COMPARISON OF COMBINED LITHIUM WITH CARBAMAZEPINE, BENZODIAZEPINES AND NEUROLEPTICS IN TREATMENT OF ACUTE MANIA IN AN INPATIENT STUDY

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Abstract — The effect of neuroleptics, carbamazepine and benzodiazepines in treatment of 83 patients with acute mania was studied. According to drug types, patients were divided into 5 groups:
1) Lithium combined with halopridol, 2) Lithium combined with one phenothiazine, 3) Lithium cobmined with two phenothiazines, 4) Lithium combined with carbamazepine, and 5) Lithium combined with benzodiazepines.
No significant differences in duration of treatment among the groups were found. According to the increased risk of extrapyramidal symptoms in treatment with neuroleptics, carbamazepine or benzodiazepines are prefered in treatment of acute mania as safer comedications.
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Key word: mania, lithium combinations.

INTRODUCTION

Medications for the treatment of patients with bipolar mood disorder (BMD) include those that decrease symptoms of mania or depression, those that prevent episodes, and those that may not act primarily on mood but that are helpful at various conditions during the course of the disorder. These medications have been categorized as following: mood stabilizers (medications with both antimanic and antidepressive actions); antimanic agents; antidepressants; adjunctive medications; and new or atypical medications that have not been fully assessed (1).

Lithium, carbamazepine and valproate, are three currently available mood stabilizers. Lithium is effective in the acute treatment of manic as well as the prevention of recurrent manic and depressive episodes (2). Carbamazepine has been studied alone and in combination with other mood stabilizers in the treatment of both phases of BMD (3-7). The data generally support the conclusion that carbamazepine effectively reduces the frequency and severity of episodes (8,9).

Clonazepam and lorazepam have also been studied alone and in combination with lithium in treatment of acute mania (10-15). These studies suggest that benzodiazepines are effective agents in treatment of mania in place of or in conjunction with a neuroleptic.

Neuroleptics are the most common drugs used combined with lithium in the treatment of acute mania. Neuroleptics may be used in treatment of mania before a mood stabilizer is started, to enhance compliance (16), or in conjunction with a mood stabilizer to reduce symptoms, while waiting for the effects of mood stabilizer to appear.

In this prospective study we tried to compare the patient response to the various type of medications combined with lithium, in treatment of acute manic phase of BMD in 83 bipolar Iranian patients admitted in Roozbeh Hospital.

MATERIALS AND METHODS

Eighty three inpatients who fulfilled DSM IV* criteria for bipolar illness, manic type, were included in the study. In a random selection patients were divided into five groups: Those treated with:

1. Lithium combined with haloperidol (n=36, 13 men, 23 women).
2. Lithium combined with one phenothiazine (n=14, 8 men, 6 women).
3. Lithium combined with two phenothiazines (n=14, 4 men, 10 women).
4. Lithium combined with carbamazepine (n=9, 5 men, 4 women).
5. Lithium combined with benzodiazepines (n=10, 5 men, 5 women).

The mean age of patients was 31±11 years. The mean dosage of drugs in each group are shown in Table 1.

All of the patients had regularly received lithium carbonate in tablet form with dose range of 900-1500 mg/day. Mean plasma levels of lithium were 0.86±0.22 mEq/L. All patients were visited at least two times by a psychiatrist to document the diagnosis and check

* Diagnostic and Statistical Manual of Mental Disorders Edition 4

inclusion as well as exclusion criteria, and global assessment of severity of illness (17) (Table 2).
The exclusion criteria were:
1) schizoaffective disorder
2) BMD mixed type
3) rapid cycling BMD and
4) substance related disorders.

Each patient underwent a complete medical including neurological examinations and each was selected to be free of any major medical illness. All of the patients were in severe manic state (global mood score = 5) at the entry to the study, and became symptom free (global mood score = 0) at discharge.

RESULTS

Mean duration of treatment in different groups is presented in Table 3. There were no significant differences among the groups in the duration that the patients became symptom free (Kruskal-Wallis Nonparametric ANOVA). There were no significant differences in duration of treatment between patients received one neuroleptic in combination with lithium and those with two neurolepties. There were also no significant differences in plasma lithium concentrations among the groups.

Table 1. Mean dosage of drugs in 5 groups

patient group (n)	psychotropic drugs	dosage (mg/day)
Lithium + haloperiodol (36)	haloperidol	20 ± 5
Lithium + one	perhpenazine (8)	28 ± 4
Phenothiazine (14)	trifluoperazine (6)	20±5
Lithium + two	chlorpromazine +	150 ± 50
Phenothiazines (14)	triflouperazine (6)	17.5±2.5
	chlorpromazine +	150±50
	perphenazine (8)	28±4
Lithium+ carbamazepine (9)	carbamazepine	800±200
Lithium+	clonazepam (5)	2*
Benzodiazepines (10)	Flurazepam (5)	15*

Values are expressed as Mean ± SD
* All of patients in this group received 2 mg/day clonazepam or 15 mg/day flurazepam in combination with lithium.

Table 2. Global Assessment Rating Scores

severity of illness	score
severe	5
moderate to severe	4
moderate	3
mild	2
very mild	1
symptom free	0

Table 3. Duration of treatment in the 5 groups

patient groups	duration of treamtnet (days)
Lithium + haloperidol	25±11
Lithium + one phenothiazine	26±20
Lithium + two phenothiazines	33±18
Lithium + carbamazepine	28 ± 21
Lithium + Benzodiazepines	26 ± 17

Values are expressed as mean ± SD
Kruskall - wallis statistic KW = 6.922
The P value is 0.32, considered non significant.

DISCUSSION

Results found in this study revealed that there are no significant differences in the duration of treatment among manic patients received one neuroleptic, two neurolepties, carbamazepine or benzodiazepines in combination with lithium. These results are supported with some other studies that compared the efficacy of carbamazepine (8,18-20) or benzodiazepines (2,21-24) with neurolepties, in treatment of acute mania.

Janicak et al (8) reviewed 16 studies of carbamazepine administered in patients with acute mania. The data generally support the conclusion that carbamazepine is effective in the treatment of acute manic symptoms. Studies comparing carbamazepine with neurolepties, have generally found the two medications to be equivalent in efficacy (18-20).

Since mood stabilizers may take up to 2 to 3 weeks to become fully effective; many patients will require adjunctive medication in the interim to control agitated, psychotic, or otherwise dangerous behavior. Both benzodiazepines and neurolepties have been shown to be helpful and often necessary to be administered for extremely agitated or psychotic patients. Though, benzodiazepines are safer (1,2,21-24); however, neurolepties have been more widely used and studied.

Results of this study support the idea that carbamazepine or benzodiazepines have the same effects of neurolepties to control the symptoms of acute mania. According to the increased risk of extrapyramidal symptoms or tardive dyskinesia during treatment with neurolepties, carbamazepine or benzodiazepines are supposedly prefered comedications in treatment of acute manic state.

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