As shown in Table II, the average haloperidol dosage for the lithium-depressed group showed the sharpest reduction (26.1 mg/day for week 8) as compared with all other groups, especially as compared with the placebo-depressed group. In the latter group, no decrease of average daily dosage of haloperidol was found (43.3 mg/day in week 8, and an average of 47.6 mg/day for all 8 weeks).

### Discussion

Although it was conducted with schizophrenic and not schizoaffective patients, this study confirms the findings of our earlier one (Biederman et al., 1979; Shalif et al., 1981) that the addition of lithium to haloperidol has a beneficial effect mainly for those schizophrenic subjects who have some depressive symptoms from the beginning of their psychotic state. This is in contrast to Carman et al’s (1981) findings, that the effect of lithium is mainly on the arousal component of the schizophrenic symptoms; yet half of Carman et al’s patients were schizoaffective and most of their respondents came from that subgroup. Our patients were mainly schizophrenic (according to the RDC criteria). When we applied the DSM–III (American Psychiatric Association, 1980) criteria for schizophrenia, 28 of the patients still met the criteria for schizophrenia (15 from the non-depressive group, 13 from the depressive group). The depressive items of the BPRS, although of possible predictive value regarding drug treatment, were not severe enough in our patients to give a clinical diagnosis of schizoaffective disorder. The Hamilton Rating Scale for Depression (Hamilton, 1967) was not used, because of the claim that it was based on a clinical population of major depressed patients and is not suitable for measuring depressive symptoms in schizophrenic patients.

The fact that depressive symptoms are part of true schizophrenia is well documented (Planansky &

### Table II

<table>
<thead>
<tr>
<th>Week</th>
<th>Depression–anxiety score ≥ 4</th>
<th>Depression–anxiety score &lt; 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Haloperidol + lithium</td>
<td>Haloperidol + placebo</td>
</tr>
<tr>
<td>1</td>
<td>42.2 (± 12.8)</td>
<td>41.7 (± 14.3)</td>
</tr>
<tr>
<td>2</td>
<td>42.8 (± 20.4)</td>
<td>47.8 (± 18.1)</td>
</tr>
<tr>
<td>3</td>
<td>39.2 (± 21.7)</td>
<td>50.0 (± 20.7)</td>
</tr>
<tr>
<td>4</td>
<td>37.5 (± 20.7)</td>
<td>51.7 (± 23.6)</td>
</tr>
<tr>
<td>5</td>
<td>35.6 (± 20.0)</td>
<td>50.2 (± 23.3)</td>
</tr>
<tr>
<td>6</td>
<td>31.7 (± 20.2)</td>
<td>50.4 (± 23.1)</td>
</tr>
<tr>
<td>7</td>
<td>27.2 (± 18.0)</td>
<td>45.6 (± 27.2)</td>
</tr>
<tr>
<td>8</td>
<td>26.1 (± 17.9)</td>
<td>43.3 (± 28.6)</td>
</tr>
<tr>
<td>Mean over 8 weeks</td>
<td>35.3</td>
<td>47.6</td>
</tr>
</tbody>
</table>

Number of patients | 9 | 9 | 9 | 9

\( F=3.3, d.f. = 4, 128, P<0.02 \). Thus BPRS scores decreased significantly more in depressed schizophrenic patients receiving lithium than in non-depressed schizophrenic patients receiving placebo.

The fact that depressive symptoms are part of true schizophrenia is well documented (Planansky &
According to our findings, those patients on the depressive side of the median were more resistant to haloperidol treatment alone (Fig. 1), even with higher dosages (Table II). As mentioned, the dosages of haloperidol were prescribed by the ward psychiatrist who was blind to the design and hypotheses of the study. The finding that the depressed patients who received placebo required clinically higher dosages of haloperidol compared with the depressed patients who received lithium is a validation of the higher BPRS scores attributed to the placebo-depressed group compared with the lithium-depressed group.

It can be concluded that the depressive schizophrenic group, otherwise resistant to haloperidol, benefited most from the addition of lithium, while the non-depressive schizophrenic patients improved their BPRS measurements whether or not lithium was added to haloperidol (Fig. 1). The beneficial effect remained significant even when thought-disorder measures were analysed separately. The possibility arises that there exists a subgroup of schizophrenic patients who, while being diagnosed clinically as truly schizophrenic by all criteria, have some special clinical features (concomitant depressive items as detected by the BPRS) that make them more resistant to neuroleptics alone, and responsive to the addition of lithium.

References


*Yaacov Lerner, MD, Senior Clinical Lecturer, Hadassah Medical School, Hebrew University, and Director, Eitanim Psychiatric Hospital; Yaacov Mintzer, MD, Staff Psychiatrist, Eitanim Psychiatric Hospital; Miguel Schestatzky, MD, Staff Psychiatrist, Eitanim Psychiatric Hospital, Doar Na'Shimshon, Israel

*Correspondence: Eitanim Government Psychiatric Hospital, Affiliated to the Hebrew University and Hadassah Medical School, Doar-na Shimshon, Israel
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Y Lerner, Y Mintzer and M Schestatzky
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