Drug Therapy in the Prevention of Recurrences in Unipolar and Bipolar Affective Disorders

Report of the NIMH Collaborative Study Group Comparing Lithium Carbonate, Imipramine, and a Lithium Carbonate–Imipramine Combination

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• **In a double-blind, long-term follow-up study, 117 bipolar patients received lithium carbonate, imipramine hydrochloride, or both and 150 unipolar patients received lithium carbonate, imipramine, both lithium carbonate and imipramine, or placebo. With bipolar patients, lithium carbonate and the combination treatment were superior to imipramine in preventing manic recurrences and were as effective as imipramine in preventing manic recurrences and were as effective as imipramine in preventing depressive episodes. The combination treatment provided no advantage over lithium carbonate alone. With unipolar patients, imipramine and the combination treatment were more effective than lithium carbonate and placebo in preventing depressive recurrences. The combination treatment provided no advantage over imipramine alone. The lithium carbonate–treated group had fewer manic episodes than the other groups. Treatment outcome, which was evaluated primarily in terms of the occurrence of major depression or manic episodes, was significantly related to characteristics of the index episode, ie, the episode that brought the patient into the study.**

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During the past two decades, it has become increasingly clear that major affective illness should be viewed longitudinally rather than solely in terms of the acute episode. There is convincing evidence from studies on the course of affective disorders that the majority of patients who have an initial episode of major depression or mania will suffer recurrences.[1,2] However, maintenance pharmacotherapy aimed at preventing the occurrence of new episodes continues to be studied far less adequately than treatment directed at the acute episode. As a result, there are major gaps in knowledge regarding the long-term treatment and management of affective disorders.

The only conclusive finding regarding long-term preventive drug treatment is that lithium carbonate is effective in preventing manic recurrences in patients with bipolar disorder.[3,4] The effectiveness of lithium carbonate and antidepressant drugs in preventing depressive recurrences in bipolar and unipolar disorders is less clear.

A review of the six studies comparing lithium carbonate against placebo in bipolar disorder[3] showed that lithium carbonate–treated patients had fewer depressive recurrences than placebo-treated patients in each of the trials but that in only one study was the difference between treatments statistically significant at the 5% level. One problem in interpreting the results for depressive recurrences is that most of the failures in placebo-treated patients occurred in those who had had a manic episode leaving a relatively small data base from which to establish statistical significance for depressive recurrences. The only controlled evaluation of an antidepressant in bipolar disorder[5] indicated that imipramine hydrochloride was equally as effective as lithium carbonate in preventing depressive

episodes but was significantly less effective in preventing manic recurrences.

Studies comparing lithium carbonate against placebo in the maintenance treatment of unipolar illness suggest an advantage for lithium carbonate.[5-11] However, the small total number of placebo-treated patients evaluated in these trials (92 in seven studies) and diagnostically heterogeneous populations pose difficulties for interpreting findings and are the primary reasons why lithium carbonate has not been approved by the Food and Drug Administration for the long-term maintenance treatment of unipolar disorder.[12] Five studies comparing lithium carbonate against antidepressants found lithium carbonate to be equally as effective as imipramine[5] and amitriptyline hydrochloride[10] and more effective than imipramine,[11] maprotiline hydrochloride,[13] and mianserin hydrochloride.[14] Two of these studies[13,14] did not use a placebo control and two others[10,11] used placebo groups consisting of only six and seven patients.

The fact that neither lithium carbonate nor antidepressants such as imipramine and amitriptyline are completely satisfactory maintenance treatments for bipolar and unipolar disorders has led to a search for alternative treatments. One alternative is the combination of lithium carbonate and an antidepressant. The rationale for the combination is that lithium carbonate will prevent manic recurrences and that the antidepressant will prevent depressive recurrences. Although a recent comparison between lithium carbonate and the combination of lithium carbonate and imipramine in patients with bipolar disorder showed no significant difference between the two treatments,[15] the combination remains a popular treatment.

To provide more definitive data regarding the long-term preventive treatment of recurrent affective illness, the Pharmacologic and Somatic Treatments Research Branch of the National Institute of Mental Health sponsored a five-hospital collaborative project evaluating several long-term maintenance drug treatments. The primary aim of the study was to determine the comparative efficacies of lithium carbonate, imipramine, and the combination of lithium carbonate and imipramine in recurrent bipolar and unipolar disorder. This article is the initial report of the study findings.

SUBJECTS AND METHODS

Patients entered the study during an episode of major unipolar depression, major bipolar depression, or mania (hereafter referred to as the index episode). To be eligible, a patient had to satisfy the following criteria: (1) a current episode satisfying Research Diagnostic Criteria (RDC)[16] for primary major depressive disorder or manic disorder; (2) a total depression or mania score of 7 or more on the Raskin Severity of Depression and Mania Scale (RSDM)[17] and a score of 60 or less on the Global Assessment Scale (GAS)[18]; (3) at least one episode of major depressive or manic disorder during the 2½ years preceding the current episode; (4) no psychiatric illness other than primary depression or mania during the preceding two years; (5) between 21 and 60 years of age; (6) no medical illness precluding use of lithium carbonate or imipramine; and (7) willingness and ability to give informed consent. Both inpatients and outpatients were eligible for the study. Diagnostic and severity of illness criteria required the agreement of two independent raters.

To qualify as having a bipolar disorder, the patient must have had at least one manic episode. To qualify as having a unipolar disorder, the patient must have had no manic episode.

The study had two phases: a preliminary phase and a maintenance phase. The purpose of the preliminary phase was to control the index episode, stabilize the patient's clinical condition, and establish stable maintenance dose levels of lithium carbonate and imipramine in preparation for the maintenance phase. The maintenance phase was the major experimental phase of the study and involved a two-year double-blind comparison of the study treatments.

Preliminary Phase

During the index episode the patient received the treatment of choice of the psychiatrist responsible for preliminary phase care. After the acute symptoms were controlled, the patient received the combination of lithium carbonate and imipramine at maintenance dose levels. Imipramine hydrochloride was maintained at 150 mg/day. Patients who were unable to tolerate 150 mg/day because of adverse reactions or medical complications could have their dosage reduced to a minimum of 75 mg/day. The serum level of lithium was targeted at 0.6 to 0.9 mEq/L. The patient was assigned to double-blind medication (ie, entered the maintenance phase) after two conditions were satisfied: (1) the patient had remained on stable maintenance doses (at least 75 mg/day of imipramine hydrochloride and a serum lithium level of 0.6 mEq/L) for two consecutive months, and (2) the patient had a score of more than 60 on the GAS and an RSDM total depression score and a total mania score of less than 7.

Maintenance Phase

Bipolar and unipolar patients were randomized separately to maintenance treatment regimens. Bipolar patients were randomly assigned to receive one of three treatments: lithium carbonate, imipramine, or the combination of lithium carbonate and imipramine. Unipolar patients were randomly assigned to receive one of four treatments: lithium carbonate, imipramine, the combination of lithium carbonate and imipramine, or placebo. Dosage was maintained at the level established during the preliminary phase. In assigning maintenance medication, a "double-substitution" technique was used to ensure patient and rater blindness. Patients assigned to the combination treatment group continued to receive the maintenance regimen established during the preliminary phase. Patients assigned to the lithium carbonate treatment group continued on their lithium carbonate regimen and had an imipramine placebo substituted for active imipramine. Those assigned to the imipramine treatment group continued to receive imipramine with a lithium placebo substituted for active lithium carbonate. Patients assigned to receive placebo had an imipramine placebo and lithium placebo substituted for active medications.

Treatments were administered for two years. Patients were seen at four- to six-week intervals, with more frequent visits if there was increased affective disturbance or adverse reactions to medication. Blood for determining serum lithium levels was drawn at each visit. Patients were evaluated at each visit by a psychiatrist who was "blind" to the identity of the patient's treatment. Necessary dosage adjustments were made by a nonblind psychiatrist who was not involved in the psychiatric evaluation of the patient.

Outcome Measures for Maintenance Phase

Treatment outcome was evaluated primarily in terms of the occurrence of affective episodes. Patients who became symptomatic were seen within 48 hours. If the patient's condition worsened, the patient was seen in five to seven days. A recurrence was declared if the clinical condition satisfied the RDC for definite major depressive disorder or mania and yielded a GAS rating of 60 or less. The recurrence was treated ad lib by a psychiatrist not involved in the maintenance treatment or evaluation of the patient. After recovering from the recurrence, patients were reassigned to their original double-blind medication. Only the first recurrence was used in the statistical analysis.

Patients were evaluated on a variety of scales. This report deals primarily with results from two global scales, the GAS and RSMD. The GAS is an interview scale for evaluating symptoms and functional impairment. Scores range from 0 (the most severely incapacitated state) to 100 (no symptoms or impairment). The RSMD provides a total depression score ranging from 3 to 15 and a total mania score ranging from 3 to 15. The GAS and RSDM were completed by a psychiatrist at each visit. Patients were also evaluated at each visit on the Hamilton Psychiatric Rating Scale for Depression, the Manic Behavior Rating Scale, the Brief Psychiatric Rating Scale, the Social Adjustment Self-Report Questionnaire, and the Life Events Scale.

Centers

The five centers participating in the study were as follows: (1) the Capital District Psychiatric Center, Albany (NY) Medical College; (2) Larue D. Carter Memorial Hospital, Indiana University, Indianapolis; (3) Maine Medical Center, Portland; (4) Western Psychiatric Institute and Clinic, University of Pittsburgh; and (5) St Paul–Ramsey Medical Center, St Paul, Minn. The aforementioned units will be referred to as centers A, B, C, D, and E, respectively, in the report of results.

RESULTS

Bipolar Patients

Background Characteristics.—There were 216 bipolar patients admitted to the preliminary phase. Background characteristics are summarized in Table 1. Forty-two percent of the patients entered the study as inpatients and 47% entered with a manic episode or mixed (manic and depressive) episode. The vast majority of the depressive episodes (95%) were classified as endogenous depression on the basis of the RDC. The sample was at extremely high risk for early recurrences because of the large number of prior episodes (median of seven). Studies of the course of major affective illness indicate that after one suffers four or five episodes, the average interval between episodes shrinks to approximately six months.[19]

Preliminary Phase.—*Early Terminations.*—Forty-six percent of the sample failed to complete the preliminary phase. Twenty percent were dropped because of noncompliance in keeping appointments or in adhering to the medication schedule. Half of the noncompliant patients terminated while they were still symptomatic. The other half were dropped during the stabilization period following control of acute symptoms, usually because they no longer wished to participate in the study. Fifteen percent of the patients were dropped because of poor clinical response. the dropouts showing a poor clinical response had been with a variety of drugs during an extended period ar terminated from the study because the treating psyc decided that the prospect of stabilizing the episode v reasonable period was remote. Four percent of the patier unable to tolerate lithium carbonate or imipramine an percent were dropped because of intercurrent illness, pre or moving from the catchment area.

Early terminators spent a median of 20 weeks in the prel phase, indicating that substantial efforts were made t patients in the study.

Rapid Cyclers.—Results for rapid cyclers were examine rately by design because of the poor prognosis for the disc *rapid cycler* was defined as a patient who had an average of four episodes a year during the preceding two years. The nine such patients. Only three reached the maintenance ph none had treatment successes.

Comparison of Completers v Noncompleters.—It is im to determine what factors differentiated patients wh dropped during the preliminary phase from those who co the preliminary phase (ie, entered the maintenance phase) wise, the capacity to generalize from maintenance phase would be restricted. Preliminary phase outcome was ana terms of nine predesignated variables: study center; sex; a at onset of the first affective episode; number of prior e level of functioning between prior episodes; severity and n the index episode; inpatient *v* outpatient admission; an used to treat the index episode. Four factors significantl entiated patients who completed the preliminary phase fr who did not ($P<.1$ by χ^2 analysis or t test for correlated mea was a critical factor. Those completing the preliminary pha an average of 5.2 years older than those not comple preliminary phase at admission to the study and 2.2 years the onset of the first episode. However, the major factor entiating those who complete the preliminary phase fro who did not were study center and inpatient *v* outpatient sions (Table 2). Much of the difference between inpatie outpatients and among study centers resulted from th outcome at the inpatient units of centers A and B. Ce inpatients were predominantly Veterans Administration h admissions with a history of frequent hospitalizations for a disorders. Center B is a statewide referral source fo patients who fail to respond at other levels of the treatme system. If the inpatient results from centers A and B are o there is no major difference in outcome between inpatie outpatients or among study centers.

Initial Treatment of Index Episode.—Eighty-three pe the patients wih a manic or mixed episode received carbonate alone or in combination with another drug. Nin percent of the patients with a depressive episode re tricyclic antidepressant, usually imipramine alone or in co tion with lithium carbonate.

Maintenance Phase.—*Dosage.*—The mean daily do imipramine hydrochloride at the start of the maintenanc was 132 mg/day (range, 75 to 150 mg/day). The mean serum lithium was 0.75 mEq/L (range, 0.45 to 1.10 mEq/L). There significant difference in dosage between patients recei drugs in combination and those receiving the drugs indi ic

Overall Outcome.—Table 3 summarizes the overall ou co

Table 1.—Demographic and Clinical Characteristics

Characteristic	Bipolar (N=216)	Unipolar (N=343)
Age, yr		
Mean ± SD	38.1 ± 12.4	38.8 ± 12.4
Sex, %		
M	42.0	33.0
F	58.0	67.0
Age at onset of 1st episode, yr		
Mean ± SD	24.9 ± 10.9	27.7 ± 11.2
Prior episodes, median No.	7.0	4.0
Index episode*		
GAS (mean)	45.0	46.1
RSMD (mean)	9.9	10.1
Inpatients, %	42.0	24.0
Manic or mixed, %	47.0	. . .

*GAS indicates Global Assessment Scale; RSMD, Raskin Severity of Depression and Mania Scale.

Table 2.—Bipolar Inpatients and Outpatients Entering Maintenance Phase*

Patients	Center A	Center B	Center C	Center D	Center E
Inpatients					
No. admitted to preliminary phase	9	51	10	8	9
% admitted to maintenance phase	33	29	80	63	67
Outpatients					
No. admitted to preliminary phase	22	3	21	28	45
% admitted to maintenance phase	55	67	76	61	64

*See "Subjects and Methods" section for names and locations of centers.

the 117 bipolar patients who entered the maintenance phase. Three outcome categories are defined: treatment failures, treatment successes, and other. *Failures* included (1) patients who were unable to complete eight consecutive weeks in the study without suffering a recurrence, (2) patients who completed eight weeks but subsequently had a recurrence, and (3) patients who had no recurrence but were terminated for adverse reactions or worsening clinical condition. *Successes* were patients who remained well and completed at least one year in the study. The "*other*" category included patients who remained well but failed to complete the first year, usually because they no longer saw the need for taking medication, experienced an intercurrent illness, or left the study area. In all, 62% of the patients were failures, 25% were successes, and 13% remained well but failed to complete one year of treatment.

One subgroup of failures warrants comment. Fifteen percent of the admissions to the maintenance phase were unable to complete eight consecutive weeks without a recurrence. Many of these patients had two or more recurrences while on their maintenance treatment regimen before being dropped or leaving the study. It can be argued that recurrences occurring during the first eight weeks of maintenance treatment represent a continuation of the index episode rather than a new episode and are not a true measure of the capacity of study treatments to prevent new attacks.[20] Conversely, many of the study patients were at high risk for an early recurrence and had already been in a stable clinical state for a number of months preceding admission to the maintenance phase. It is not inconceivable that some of these patients would experience a new episode during the first few months of the maintenance phase. This issue may be of more theoretical than practical importance for the study. Comparisons among treatments were not significantly affected when this subgroup was omitted from the analysis.

Outcome for Individual Treatments.—Outcomes for the three treatment groups are summarized in Table 4. Lithium carbonate and the combination treatment produced a significantly higher percentage of treatment successes (33%) than did imipramine (8%) ($P<.05$ by χ^2 analysis). The difference among treatments was attributable to the high incidence of manic recurrences in the imipramine-treated group. Fifty-three percent of the imipramine-treated patients had a manic or mixed recurrence, compared with 26% of the patients treated with lithium carbonate and 28% receiving the combination treatment. There was no significant difference ($P>.05$) among treatments in the occurrence of depressive episodes. Table 4 does not include three rapid cyclers, two of whom had a recurrence while receiving lithium carbonate and one of whom failed to complete one year of the combination treatment because of noncompliance.

Actuarial and Kaplan-Meier life-table methods were used to analyze the course of illness for the three treatment groups.[21,22] These methods are ideal for long-term clinical trials because they take into account the varying lengths of time that patients are in the study as well as the outcome of treatment. In the actuarial method, the maintenance period was partitioned into a series of three-month intervals. The Kaplan-Meier life table is continuous, with no grouping of measures. There were no major differences between results from the two methods. The actuarial curves are presented in Fig 1. The statistical significance of the overall difference in the course of illness among treatments was tested by the Generalized Savage Test that yields an aggregate χ^2 statistic.[23] The difference among treatments is statistically significant at the .05 level. Individual treatment curves were compared with the Generalized Savage Test. Since type 1 error (the probability of detecting a difference between groups when no true difference exists) increases with the number of comparisons conducted between individual groups, one requires a more stringent P value for determining statistical significance between individual groups than the .05 level used for the overall comparison. Bonferroni's equation[24] is one means for compensating for the inflation in type 1 error that results from multiple comparisons. The equation indicates that for individual comparisons between three groups, an α-level of 0.016 is required to achieve a true type 1 error of .05. Using this criterion, the differences between lithium carbonate and imipramine and between the combination treatment and imipramine were statistically significant. The difference between lithium carbonate and the combination treatment was not significant.

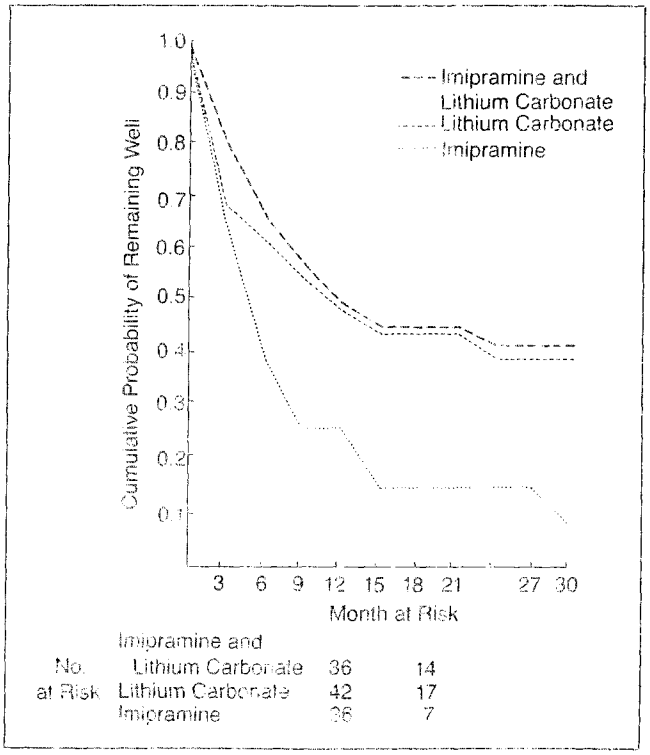
Relationship of the Index Episode to Outcome.—Maintenance phase outcome was analyzed in terms of the nature and severity of the index episode. For the purpose of analysis, the nature of the episode was classified as "manic or mixed" or "depressed." Severity was classified as "moderate" or "severe." Severity was defined on the basis of GAS and RSDM scores. *Moderate severity* was defined as a GAS score of 51 to 60 (the range of "moderate impairment" on the GAS) and an RSDM total depression or mania score of 7 to 11. A *severe episode* was defined by a GAS score of 50 or less or an RSDM total depression or mania score of 12 or more.

Maintenance phase outcome was significantly related to the

Table 3.—Maintenance Phase Outcomes for Bipolar and Unipolar Patients

Outcome	% Bipolar (N=117)	% Unipolar (N=150)
Failure		
Unable to complete 8 consecutive weeks without a recurrence	15	17
Completed 8 consecutive recurrence-free weeks, subsequently had recurrence	45	30
Completed 8 consecutive recurrence-free weeks, subsequently terminated for adverse reaction or worsening clinical condition	2	4
Remaining well		
Terminated while in good clinical state during year 1	13	13
Terminated while in good clinical state during year 2	3	3
Remained well for study duration	22	33

Fig 1.—Life-table probability of remaining well for each treatment for bipolar patients.



index episode had been manic or mixed responded much better to lithium carbonate and the combination treatment than to imipramine. By contrast, there was no significant difference among the three treatments for patients who had a depressive index episode. The treatment success rates for patients who had suffered a manic or mixed index episode were 53% for lithium carbonate, 47% for the combination treatment, and 8% for imipramine ($P<.05$ by χ^2 analysis). The success rates for patients who had had a depressive index episode were 22% for lithium carbonate, 18% for the combination treatment, and 9% for imipramine ($P>.05$).

Outcome at Individual Centers.—The percentage of successes for the lithium carbonate–treated group was greater than that for the imipramine-treated group at each of the five centers. The combination treatment produced a pattern of success at the five centers similar to that for lithium carbonate.

Table 4.—Maintenance Phase Outcome for Bipolar Patients by Treatment Group

Outcome	Imipramine Hydrochloride (N=36), %	Imipramine and Lithium Carbonate (N=36), %	Lithium Carbonate (N=42), %
Failure			
Depression	28	22	29
Manic-mixed	53	28	26*
Adverse reaction	0	3	0
Remaining well			
Terminated well during year 1	11	14	12
Remained well for study duration or terminated well during year 2	8	33	33*

*Differences among treatment groups statistically significant ($P<.05$, χ^2 analysis).

Adverse Reactions.—Side effects were reported by 94% of th patients receiving the combination treatment, 81% of the patient treated with lithium carbonate, and 61% of the patients treate with imipramine. Reactions judged to be of more than mild severit for at least two visits were reported by 19% of the patients in th combination treatment group, 16% in the lithium carbonate trea ment group, and 14% in the imipramine treatment group. In th combination treatment group, the most common reactions, in orde of prevalence, were dry mouth, fine tremor, constipation, an excessive sweating. In the lithium carbonate–treated group, poly uria and/or polydipsia, fine tremor, dry mouth, and constipatio were the most prevalent reactions. The most common reactions i the imipramine-treated group were dry mouth, fine tremor, an excessive sweating. Only one patient was dropped from th maintenance phase because of side effects. A patient receiving th combination treatment (150 mg/day of imipramine hydrochlorid and a serum lithium level of 0.69 mEq/L) was taken off th medication regimen because of a progressive increase in the serur creatinine level and the presence of protein in the urine.

Unipolar Patients

Background Characteristics.—There were 343 unipolar ad missions to the preliminary phase. Background characteristics ar summarized in Table 1. The severity of the index episode fo unipolar patients was similar to that for bipolar patients. The inde episode was classified from the RDC as endogenous depression fo 89% of the patients. Twenty-five percent of the patients entere the study as inpatients, primarily at center B, which contribute three fourths of the inpatient sample. The sample had a median o four prior episodes, making it a group at high risk for an early recurrence.

Preliminary Phase.—*Early Terminations.*—Fifty-four per cent of the sample failed to complete the preliminary phase. Thirty-two percent were dropped because of noncompliance or because they no longer wanted to participate in the project. Approximately two thirds of these noncompliant patients were symptomatic when they left the study. Twelve percent of the sample were dropped because of a poor clinical response and 9% were unable to tolerate lithium carbonate, imipramine, or the combination of the two drugs. Four percent were dropped because of intercurrent illness, pregnancy, or moving from the area. Early terminators spent a

Table 5.—Percentage of Unipolar Patients Entering Maintenance Phase by Level of Functioning Between Episodes and by Study Center*

Level of Functioning	Center A	Center B	Center C	Center D	Center E	All
No impairment						
No. admitted to preliminary phase	20	21	9	46	25	121
% admitted to maintenance phase	60	52	78	57	68	60
Some impairment						
No. admitted to preliminary phase	46	63	13	54	37	213
% admitted to maintenance phase	28	22	46	44	46	35

*See "Subjects and Methods" section for names and locations of centers.

Table 6.—Maintenance Phase Outcome for Unipolar Patients by Treatment Group

Outcome	Imipramine Hydrochloride (N=39), %	Imipramine and Lithium Carbonate (N=38), %	Lithium Carbonate (N=37), %	Placebo (N=34), %
Failure				
Depression	33	26	57	65*
Manic-Mixed	8	5	0	6
Adverse reaction	3	3	0	0
Remaining well				
Terminated well during year 1	5	18	16	9
Remained well for study duration or terminated well during year 2	51	47	27	21*

*Differences among treatment groups statistically significant ($P<.05$, χ^2 analysis).

median of 18 weeks in the preliminary phase.

Rapid Cyclers.—Nine rapid cyclers were admitted to the preliminary phase. Only two completed the preliminary phase and both were dropped because of treatment failures during the first six months of the maintenance phase.

Comparison of Completers v *Noncompleters.*—Preliminary phase outcome was analyzed in terms of the same factors used for the bipolar sample. Four factors significantly differentiated patients who completed the preliminary phase from those who did not ($P<.10$ by χ^2 analysis or t test for correlated measures): age at admission to the study; age at onset of the first episode; study center; and level of functioning between episodes. As with the bipolar sample, those who completed the preliminary phase were older than those who did not at admission to the study (2.7 years) and at the onset of the first episode (2.2 years). Study center was also a critical factor. However, the factor that most sharply differentiated those who completed the preliminary phase from those who did not was the level of functioning between prior episodes. Three levels of functioning, derived from patient history forms, were used in the analysis: (1) *minimal or no impairment*, defined as a complete recovery between episodes with absent or minimal depressive symptoms and no discernible impairment in social adjustment or other areas of functioning; (2) *slight impairment*, defined as sustained or intermittent periods of slight depressive symptoms or difficulty in functioning; and (3) *mild or moderate impairment*, defined as mild or moderate depressive symptoms much of the time and/or substantial difficulty in several areas of functioning. The first category defines the classic patient with recurrent affective illness, ie, well-defined episodes with clear-cut onset and recovery and euthymia between episodes. These patients constituted only 36% of the sample. The other two categories define patients with varying degrees of symptoms or impairment of functioning between episodes. The group with slight impairment accounted for 46% of the sample and the group with mild or moderate impairment accounted for 18%.

Table 5 shows the percentage of patients completing the preliminary phase at each study center by level of functioning between episodes. The slightly impaired and mild to moderately impaired subgroups did not differ in preliminary phase outcome and are combined in the table. There are three important findings in the table. First, the group with no history of impairment between episodes had a much higher percentage of subjects completing the preliminary phase (60%) than did the group with a history of impairment (35%). Second, the difference between the not impaired and impaired groups was consistent across centers. In no center did even half of the patients with a history of impaired functioning complete the preliminary phase. Third, as was the case with the bipolar sample, centers A and B had the lowest percentages of subjects completing the preliminary phase. This characteristic is attributable, in large measure, to the extremely low percentage of subjects completing the study among patients with a history of impaired functioning at the two centers.

Initial Treatment of Index Episodes.—Ninety percent of the patients were treated with an antidepressant, usually imipramine, or the combination of an antidepressant and lithium carbonate. The remaining 10% were treated with lithium carbonate, neuroleptics, or electroconvulsive therapy.

Maintenance Phase.—*Dosage.*—The mean daily dosage of imipramine hydrochloride at the start of the maintenance phase was 137 mg/day (range, 75 to 150 mg/day). The mean serum level of lithium was 0.66 mEq/L (range, 0.43 to 1.05 mEq/L). There was no significant difference in dosage between patients receiving the drugs in combination and those receiving the drugs individually.

Overall Outcome.—Table 3 summarizes the overall outcome for the 150 patients admitted to the maintenance phase. In all, 51% of the patients were classified as failures, 36% were classified as successes, and 13% remained well but failed to complete one year of treatment.

Outcome for Individual Treatments.—The outcome for the individual groups is summarized in Table 6. There were significant differences among treatment groups for both successes and depressive recurrences ($P<.05$ by χ^2 analysis). Imipramine and the combination treatment were superior to lithium carbonate and placebo in both categories. Lithium carbonate's only advantage was with manic episodes. The seven study patients who experienced a manic episode included three in the imipramine treatment group, two in the combination treatment group, two in the group receiving placebo, and none in the group treated with lithium

Fig 2.—Life-table probability of remaining well for each treatment for unipolar patients.

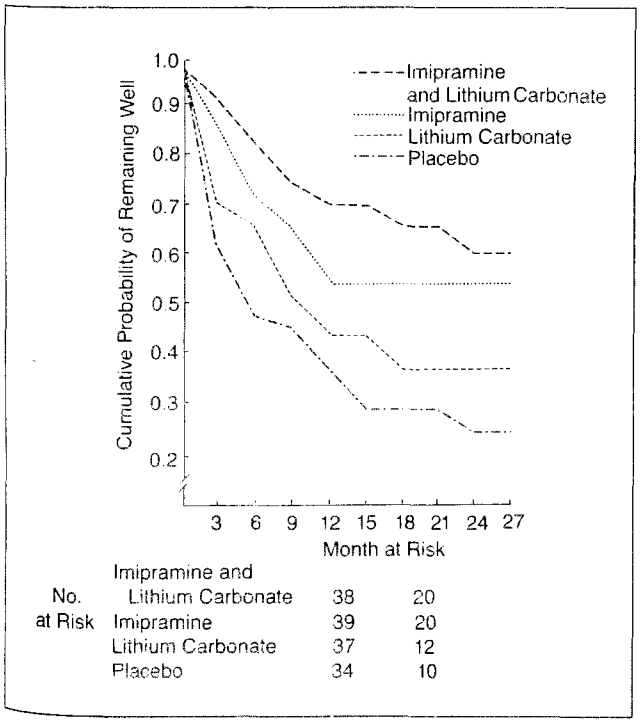
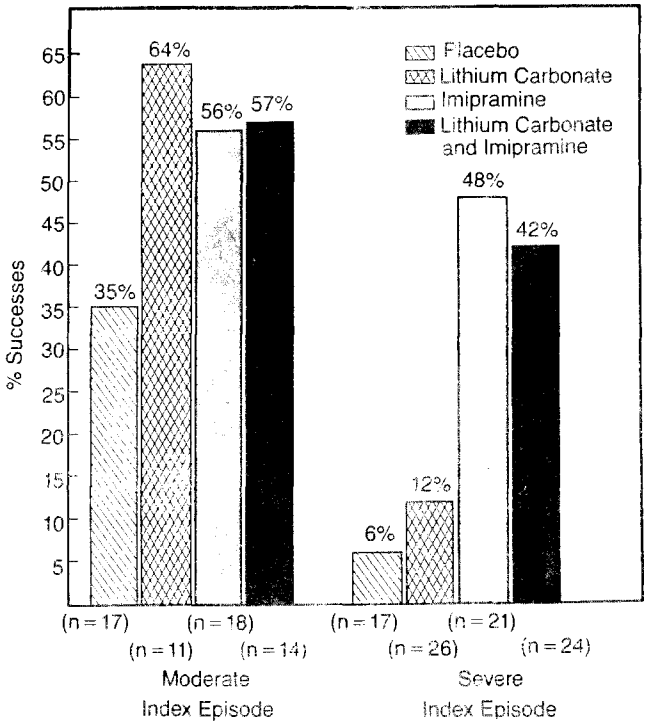


Fig 3.—Maintenance phase treatment successes for unipolar patients by severity of index episode.



carbonate. Table 5 does not include the two rapid cyclers, one of whom had a recurrence while receiving imipramine and the other while receiving the combination treatment.

Actuarial and Kaplan-Meier life-table methods were used to analyze the differences in course of illness among the four treatments. The actuarial curves are presented in Fig 2. The overall difference among treatments was statistically significant at the .05 level, as determined by the Generalized Savage Test. Bonferroni's equation was used to determine the appropriate α-level for comparing individual groups. To compare four groups, one requires a P value of .008 to achieve a true type I error of .05. With the use of this stringent criterion for statistical significance, the differences between imipramine and placebo and between the combination treatment and placebo were statistically significant. Comparisons between imipramine and lithium carbonate and between the combination treatment and lithium carbonate yielded P values greater than .008 but less than .05. Comparisons between imipramine and the combination treatment and between lithium carbonate and placebo were not significant. In sum, the analyses indicated that both imipramine and the combination treatment were significantly superior to placebo, whereas lithium carbonate was not. The imipramine and combination treatments were also superior to the lithium carbonate treatment, but the differences failed to reach statistical significance at the .008 level.

Relationship of the Index Episode to Outcome.—Maintenance phase outcome was analyzed in terms of the severity of the index episode and in terms of RDC-defined subtypes of depression characterizing the episode (ie, endogenous, agitated, retarded, situational, simple, and psychotic). Outcome was not significantly related to the subtype of the index episode. Severity, however, proved to be a critical factor. Figure 3 shows the percentage of successes for each treatment group by severity of the index episode. For patients who had a moderate index episode (ie, a GAS score of 51 to 60), the success rate for the three active medication groups was significantly greater than that for placebo ($P<.05$ by χ^2 analysis). There was no major difference in success rate among the three drug groups. For patients who had a severe index episode (ie, a GAS score of 50 or less), the success rates for imipramine and the combination treatment were significantly higher than those for lithium carbonate and placebo. There were no significant differences between imipramine and the combination treatment or between lithium carbonate and placebo. Of particular interest is the finding that the lithium carbonate–treated group had the highest success rate among the three drug treatment groups with patients who had a moderate index episode (64%) and the lowest success rate with patients who had a severe index episode (12%).

Outcome at Individual Centers.—The superiority of imipramine and the combination treatment over lithium carbonate was relatively consistent across centers. Only center C had greater success with lithium carbonate than with imipramine or the combination. However, this center had only a small unipolar sample (approximately four patients in each treatment group).

Adverse Reactions.—Side effects were reported by 84% of the patients receiving the combination treatment, 79% of the patients treated with lithium carbonate, 78% of the patients treated with imipramine, and 76% of the patients receiving placebo. Reactions judged to be of more than mild severity for at least two visits were reported by 36% of the patients in the combination group, 25% in the imipramine-treated group, 14% in the lithium carbonate–treated group, and 3% in the placebo-treated group. In the combination treatment group, the most common reactions, in order of prevalence, were dry mouth, fine tremor, constipation, and polyuria and/or polydipsia. In the lithium carbonate–treated group, dry mouth, fine tremor, headache, and lethargy were the most prevalent reactions. The most common reactions in the imipramine-treated group were dry mouth, excessive sweating, polyuria and/or polydipsia, and fine tremor. The most prevalent reactions in the placebo-treated group were dry mouth, constipation, and fine tremor. Two patients were dropped from the maintenance phase because of side effects or medical complications. A patient treated with imipramine hydrochloride (150 mg/day) had congestive heart failure. A patient receiving the combination treatment (150 mg/day of imipramine hydrochloride and a serum lithium level of 0.95 mEq/L) suffered loss of memory and fine hand tremor that interfered with social and vocational functioning.

COMMENT

Bipolar Study

The bipolar phase of the study produced three mai findings. First, lithium carbonate was significantly mor effective than imipramine in protecting against manic re currences and was equally as effective as imipramine i protecting against depressive recurrences. Second, th combination of lithium carbonate and imipramine provide no advantage over lithium carbonate alone. Third, lithiur carbonate was more effective with patients whose las episode (ie, the index episode) was manic than with patient whose last episode was depressive.

The first finding confirms results from the only othe study comparing lithium carbonate against imipramine in bipolar population. The Veterans Administration–Nationa Institute of Mental Health (NIMH) Collaborative Study o Lithium Therapy[5] reported that 54% of imipramine-treate patients experienced a manic episode compared with 11% o patients receiving lithium carbonate. The current stud found that 53% of the patients treated with imipramine suffered a manic episode, compared with 26% receiving lithium carbonate. In both studies, lithium carbonate and imipramine were equally effective against depressive recurrences. Because there was no placebo-treated group in this study, it is not possible to determine if the high incidence o manic recurrences for imipramine-treated patients re sulted from imipramine-induced mania or from failure o imipramine to prevent naturally occurring manic episodes. However, the fact that the VA-NIMH study showed no major difference between imipramine and placebo in the incidence of mania provides support for the latter interpretation. Regardless of how one interprets the finding, the use of imipramine for the long-term preventive treatment of bipolar disorder is not recommended.

The second finding, regarding the comparability of lithium carbonate and the combination treatment, confirms results from the only other study comparing lithium carbonate against the combination of lithium carbonate and a tricyclic antidepressant in patients with bipolar disorder. Kane and colleagues[15] reported no significant difference in preventive effectiveness between lithium carbonate and the combination of lithium carbonate and imipramine. There seems to be no advantage to using the combination instead of lithium carbonate for the long-term preventive treatment of bipolar disorder.

The third finding, regarding the greater efficacy of lithium carbonate with patients whose index episode was manic, confirms results from both the VA-NIMH study[5] and the trial by Kane and co-workers.[15] Lithium carbonate preventive therapy is especially indicated for this subgroup of patients.

Unipolar Study

The unipolar phase of the study also produced three main findings. First, overall imipramine was significantly more effective than lithium carbonate in protecting against depressive recurrences. Second, lithium carbonate's preventive efficacy was related to the severity of the index episode. Lithium carbonate was equally as effective as imipramine with patients whose index episode was of moderate severity (as defined by global scales of psychopathology and functional impairment) but significantly less effective than imipramine with patients whose index episode was severe. With the latter subgroup, lithium carbonate was no more effective than a placebo. Third, the combination of lithium carbonate and imipramine provided no advantage over imipramine alone.

The finding that imipramine was more effective overall than lithium carbonate in preventing depressive episodes is at variance with results from two other multihospital collaborative studies. The VA-NIMH study found lithium carbonate to be equally as effective as imipramine[5] and a British Medical Research Council (MRC) study reported no significant difference in effectiveness between lithium carbonate and amitriptyline.[10] Both studies used designs similar to that used in the current study.

One possible explanation for the difference in results between the current study and the MRC and VA-NIMH studies is that there may have been differences among the patient populations. Unfortunately, the report of the MRC study does not provide information on sample characteristics other than age and sex. Thus, it is not possible to compare studies in terms of the severity of illness and other pertinent characteristics of the study samples. Comparison of the VA-NIMH study to the current study is also difficult because the two studies used different measures of psychopathology and impairment. However, the VA-NIMH patient sample was considerably less ill in terms of the frequency of prior episodes. The mean number of prior episodes for the VA-NIMH sample was 1.5, compared with four for the current study (unpublished findings, R.F.P., January 1984). Another difference between the two studies is that the VA-NIMH study attracted a far greater proportion of patients with classic recurrent affective illness characterized by clear-cut onset and recovery of episodes and euthymia between attacks. The VA-NIMH study was initiated in 1967, when lithium carbonate was still an investigational drug and long-term preventive drug therapy was not a widely prescribed practice. The study centers were among the few places where lithium carbonate was available. In this current era, many of the patients referred to the VA-NIMH study probably would have been treated satisfactorily in the community and would not have been referred to or sought treatment at the medical centers that participated in the current study. Thus, there were somewhat different populations in the two studies, which might have contributed to the difference in results.

The only controlled study showing an advantage of lithium carbonate over a tricyclic antidepressant[11] admitted only patients who were able to remain euthymic for six months following recovery from a depressive index episode. Further, patients had to remain euthymic for an additional six weeks during a dosage-stabilization period with imipramine. The severity of the prior episode was not reported. However, the fact that patients had to remain euthymic for at least 7½ months indicates that patients with relatively short intervals between episodes and patients who were not euthymic between episodes were excluded from the study. The report for the study did not indicate what proportion of patients who recovered from the index episode were able to satisfy the stringent admission criteria. In the current study, these criteria would have excluded approximately half of the eligible sample.

The only other trials comparing lithium carbonate and antidepressants in patients with recurrent unipolar disorder were conducted by Coppen and co-workers who concluded that lithium carbonate was superior to the tetracyclic antidepressants maprotiline[13] and mianserin.[14] Patients admitted to the studies had been attending a lithium clinic for at least the preceding year and, presumably, had been episode free during this period. This population was different from that represented in the current study.

It is of interest to note that the three studies reporting the superiority of lithium carbonate over an antidepressant[11,13,14] used relatively stable samples that had been euthymic or episode free for periods of at least seven months to a year. The two studies reporting equal effectiveness of lithium carbonate and an antidepressant[5,10] initiated treatments within a relatively short period after recovery from an acute episode in patients with less stable histories. The current study also found lithium carbonate and an antidepressant to be equally effective, but only with patients whose index episode was of moderate severity. The antidepressant proved superior when severe episodes were involved.

The provocative finding that the response to preventive lithium carbonate therapy was related to the severity of the last (index) episode must be interpreted with caution. This is a preliminary finding and requires further exploration. For example, it is important to determine whether patients with a moderately severe index episode differed from patients with a severe index episode in ways other than the severity of depressive symptoms or degree of functional impairment. Factors such as the frequency and severity of prior episodes, nature of the depressive symptoms, and age should be examined. However, for the present, if one assumes that the finding is not a function of confounding by other variables and that the severity of the last episode is a good estimate of the severity of the next episode, the results strongly suggest that lithium carbonate is relatively ineffective in preventing severe unipolar depression.

There is a possible explanation for the relationship between lithium carbonate's preventive efficacy and severity of the index episode. Many clinicians suggest that maintenance lithium carbonate therapy may not prevent the appearance of episodes, but rather may act by dampening emerging recurrences sufficiently to prevent a full-blown attack. If attenuation rather than prevention is the main action of long-term lithium carbonate therapy, lithium carbonate could have the capacity to dampen milder depressive recurrences but be relatively ineffective against the more severe recurrences. This explanation will be explored in future analyses that will examine the severity of recurrences for each treatment group as well as the presence of symptoms that did not reach the severity of a recurrence.

The findings provide no evidence that the combination treatment has any advantage over imipramine for unipolar patients or lithium carbonate for bipolar patients. The relatively high percentage of unipolar patients in the combination group who experienced adverse reactions of more than mild severity (36%) is further reason for caution in use of the combination.

In sum, it would seem that an antidepressant such as imipramine is the preferable choice for long-term preventive treatment following recovery from an acute episode, if for no other reason than the fact that the VA-NIMH and MRC studies found the antidepressant to be equally as effective as lithium carbonate and the current study found the antidepressant to be more effective. The results from the current study and from the three studies showing superiority of lithium carbonate over antidepressants suggest that lithium carbonate may be a useful treatment for milder forms of recurrent unipolar depression characterized by less severe episodes or by less frequent episodes with good functioning between attacks. Lithium carbonate, because of its strong antimanic properties, may also be of value where there is suspicion of a latent bipolar disorder (eg, because of a well-documented familial history of bipolar illness).

General Comments

Findings from the bipolar and unipolar phases of the study suggest that long-term results with imipramine and lithium carbonate parallel the effects of the drugs with acute episodes. Lithium carbonate is an effective treatment for acute mania and is also effective in preventing or dampening manic recurrences. Lithium carbonate is regarded as a moderately effective treatment for acute bipolar depression and provides moderately effective protection against bipolar depressive recurrences. Lithium carbonate is not regarded as a particularly effective treatment for acute unipolar depression and, at least in this study, is not an effective preventive treatment with recurrent unipolar depression. The same parallels exist for imipramine. Imipramine is not an effective treatment for acute mania and is not effective in protecting against manic recurrences. Imipramine is a moderately effective treatment for acute bipolar depression and provides moderately effective protection against bipolar depressive recurrences. Imipramine is a standard treatment for acute unipolar depression and is also an effective preventive treatment for recurrent unipolar depression.

The relatively high percentage of dropouts during the preliminary phase highlights a problem in conducting therapeutic research at medical centers based at major universities. In many cases, patients who appear for treatment at these centers have filtered through a screening process via failure to respond to traditional treatments in the community. In addition, these patients often have a history of poor compliance in taking medication. The fact that the bipolar sample for the current study had a median of seven prior episodes and the unipolar sample had a median of four attests to the difficulties that had already been experienced in treating these patients. In addition, approximately two thirds of the sample entering the preliminary phase had a history of substantial functional impairment or persistent or intermittent symptoms between episodes, even after patients with an RDC diagnosis of chronic and intermittent depressive disorder had been excluded. The presence of varying degrees of impairment and symptoms between episodes only adds to the problems involved in treating the patients. This is not to suggest that long-term therapeutic studies should not be conducted at university-based medical centers, only that the aforementioned problems should be recognized in the design of studies and interpretation of results.

Finally, the current study and other studies of long-term preventive drug therapy indicate that even when lithium carbonate and antidepressants are judged to be effective, the drugs are not panaceas. The finding that only 25% of the bipolar sample and 36% of the unipolar sample in the current study were judged to be treatment successes confirms the need for further careful study of long-term preventive drug therapy, focusing not only on lithium carbonate and the tricyclic antidepressants but also on alternatives such as carbamazepine for bipolar disorder and other classes of antidepressants for unipolar disorder. The use of psychotherapeutic approaches in conjunction with drug therapies also warrants investigation.

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