LEBANESE AMERICAN UNIVERSITY

TREATMENT OF ACUTE MANIA: A COMPARATIVE STUDY

by

HALA ISSAM TAISSOUN

A thesis
Submitted to the Pharmacy
Division in partial fulfillment of the
requirements for the degree of Parm-D

Byblos, Lebanon
July, 1999

LEBANESE AMERICAN UNIVERSITY

"THESIS RELEASE FORM"

I, Hala I. Taissoun

Authorize the Lebanese American University to supply copies of my thesis to libraries or individuals upon request.

_____
Signature

_____
Date

LEBANESE AMERICAN UNIVERSITY

TREATMENT OF ACUTE MANIA:
A COMPARATIVE STUDY

by

HALA ISSAM TAISSOUN

[redacted]

Dr. Lydia Sholy — Advisor

MUNIR KHANI, M.D.

[redacted]

Dr. Munir Khani — Committee Member

[redacted]

Dr. Akram Saab — Committee Member

Date of Thesis presented : July 7th, 1999

TABLE OF CONTENTS

LIST OF TABLES

Table 1. Demographic Variables of Antimanic Drug Groups

Patient Profile	Lithium (N=5)	Carbamazepine (N=8)	Valproate (N=4)	χ^2 (P value)
Age, mean (SD) y	41.6 (12.5)	40 (9.7)	34 (11)	[a]
Gender, N (%)				0.58
Men	1 (20)	2 (25)	2 (50)	
Women	4 (80)	6 (75)	2 (50)	
Psychosis, N (%)				0.72
With psychosis	3 (60)	3 (37.5)	2 (50)	
Without psychosis	2 (40)	5 (62.5)	2 (50)	
Family History of mania, N (%)				
With history	3 (60)	2 (25)	1 (25)	0.39
Without history	2 (40)	6 (75)	3 (75)	
Prior Admissions,mean (SD)	4.6 (2.6)	4.5 (6.7)	7.25 (4.19)	[b]
Duration of Stay, mean (SD) day:	36 (8.22)	32.9 (14.09)	31 (24.29)	[c]

[a] ANOVA (F=0.61, P=0.55)

[b] ANOVA (F=0.43, P=0.66)

[c] ANOVA (F=0.12, P=0.89)

Table 2. patient Severity Score							
	Day 1	Day 3	Day 7	Day 10	Day 14	Day 21	Day 30
Lithium	13	11	7	6	6	5	5
	12	9	7	4	4	4	3
	9	5	3	1	3	2	1
	13	10	9	7	6	3	4
	12	9	4	2	2	1	0
	11.8	*8.8*	*6*	*4*	*4.1*	*3*	*2.6*
CBZ	13	6	3	3	2	2	2
	10	7	5	6	7	4	
	10	9	4	5	3	2	3
	9	7	5	4	1	1	
	11	7	8	5	7	6	6
	10	9	6	5	4	5	3
	19	13	12	5	3	4	3
	9	6	5	3	5	2	2
	11.25	*8*	*6*	*4.5*	*4*	*3.25*	*3.17*
valproate	14	14	11	8	6	5	
	13	13	5	4	5	5	
	16	9	9	8	8		
	15	11	5	6	5	5	5
	14.5	*11.75*	*7.5*	*6.5*	*6*	*5*	*5*

Table 2. Comparative Adverse Effects of Antimanic Drug Groups

Adverse Effect	Lithium (N=5)	Carbamazepine (N=8)	Valproate (N=4)
Renal Insufficiency			
Polyuria/ Polydypsia			
EPSE	1 (20%)	2 (25%)	2 (50%)
Nausea			1 (25%)
Vomiting			
GI	1 (20%)	3 (37.5%)	
Thyroid	2 (40%)	1 (12.5%)	1 (25%)
Rash			1 (25%)
Sedation	4 (80%)	4 (50%)	4 (100%)
Blood Dyscrasias			
Anticholinergics	1 (20%)	3 (37.5%)	1 (25%)
Arrhythmics			
Weight gain	3 (60%)		
Increased Liver Enzymes		1 (12.5%)	3 (75%)
Convulsions			
Ataxia			
Anorexia		1 (12.5%)	1 (25%)
Vertigo		2 (25%)	

Table 5. Rank Order of Neuroleptic Use

Neuroleptic	Patient (n) [a]	Daily Dose [b]	S.D. [c]
Chlopromazine	9	222.22	176.97
Clozapine	3	166.67	202.07
Propericiazine	7	27.14	12.54
Haloperidol	11	24.55	9.07
Zuclopenthixol	4	50.00	0.00
Olanzapine	1	10.00	0.00
Terfluzine	2	300.00	0.00
Solian	1	400.00	0.00
Risperidone	1	6.00	0.00

a Some patients received more than one neuroleptic

b mean dose in mg

c Standard Deviation

Table 4. Rank Order of Benzodiazepines

Benzodiazepines	Patient (n) [a]	Daily Dose [b]	S.D. [c]
Clonazepam	3	13.83	20.52
Chlorazepate	3	62.50	35.47
Lorazepam	1	3.00	0.00
Diazepam	2	30.00	0.00

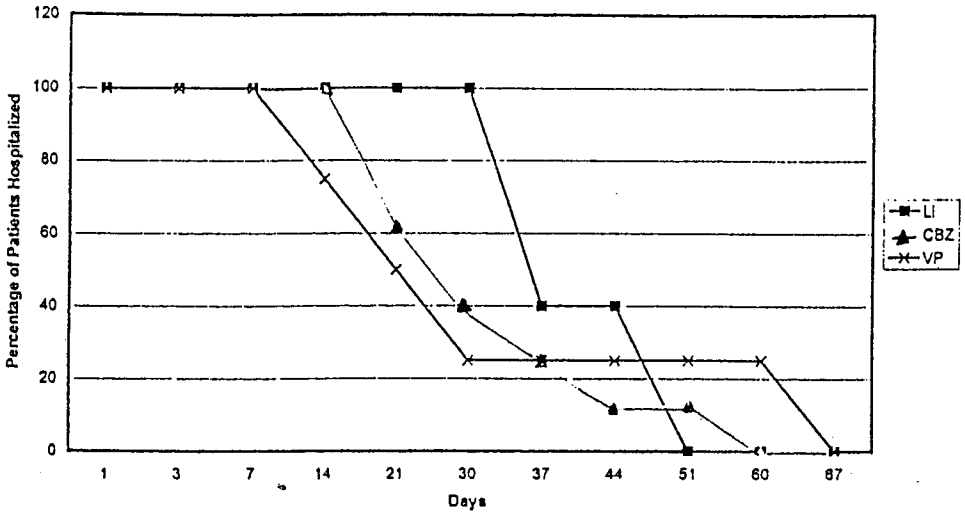
a Some patients received more than one neuroleptic

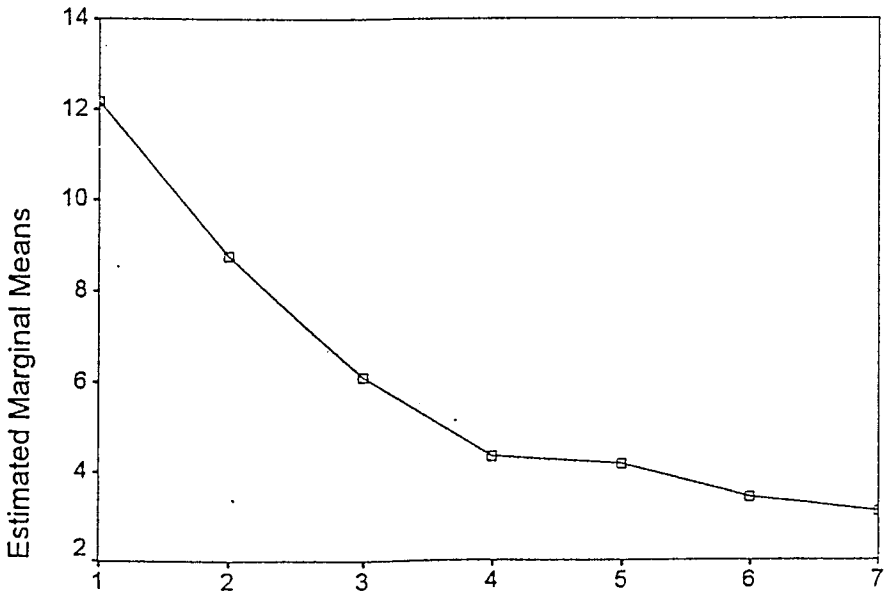
b mean dose in mg

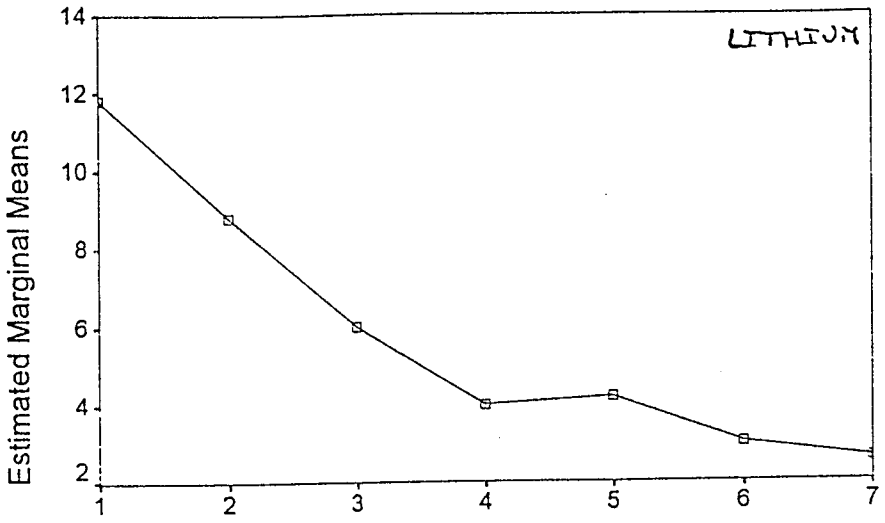
c Standard Deviation

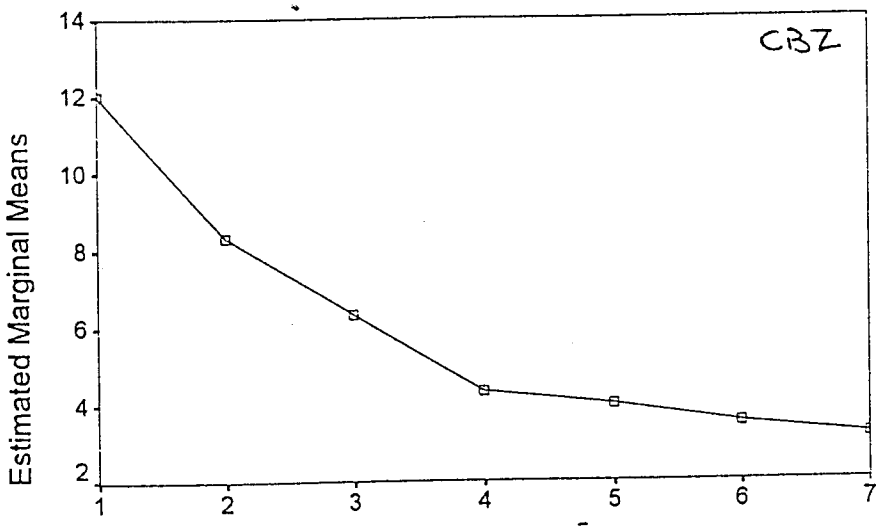
LIST OF ILLUSTRATIONS

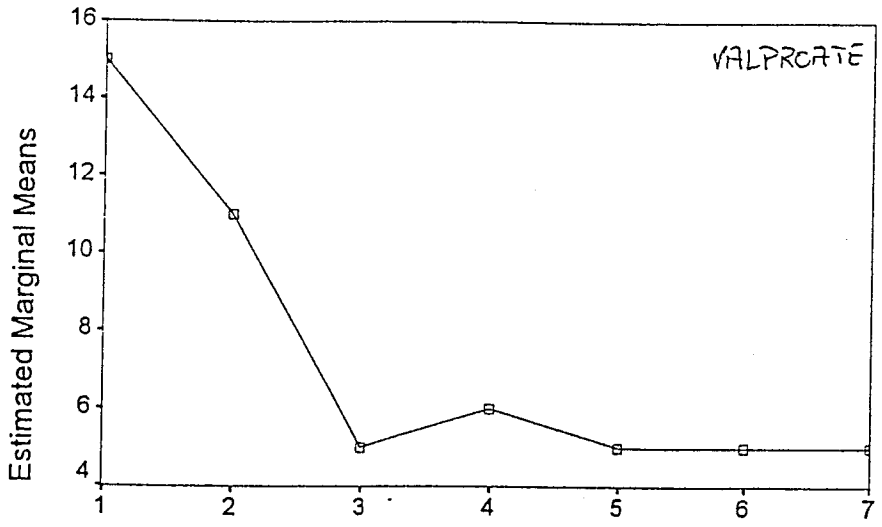
Figure 1. Drug Response Curve











ABSTRACT

Background:
Bipolar disorder is a relatively common disorder and is characterized by " unpredictable swings in mood from mania to depression".
Mania is a disease state which induces difficulties in work performance and psychosocial functioning requiring rapid and effective treatment in order to allow the patients to return to normal function.
It is a very serious illness characterized by a high rate of recurrence and a deteriorating course.
The treatment of acute mania should not only be effective and well tolerated but also anticipate and modify the future course of illness.
Lithium, anticonvulsants, antipsychotics and ECT are recognized treatments for acute mania.
Although lithium is considered by most as the treatment of choice, the position of anticonvulsants and ECT is currently gaining ground.

Objectives:
This study is aimed at determining which treatment is most adequate for acute mania.
Each treatment modality will be discussed separately before comparing the three strategies for efficacy, safety and time taken to achieve the goals set.

Methods and data analysis:
All patients diagnosed with acute mania will be considered for this study.
A non-randomized, open-label, comparative study will be conducted in a single center where patients will be assigned into three groups: the ones receiving lithium, the ones on anticonvulsants(carbamazepine or valproate) and finally patients receiving ECT.

Treatments are given depending on the patients' physician.
All information concerning patients will be available through their files or medical records.

The study data will be entered into a patient information database, using the SPSS Data Entry Program.

Significance:
Different studies have been conducted lately comparing various treatments of mania.
Most of these have come out with contradicting results. So the question remains open as to which strategy should the first line treatment for acute mania.
And because mania is such a severe disease with many complications, it would be interesting to find the answer.

Introduction

A-Definition(1)

Bipolar disorder(BP) is a common disease affecting about 1.5% of the population.
It is a major psychiatric condition characterized by "unpredictable swings of mood from mania(or hypomania) to depression".
The mood fluctuations are chronic and should be present for at least 2 years before the diagnosis is made.
Manic episodes typically emerge over a period of days to weeks and if untreated may last as long as 8 to 12 months.
Bipolar disorder is associated with a high rate of recurrence and half of the patients experience difficulties at work and in psychosocial functioning.
The age of onset is between 20 and 30 years of age.
The prevalence is similar in men and women but there are gender differences in the course of the disorder, with men having more manic and women having more depressive episodes.

1-Clinical Manifestations:(2)

Essential features of hypomania include a distinct period of elated, expansive or irritable mood lasting at least 1 week. Three or more of the following symptoms must also co-exist: inflated self-esteem or grandiosity, decreased need for sleep, talkativeness or pressured to keep talking, flight of ideas, distractibility, increase in goal-directed activity and involvement in risky activity that have a high potential for painful consequences. Mania ,on the other hand , is essentially a more severe form of hypomania characterized by psychotic symptoms and/or severe functional impairment usually warranting hospitalization.

In both mania and hypomania the increased psychomotor activity, excessive social extroversion, impulsivety and impaired judgment constitute disturbances that affect the individual's job, social life and relationships with others.
Delusions and hallucination, when they occur, are usually mood congruent.

2-Diagnosis:

In order to diagnose BP, one must first rule out activation by a stimulant, a sympathomimetic compound or an anti-depressant as well as secondary mania induced by hypothyroidism, AIDS or any neurologic disorder.

It should be noted that mania is defined in the DSM-IV(2) and the International Classification of Diseases as a patient having suffered at least one manic, hypomanic or mixed episode.

The differential diagnosis:
The criteria for diagnosis of BPI state that the individual should have had at least one manic episode or at least one manic episode plus a mixed or major depressive episode usually warranting hospitalization.
The manic episode should not be accounted for by a psychotic disorder.
BP II is characterized by a hypomanic plus a major depressive episode.
If the depressive and manic symptoms are of at least 2 years duration and are of sub-syndromic proportions that are not enough to meet criteria for a major depressive or a hypomanic episode, the diagnosis of a Cyclothymic Disorder should be considered.

Patients with BP I may exhibit psychotic symptoms consistent with a major psychotic disorder . However the individual with the psychotic disorder will have psychosis in the absence of mood symptoms but the patient with BP I will not. A diagnosis of a schizo-affective disorder should be considered when such a conflict arise.

BP are diagnosed according to the clinical features of the current or most recent episode(i.e. mania, depression...).

The severity of the episode can be qualified as mild(minimum symptom criteria are met for a manic episode), moderate(extreme increase in activity or significant impairment in judgment), severe (without psychotic features) severe (with psychotic features either mood-congruent or mood-incongruent), in partial remission, in full remission or unspecified.

3-Etiology and pathophysiology:

The underlying pathophysiologic mechanism that might account for the rapid mood swings of BP remains elusive.
Cellular models of changes in membrane Na+ and K+ activated ATPase and proposals of disordered signal transduction mechanisms involving either the phosphoinositol system or guanine nucleotide binding proteins have received the most attention(1).
Lithium decreases the supply of free inositol used to maintain the lipid precursors involved in intracellular signaling and blocks stimulation-induced increases in GTP binding capacity. Reduction of GTP and downstream effects on protein kinase C are being investigated s possible explanations for the therapeutic effectiveness of Lithium.
Neurophysiologic studies suggest an altered circadian rhythm in BP patients.
Neuroimaging techniques have also identified a higher rate of subcortical white matter abnormalities.

Twins, family and adoption studies provide compelling evidence for partial genetic etiology but mode(s) of inheritance and number of genes involved have not been identified.
Majority of linkage studies assumed a classical mendelian inheritance attributable to a single major gene.
Conflicting evidence has been substantiated until now.
On one hand, concordance rate for monozygotic twin pairs approaches 80% and segregation analyses are consistent with autosomal dominant transmission. On the other hand, there seems to be less than full concordance in monozygotic twins and at least 4 susceptibility loci identified (3).

Many groups are currently investigating the genetic basis of BP, with interest focused on both identification and confirmation of susceptibility loci on various chromosomes.
However to date, no specific mutation or genetic polymorphisms have been identified that predispose to the disorder.
Pettigrew and Miller(4) hypothesized that BP is the result of a genetic propensity for slow interhemispheric switching mechanism that become "stuck" in one or the other state.

Hemispheric activation "stuck" on left is expressed by mania while that on the right results in depression.
Most studies reject a single locus inheritance model but the number of implicated loci is so wide that it becomes difficult to narrow the field of search.
Among others, chromosomes 4, 18, 21 and X were believed to be involved (5-17).

B-Treatment:(18)
10-15% prescriptions written in US are for medication intended to affect mental processes: to sedate, stimulate or otherwise change mood, thinking or behavior. This large market spurred a certain number of studies in the hope of finding the best treatment for several psychiatric diseases including mania.

Treatment must address the acute mania episode as well as reducing the frequency of mania episodes.
It has been estimated that without adequate treatment the average woman will loose about 9 years of life, 14 years of effective activity and 12 years of normal health.
Any patient who has experienced two or more episodes of affective disorder within a 5-year period is candidate for long-term prophylaxis with a mood stabilizing agent.
Factors affecting such a decision include the number, frequency and severity of previous episodes.

1-Lithium

Lithium salts(carbonate and citrate) were introduced in psychiatry in 1949 for the treatment of mania but it was not used as such in the US until 1970 due to concerns about safety.
John Cade described the benefits of lithium in the treatment of acute mania.
Later on, a number of case reports hinted to the usefulness of lithium in preventing BP relapse. Lithium was shown to decrease the frequency, duration and severity of manic episodes.
Having proved its efficacy against placebo in controlled clinical trials, lithium is the most widely recommended drug for this purpose.

1.a-Mechanism of action

Therapeutic concentration of Lithium have relatively no discernible psychotropic effects in normal individuals.
The precise mechanism of action is unknown.
The important characteristic of lithium is its small gradient of distribution across biological membranes(unlike sodium and potassium).
It can replace sodium in supporting a single action potential but it is not a substrate for sodium pump.

In the CNS, the effect of lithium on the metabolism of biogenic monoamines implicated in the pathophysiology of mood disorders was investigated.
In animal brain tissue, lithium concentration reached 1-10meq/lit and it was found to inhibit depolarization-provoked and Calcium-dependant release of NE and DA but not serotonin from nerve terminals.
Lithium may enhance the release of serotonin(especially from hippocampus); it may also slightly alter the reuptake and presynaptic storage of catecholamines so as to increase the inactivation of amines.
Lithium has little effect on catecholamine-sensitive adenyl cyclase activity or on binding of ligands to DA or adrenergic receptors in brain tissue even though lithium was noted to alter hormone responses mediated by adenyl cyclase and phospholipase C in other tissues.
The effect of lithium on Na, K, Mg and glucose may contribute to its therapeutic effect.
In general, the hypothesis of transmission-modulated lithium action is appealing for both antimanic and mood-stabilizing action.

1.b-Pharmacokinetics

The required dose of lithium must lead to a certain plasma concentration at which relapse is prevented and adverse effects are kept to a minimum.
Several studies were conducted to determine the safe and effective concentration range (19).
By taking most of the findings into consideration the recommended target plasma concentration is 0.75 to 1.25meq/lit(10-12 hrs after oral dose).
In acute mania the range is slightly higher: 0.9-1.1meq/lit.
A 0.6-1.0meq/lit concentration is adequate for long term use in the prevention of recurrence.

Recommended concentrations are obtained at doses of 900-1500mg/day (15mg/kg) in outpatient and 1200-2400 mg/day for hospitalized patients. Because of low margin of safety of lithium and short half-life, during the initial distribution is best to give divided daily doses.
Peak plasma concentrations are reached in about 2-4 hrs after an oral dose.
Slow release preparations provide a slower rate of absorption but absorption is erratic and the incidence of lower intestinal tract symptoms increase.

Lithium is at first in the extracellular fluid and then it accumulates in the tissues.
There is no binding to plasma proteins.
Passage through BBB is slow and at steady state the concentration in CSF is approximately 40-50% that in plasma.
This variation explains that there is no direct relationship between serum concentration and therapeutic outcome.
And so, clinical response and adverse effects must be taken into account in addition to plasma concentration.

95% of lithium undergoes elimination in urine.
Elimination half-life varies between 20 to 24hrs following a single dose.
On repeated administration lithium excretion increases the first 5-6 days then steady state is reached.
80% of filtered lithium is reabsorbed by the proximal renal tubules.

Concentration in blood is crucial so regular tests should be done.
Serum levels should be monitored every 3-4 days during the first 2 weeks, then weekly for the next 4 weeks and monthly for the next 3-4 months.

1.c-Efficacy

Several trials described the efficacy of lithium in the treatment of acute and the in prevention of recurrent mania.
However, its effectiveness in clinical practice is less than that predicted in trials.

In several trials conducted in the 1970s, less than a third of patients receiving lithium relapsed compared with 80% on placebo(65). Unfortunately, long term follow-up studies were not consistent with these findings.

Two UK studies(20,21) observed a rise in hospital admissions for mania during the period in which lithium was prescribed widely for BP prophylaxis.
And three US studies(22-24) concluded that less than 50% of the participating patients remained well despite being on lithium therapy. Overall, 40-50% of patients on lithium relapse. Some of the clinical factors associated with this poor response are a negative family history, an unstable premorbid personality and a rapid cycling pattern of illness. It has been estimated that following the first episode some 5 years of lithium prophylaxis is needed to avoid a subsequent one.
When lithium is stopped suddenly, the highest risk of recurrence occurs within the next 14-21 days (25). It is better reduced gradually over 4-6 weeks.

A more recent study by Baldessarini (26) found that gradual discontinuation of lithium may decrease high risk of early morbidity in BP patients after long term maintenance lithium therapy.
Recurrence time differs by 5.6 fold when comparing abrupt discontinuation (1-4 days) VS gradual discontinuation (15-30 days).
The recurrence rate in first year was 6.5% VS 2.3% but similar thereafter.
Patients remained stable for 3 years when off lithium 20 times more frequently after gradual than rapid discontinuation(37 VS 1.8%).
Ratios of median survival times after gradual/rapid lithium discontinuation were similar.
Slow removal of lithium may reduce and not only delay recurrence.

In view of all this data, lithium should probably be continued indefinitely once started, in order to avoid any recurrences.

It should be noted that in acute mania, treatment with lithium can be postponed until some degree of behavioral control and metabolic stability has been attained with antipsychotic drugs, sedatives or anticonvulsants. Improvement of patient can take as long as 7 days to appear and in some patients up to 3 weeks.

1.d-Adverse effects

50-75% of patients on lithium experience at least one side effect(32,66).
In the early phase of treatment, GI problems(nausea, loose stools), sedation, polydipsia/ polyuria and hand tremor are reported.
These are minor and usually improve on continued treatment by decreasing lithium dose or by once a day administration.
Difficulty with memory and weight gain appear later on.
Lithium is also known to cause cutaneous problems, sexual dysfunction (by decreasing libido), alteration of cardiac repolarization and rhythm and some cases of hyperparathyroidism were observed(66).

Long term effects:
→Renal
Lithium therapy causes an initial transient increase in the excretion of 17-hydroxycoticosteroid, Na, K and water for a period of 24 hrs.
In the next 4-5 days, the excretion of K becomes normal and Na is retained.
Edema and Na retention are self-limited and disappear after a few days.
Long term lithium use can be associated with impaired renal concentration but this is usually reversible.
The mechanism is thought to be due to a dose-related inhibition of vasopressin-sensitive adenylate cyclase in the kidney.
It occurs in 25% of patients and leads to polyuria and thirst.
Lithium may also stimulate thirst directly by reducing the salivary flow.
Permanent damage to the glomeruli is debatable even though Gay and Olie(66) reported changes in the morphology of the kidney after 10 years of treatment with fibrosis, tubular atrophy and glomerular sclerosis but no decrease in filtration rate.

Renal function should be checked every 6-12 months.
Impaired renal function is not an absolute contraindication to lithium.
Sodium deficiency causes a decrease in lithium clearance leading to potential intoxication.
This can explain the possible interaction between lithium and thiazides.
On the other hand there seems to be little effect on lithium with loop diuretic administration.

→Thyroid

Lithium, by affecting TSH, may cause hypothyroidism in 5% patients and subclinical hypothyroidism in 5-35% patients.
This is observed mostly in women 6-18 months after the initiation of lithium.
This may predispose patients to depression or rapid cycling BP.
Thyroid function should be monitored every 6-12 months.
Replacement therapy could be initiated if needed.

Tremont and Stern (27) postulated that both ECT and lithium are associated with cognitive side effects that cause decreased patient compliance and treatment satisfaction.
Both therapies have effect on HPT axis activity.
The addition of T_3 to ECT irrespective of the number of stimulations induced better memory function.

Studies in BP patients on lithium showed that cognitive deficits were related to decreased thyroid status but not lithium levels.
So when T_3 was added to lithium, there was an improvement.
This may cause better compliance and decreased morbidity.

→Body weight

A patient may gain up to 4 kg during the 2 first years of treatment.
Weight gain may be due to sodium retention, thyroid changes, insulin-like action of lithium and a direct effect on appetite(66).
The prevalence of obesity is 3 times higher than in the general population.
This side effect can be particularly bothersome, especially in women and may cause treatment discontinuation.

1.e-Pregnancy

Use of lithium in pregnancy may result in neonatal goiter, CNS depression, hypotonia and cardiac murmur.
These reverse with time.
Lithium in early pregnancy causes cardiovascular anomalies of the newborn called Ebstein's anomaly in 1/5000 cases as compared to anticonvulsants that pose a risk of irreversible spina bifida in 1/100 cases.

Maximum risk of relapse occurs within the first two weeks of delivery in 25-30% patients.
Lithium should be restarted 24hrs after delivery and the mother must avoid breast feeding.

1.f-Toxicity

Toxic concentration ranges from 2.0 to 3.0 meq/lit. These values are close to the therapeutic values warranting close monitoring of serum levels.
Acute intoxication presents with vomiting, diarrhea, coarse tremor, ataxia, coma and convulsions.
Milder symptoms include nausea, vomiting, abdominal pain, diarrhea, sedation and mild tremor.
Nervous system involvement: confusion, hyperreflexia, tremor, dysarthria, seizures, cranial nerve and focal neurological signs processing to coma and death.
These may be irreversible.
Cardiac arrhythmias, hypotension and albuminuria were observed.

If levels are below 1.0 to 1.2 meq/lit with no vomiting, lithium can be continued carefully in addition to monitoring.
If levels are between 1.2-1.7meq/lit, lithium is better withheld for 48hrs at least.
In case of vomiting of diarrhea, lithium should be stopped immediately because the dehydration will add to lithium toxicity.

A concentration of more than 2 meq/lit may lead to brain damage, one of 3-4 meq/lit can prove fatal.
There is no antidote for lithium intoxication.
Treatment is supportive.
Vomiting due to increased lithium decreases the absorption.
Increasing lithium clearance may be of benefit. This can be achieved by increasing urinary flow by increasing fluid intake.
Dialysis can be life saving in severe poisoning i.e. 4.0meq/lit.

1.g-Noncompliance

Noncompliance is probably the most common reason for the failure of lithium therapy mostly due to intolerable side effects.

About one third to one half of patients on lithium stop it against medical advice.

In a Danish study (28), 38% of patients that discontinued lithium relapsed during a two year period.
Silverstone and Romans (19) conducted a study on 120 patients. Of these, 18(32%) of 52 stopped taking lithium against medical advice 17 relapsed within two years.
A literature review of 14 studies (29) found that more than half of the new episodes occurred within 3 months after stopping lithium.
There is also a high risk of suicidal behavior.
This recurrence rate is 28 times higher than that expected in the normal cycling of mania.
Treatment with lithium for less than two years is of no use and may even be harmful to patients.
The decision to recommend indefinitely prolonged maintenance treatment based on balancing frequency and severity of past episodes of BP, age and estimated reliability of patients and risk of side effects.

1.h-Drug Interaction

-Diuretics: because of their action on the distal part of the nephron, thiazides increase lithium serum levels as opposed to the diuretics that act on the proximal tubules that favor a decrease in lithium levels.
Osmotic diuretics increase lithium clearance.

-Lithium is often used in addition to antipsychotics, sedatives and antidepressants.
A few case reports suggested a risk of increased CNS toxicity when haloperidol is added to lithium.
Antipsychotic drugs may mask lithium toxicity signs.
Urinary retention as an anticholinergic effect of TCAs can be a problem with lithium-induced diuresis.

-Some NSAIDs(especially indomethacin) can decrease clearance by facilitating proximal tubular reabsorption and increase plasma lithium concentration.

-Agents that increase GI motility may change lithium concentration in blood.

-Some interaction with ACEI especially in elderly patients.

2-Anticonvulsants

Anticonvulsants are a potential alternative to lithium.
They have comparable efficacy but with fewer adverse effects and better compliance(30).

2.a-Carbamazepine

Carbamazepine(CBZ) is an antiseizure agent.
It was shown to be effective in the treatment and the prevention of mania episodes.
In 4 controlled comparative trials of CBZ and lithium (31), CBZ did not demonstrate conclusive prophylactic efficacy. But this is probably due to the lack of distinction between bipolar and unipolar patients.
In 5 trials (32), considering CBZ in the prophylaxis of BP disease it was found to be equal to lithium.
In the management of patients prone to relapse or with rapid cycles, the combination of lithium and CBZ may be more effective than either drug alone (33).
This study also reported a loss of efficacy in patients already stabilized on carbamazepine.

The initial dose of CBZ is 100mg BID and it can be increased weekly to a maximum of 400mg bid. Slow dosage escalation is necessary to avoid neuromuscular and cognitive side effects.
The therapeutic concentration should be in the range of 6-12µg/ml.

20-50% of patients on carbamazepine experience side effects.
Adverse effects include sedation, GI symptoms, vertigo and ataxia.
CNS side effects occur with plasma levels higher than 9µg/ml.
15% of patients develop rash.
Blood dyscrasias can occur in the early stages especially leucopenia in 10% patients.

CBZ induces liver enzymes in 5-10% patients thus accelerating its own elimination.
It can take two weeks for its metabolism to stabilize.
The enzyme induction also leads to the reduction of a wide range of other medications.
It may be also the cause of the fall in circulating thyroid hormones.
CBZ causes neural tube defect in 1% newborns.

2.b-Valproic acid

There are two forms of valproic acid derivatives: sodium valproate and divalproex which is a mixture of valproic acid and sodium valproate.
Valproate appears to be especially effective in the treatment of rapid cycling BP and in patients resistant to lithium.
Combining it to lithium may benefit patients that do not respond to either agent alone.
Several trials attested to its efficacy in the treatment of acute mania and in the prevention of recurrent episodes (34-38).

In one study (39), divalproex was administered to 21 manic patients age 60-82.
The median dose was 1405 mg/day(plasma level = 72µg/ml).
20 patients received in addition a neuroleptic drug.
90% patients rated much to very much improvement.
Sedation occurred in 2 patients which necessitated decreasing the dose.
The study suggested the effectiveness of valproex in acute mania but advised caution because of its retrospective nature and the use of neuroleptics.
On the other hand, Bowden searched for the benefit of divalproex in prophylactic treatment of BP (40).
The spectrum of efficacy of valproate is somewhat broader than that of lithium, extending to patients with certain more severe forms of mania(ex: mixed mania).

Pretreatment plasma GABA activity correlated with the magnitude of improvement in manic symptoms with valproate.
Studies of comparable clinical benefits of lithium and valproate point to the possibility of overlapping effects on specific G protein-linked signal transduction for lithium and valproate but not for carbamazepine.

The medication is usually started at 250mg BID or TID targeting a plasma concentration of 50-100mg/lit.
However, Martinez et al (41) conducted a pilot study on the tolerability of a dosing strategy on divalproex starting with 30mg/kg/day followed by 20mg/kg/day. This requires much higher doses than usually recommended.
Loading at this level was found to attain therapy levels faster, and decrease the latency of therapeutic effect.

Another study(42) involved 65 patients who were given 750mg/day for 2 days followed by 1000mg/day on days 3-5. The dosage was clinically adjusted later on for the 21 remaining days.
It concluded that patients with a plasma level between 45 and 100µg/ml are much more likely to have an efficacious and adverse effect-free response than patients with lower or higher valproate serum levels.

Adverse effects include sedation, headache, ataxia and GI disturbances. Weight gain and total alopecia can also be present.
It causes less risk of blood disturbances than CBZ with only 0.4% of reported leucopenia.
Major and minor congenital malformations were reported in babies in addition to a higher incidence of neural tubal defect with 1.3% having spina bifida.

3-Antipsychotics

Lithium is not often employed as sole treatment due to its slow onset of action and potential difficulty in the safe management in highly agitated patients.
Initially, a neuroleptic or a potent benzodiazepine(lorazepam or clonazepam) is used to attain a degree of control of acute agitation and greater stability of fluid and electrolytes.
Most neuroleptics are effective in the treatment of acute mania and are often used concomitantly with the institution of lithium therapy or anticonvulsant agents(43).
Antipsychotic agents, given as orally or as depot injections, are used in the prophylaxis of BP patients.

In two studies, the addition of a depot antipsychotic to lithium decreased the number of manic episodes in patients doing poorly on lithium (44,45). Lithium and an antipsychotic are considered by some to be the best maintenance treatment of mania (46).

There is also proof that switching patients not responding properly to lithium to an antipsychotic reduced the number of manic episodes (47). In order to prove that neuroleptics can be used as primary medication in all grades of severity of manic illness, a daily dose of 496±379mg of Chlorpromazine equivalents(as opposed to prior studies with much higher dosages) was administered.
The amount of daily medication depended on the severity of the illness. Neuroleptics appear to have causal effect; different application forms have no effect on the dosage but do affect length of stay(46.6±35.7 days), which is also affected by age, sex, severity of illness and compliance (48).

However a placebo controlled, trial did not show any benefit in the addition of an antipsychotic to lithium (49).
Two more recent studies stated that patients with recurrent mania that failed on lithium or CBZ, had a decrease in the frequency of episodes when given a regular injection of a depot antipsychotics (50,51).

The treatment with a depot antipsychotics is especially beneficial in patients not compliant with oral medication.
There is however a higher prevalence of tardive dyskinesia when neuroleptics are used for BP than when used for schizophrenia.

Clozapine also proved to be effective as an adjunct treatment.
In some cases, Clozapine given as a sole agent resulted in clear cut improvement(52).
Risperidone is also considered as a promising agent especially for BP with psychotic symptoms. However, there is still no consensus on its efficacy due to opposite results in clinical trials(52).

4-Antidepressants

The depressive component of BP may also require treatment in patients with recurrent depressive episodes.

However, antidepressants are considered by many to carry a risk of increased rate of mood-cycling or time spent in manic moods and additional benefit of antidepressant or other mood-stabilizing agents to lithium is not proven.
Consequently, they should not be prescribed on a long term basis especially without the cover of a mood stabilizer.

Sedative doses of potent anxiolytics can be used early in mania treatment. (No adequate studies of possible long-term preventive effect of antipsychotics in manic-depressive illness were conducted).

TCAs are believed to induce rapid cycling mania mostly in women.
A recent survey suggested that shot-acting SSRIs are less likely than TCAs to precipitate manic episodes.
But in a study conducted by Howland(53), SRIs used for depression induced mania in 11 patients with personal or family history of hypomania or mania(i.e. at risk for BP). The episodes were severe with psychotic features.
This suggests that there is a need to compare rate of drug-induced mania for SRIs and TCAs.
Bupropion is also under study.

5-Psychological treatment

A standardized educational program can be very useful in improving the compliance.
Family as well as patient therapy are required.
Signs of relapse should be recognized by the patient or a parent and proper medication such as a sedative, a benzodiazepine or a sedative antipsychotic could abort a manic episode.
More research is still needed to establish the usefulness of such a program.

6-ECT

Problems associated with pharmacotherapy include acceptability, tolerability, adherence, incomplete remission and high rate of recurrence after drug discontinuation.
A widely accepted alternative is electroconvulsive therapy.

ECT is most frequently used to treat medication-resistant depression, depression with suicidal ideas, acute mania and severe psychiatric illness.
In a study involving 55 patients over a 4 year period with major depression, non-affective psychotic disorders, mania and others, there was a positive responses to ECT in 74.5 % of patients.
Best responses were observed with major depression and mania.
18.1% patients had transitory, minor complications(54).

The procedure consists of a brief unilateral or bilateral electrical stimulus applied to the brain of the patient who is anesthetized with a short-acting hypnotic drug and a muscle-depolarizing agent.
The treatment is usually administered three times a week for 6-12 sessions.
Before ECT, a thorough medical and anesthetic history, a complete physical exam, EEG and lab studies must be obtained to rule out anemia, electrolyte imbalance and cardiopulmonary and neurologic risk factors.
During ECT, heart rate, oxygenation, blood pressure and EEG are monitored continuously(55).
Each general seizure lasts about 50 seconds.
At first there is an intense parasympathetic stimulation followed by a transient bradycardia and then a sympathetic driven tachycardia.
Blood pressure decreases at first and then there is a hypertensive phase.

The curative mechanism of ECT is unclear.
In humans, ECT increase postsynaptic dopamine receptor sensitivity and decreases prolactin levels.
In animals, it induces an increase in NE levels but has an equivocal effect on serotonin and acetylcholine levels.
ECT causes transient acute increase in endorphins but this effect is not sustained.

Side effects include confusion that ranges from disorientation to temporary retrograde and anterograde short-term memory impairment.
There is no evidence of structural or neuronal changes in the brain(55).
On the other hand, Chamberlain and coworkers(56) stated that ECT-induced memory dysfunction is a significant side effects, and that it is due to neuronal insults due to release of excitatory amino acids and activation of their receptors, which produces cation and water flux and reversible oxidative stress.

If no maintenance antidepressant or lithium is used, relapse occurs in 30-60% of patients within 6 months after ECT.
Medication decreases relapse rates by 66%.
However, a small number of patients require weekly or monthly ECT.

7-Comparative efficacy of treatments

There is no treatment of choice for mania.
Conflicting evidence support different treatment modalities.

Kusumakar and colleagues(57) reviewed and rated articles for the quality of evidence using the Periodic health Examination guidelines and came up with the following conclusions:
Lithium and divalproex were found to be effective in classical pure mania. Divalproex and carbamazepine were better in mixed states.
Divalproex is superior to carbamazepine and lithium when mania is part of a rapid-cycling course.
Typical neuroleptics are useful in acute mania especially if psychotic symptoms appear, while atypical neuroleptics are better in refractory mania.

Benzodiazepines are not primary antimanic agents but adjuncts to mood-stabilizers or neuroleptics.
ECT is a broad-spectrum treatment.

Another study by Sajatovic(58) included 96 patients. Twenty nine were on lithium monotherapy, 17 on anticonvulsant monotherapy, 42 on multiple mood-stabilizers and 8 on no mood stabilizers.
Mean inpatient stay was highest in multiple mood stabilizers(30±20 days), then lithium monotherapy(20±14 days), then anticonvulsant monotherapy(17±9 days) and last no mood stabilizers(17±14 days).
It is to be noted that the anticonvulsant monotherapy group included patients who had more comorbid psychiatric illnesses than the group on multiple mood stabilizers. Also, patients in the group on no mood stabilizers leave hospital against medical advice.
Compliance was poor in all groups.

Steffens and Krishnan(59) used a decision analysis software program to compare lithium, valproate, carbamazepine, ECT, clonazepam and neuroleptics. These were evaluated for efficacy, tolerability and cost using data from the literature and billing information. The three top choices were respectively valproate, carbamazepine and lithium. However, one should keep in mind the discrepancies between Literature and clinical findings.

8-Combination treatment

Many patients fail to respond to monotherapy with any of the regular agents. Several combination treatments may be an alternative.
Suppes proposed a treatment algorithm (60)to optimize the management of manic patients, but it failed to take into consideration the different types of mania(mixed, rapid cycling...), the use of carbamazepine and ECT as potential treatments and more complex combinations.

Several studies compared different combination treatments in the management of acute mania as well as prophylaxis of manic episodes. Each advocates a different modality according to clinical trials.

One article(61) reviewed the results of trials over 16 years.
No clinically important baseline differences existed between the groups.
However, significant differences were noted after 8 weeks of treatment.
Best responses were observed with series of 9 ECT treatment with sparing use of neuroleptics and lithium maintenance therapy.
The next best outcome was with lithium and low-dose neuroleptics or risperidone.
Carbamazepine and lithium had fewer side effects than haloperidol (moderate dose) with lithium but with equivalent therapeutic results.
Monotherapy with either lithium or carbamazepine was less effective than any combination treatment.

Two studies (62,63) observed that psychiatrists often resort to polypharmacy. However, the results of several controlled trials have been negative.
The only combination that seems to be useful is that of lithium plus valproate.

Lithium pharmacokinetics do not change although statistically, but not clinically significant change is noticed in valproate pharmacokinetics.
It is not known whether the drugs interact to augment response, many of their effect in CNS being different, and with no indication of pharmacodynamic opposing interactions.
Lithium and valproate may differ with regard to clinical variables that predict response to treatment.

Because ECT seems to be the treatment with the most rapid improvement, several trials included ECT in addition to a maintenance medication.

Zarate and coworkers(64) conducted a study to determine the safety and efficacy of ECT+ (valproate or carbamazepine) using two groups: ECT-anticonvulsants and ECT alone.
Patients on ECT-anticonvulsants had a shorter duration of seizures but no difference was noted in the number and type of ECT or side effects.

Jha(65) conducted a case control study over 8years to investigate side effects of combined lithium/ECT. The study compared 31 patients on lithium/ECT with 135 patients on ECT only.
No significant differences between groups was observed when considering neurotoxicity.

Method

1-patient Sample

All admissions to the Hopital Psychiatric de la Croix from march 15th 1999 till june 15th 1999 were evaluated.
A total of 18 patients diagnosed with BP using DSM-IV criteria were screened.
Patients were excluded for the following reasons: refusing medication, discharge from hospital against medical advice, substance abuse or treatment of a concomitant severe illness.
The patient population was representative of a general adult psychiatric inpatient service.
Treatment occurred under ordinary and nonprotocol clinical conditions as prescribed by different physicians in the hospital.

Refer to Table 1.1.
Patients ranged in age from 20 to 51 years. Mean age ± SD=41.6±12.5 for lithium, 40± 9.7 for carbamazepine and 34± 11 for valproate.
Sixty percent of patients in the lithium group showed psychotic features compared to 37.5% in the carbamazepine group and 50% in the valproate group.
A family history of mania was noted in 60% of patients in the lithium group but only 25% in the two other groups.
There was no statistical difference between the three groups concerning age, gender, psychotic features, family history of mania and prior admissions.
Only one patient had a prior history of substance abuse.

2-Clinical assessments

Data were collected from patient records and personal interviewing.
Rating were derived primarily from physician and nurses progress notes and personal patient observation.
Information obtained were about (1) demographic characteristics, (2) manic, depressive and psychotic symptoms during hospitalization, (3) prior treatments, hospitalizations, medical and family histories and psychiatric diagnoses, (4) daily medication and serum medication levels during hospitalization.

A rating scale with scores ranging from 0 to 3 included the following information: grandiosity, need for sleep, talkativeness, flight of ideas, distractibility, goal directed activities, involvement in pleasurable activities and mood changes was used to determine the improvement of patients.
The disease status was rated on admission(baseline), then on the first, third, seventh, tenth, fourteenth, twenty-first and thirtieth days.

A severity score was constructed by adding the level of severity for each day and for each item on the rating scale. A score between 0-3 meant no or mild symptoms, 4-11 mild to moderate symptoms, 12-18 moderate to severe symptoms and 19-21 severe symptoms.

3-Statistical Analysis

Statistical evaluation used the ANOVA test and the χ^2 test to compare the demographic variables of the three groups.
Improvement was evaluated using a constructed scale as stated above using the SPSS.

Results

Please refer to table 1.1 for the specific demographic data of each treatment group.
There were no significant statistical differences between the three groups.
One patient was excluded for leaving the hospital against medical advice after one week of treatment.

1-Dosage regimens

Three patients(60%) received 800mg of lithium per day, 1(20%) 400mg per day and 1patient 600mg per day. Lithium blood levels were taken after one week and then every month or if signs of toxicity occur.

In the carbamazepine group, 4 patients(50%) received 600mg/day and the rest 400mg/day in a controlled release form.
No serum levels were taken.
Both the doses for lithium and carbamazepine were within normal range.

Two patients(50%) in the valproate group received 1000mg in the controlled release form, one patient 2000mg/day also in the controlled release form and one 500mg/day.
The standard initiation dose is 500-750mg/day. Two patients receive higher than normal amounts of medication.

2-Outcome measures

Both length of stay and clinical improvement are predictors of the patients' response to the medication and thus are considered outcome measures.

2.a-Length of stay

The individual drug response curves of the three antimanic agents are shown in figure 2.1.
There is a difference in time to improvement. Patients on valproate leave the hospital earlier than the others, as soon as the fourteenth day. The curve then plateaus from the 30th to the 60th day with 25% of patients still hospitalized.

Lithium patients remain the longest in the hospital. Discharge from hospital is observed only after one month.
Patients on carbamazepine are not discharged until the 21st day but from then on the curve decreases gradually and on the 44th day only 12.55 patients are still hospitalized.
In table 1, the mean duration of stay is 36 ± 8.22, 32.9 ± 14.09 and 31± 24.29 for lithium, carbamazepine and valproic acid respectively. There are no statistical differences between the three groups.

2.b-clinical improvement

Mood change is an important parameter for the evaluation of clinical improvement.

After one month, in the lithium group, 4(80%) had a euthymic mood with one remaining elevated.
In the valproate group, after one month, 2(50%) remained irritable and 2 exhibited euthymic mood.
Finally, in the carbamazepine group, two(25%) remained irritable, one(12.5%) expansive and 5(62.5%) became euthymic.

Response to the medication was evaluated with the help of the rating scale discussed above.
Refer please to table 2.1 as well as figures 2.3, 2.4 and 2.5.

In the lithium group, Patients have a baseline score of11.8. They improve gradually till the 10^{th} day where they reach a score of 4. The curve then plateaus and after one month of hospitalization, the score of 2.6.
Improvement is statistically significant until the 10^{th} day.
Patients on carbamazepine have a baseline score of 12. They also improve gradually till the 10^{th} day where the score becomes 4.5. From then on, the slope of the curve becomes less steep. On the 30^{th} day, the average score is 3.17 with 6 patients remaining in the hospital.
In the valproate group, the curve starts at a higher baseline of 14.5 and decrease very rapidly to reach 7.5 on day 7. Then the curve decreases slowly to reach a score of 5 on the 30^{th} day. However By then, only one patient remains.

3-Adverse effects

Refer to table 3.1.

All patients in the valproate group experienced sedation compared to 80% in the lithium group and 50% in patients receiving carbamazepine.
This high rate of sedation is not entirely due to the antimanic drugs. It may be explained by the combined use of neuroleptics (chlorpromazine, haloperidol...), benzodiazepines and promethazine.
EPSE was observed in 50% of patients on valproic acid while those on lithium and carbamazepine noted 20 and 25% respectively.
It should be noted that EPSE had a relatively high incidence keeping in mind that even though 64.7% of patients were on haloperidol, 41.18% were on trihexylphenidyl(Artane®) and 11.76% were on benzhexol.
Liver enzymes increased in 75% of cases in the valproic acid group but only 12.5% in the carbamazepine group and it was not observed in the lithium group.
Nausea and rash were only observed in then group on valproic acid with 25%.
GI side effects occurred in the lithium group 20% and in the carbamazepine group 37.5%.
Thyroid and anticholinergic side effects were observed in all groups.
Weight gain was only observed in the lithium group with 60% cases.
Vertigo in the CBZ group with 25%.
Anorexia in the CBZ and valproic acid groups with 12.5 and 25 % respectively.

4-ECT

Three patients received ECT, one in each of the groups.
ECT was not considered as a treatment entity. It was administered as adjunctive treatment in very agitated or violent patients.
The number of session ranged between 6 and 8 with each session consisted of 30minutes.
Patients were administered nesdonal 200mg, succinyl 20mg and atropine 0.5mg prior to the procedure.
An ECG was done each time.
In all three cases, amnesia was a notable side effect.

5-Adjunctive medication

Neuroleptics and benzodiazepines were given concomitantly in all three groups.
Tables 5.1 and 5.2 give us the specific drugs with their respective dosages.

Discussion

The results obtained from this study indicate that all three medications are effective in controlling manic symptoms.
Neither psychosis, positive family history nor prior admissions seem to affect the clinical outcome.

Creed and coworkers postulated that there was a certain number of variables involved in predicting the length of stay including diagnosis, social behavior scale score, specific psychiatric symptoms and variables at discharge(ECT, tranquilizers and antidepressant use).
These and others must be taken into consideration in future studies.

The duration of hospitalization of patients in either group is comparable. However, figure 1 shows that patients on carbamazepine and valproate leave the hospital earlier than those on lithium and this is probably due to the fact that lithium takes more time than the other two drugs to exert its action or that the sedative effect of carbamazepine and valproate plays an important role specially during the early phase of the treatment.
One should keep in mind that none of the patients in the valproate group had marked improvement at any time during hospitalization. This could be due to the fact that valproate takes a longer time before exerting its full action rather than it being less effective or that patients have a worst baseline score in this group.
Clinical outcome differs between the groups. Patients on valproate do not improve markedly. They improve faster than the patients on lithium but not as well.
Patients in the lithium group end up with an average score that is lower than that of patients on carbamazepine. However, the individual scores of each patient(and thus his actual improvement) are better than for patients on lithium where only one patient has a score of 0 and two have scores of 4 and 5.
Patients in both groups improve gradually and after on month, they reach lower scores than patients in the valproate group.

Another parameter to consider in order to evaluate clinical improvement is mood change. After one month, 80% of patients on lithium reverted to normal as compared to 62.5% on carbamazepine and only 50% in the valproate group.

Side effects were more important in the groups receiving carbamazepine and valproate and this is contrary to all literature data.
Adverse effects such as sedation, EPSE and anticholinergic problems were probably due to the adjunctive therapy.
Increase in liver enzymes in the valproate group is much higher than the usually observed rates of around 40%.
GI side effects normally range between 9-16%. These figures are much lower than the ones reported in this study.
Weight gain is a normal side effect of lithium.
Thyroid problems(hypothyroidism and goiter) usually occur in 5-35%, with long term use, of cases and the figures of the study are close to these.

The limitation of the study may explain some of the results.
The duration of the study was short. This explains the small sample size. A larger number of patients would have been more indicative.
All the patients come from a poor socio-economic background. This is one of the facts that account for lithium not being used often because of probable poor compliance.
Neuroleptics and benzodiazepines are used on a regular basis. They are not considered as an adjunctive treatment but as part of the main protocol. These drugs are not stopped later on in the treatment as usually done in literature studies.
This may account for the low loading doses of antimanic agents. Also, part of the clinical outcome may be due to these drugs(which have some antimanic properties) and so the improvement may not be entirely due to the antimanic medication.
The adverse effects in the study are not similar to the usual trend found in literature. This is probably due to the addition of the neuroleptics and the benzodiazepines added to the medication regimen. They probably account for the bigger part.

Conclusion

Valproate does not seem as promising as stated in the literature. On the other hand, carbamazepine seems to be a logical alternative for lithium. However the latter should still be considered as the treatment of choice for acute mania and as prophylactic treatment.
Neuroleptics and benzodiazepines should be used more sparingly so as to be able to differentiate between the effects of these and the antimanic drugs. And keeping in mind that antidepressants may precipitate mania or cause cycle acceleration and that neuroleptics may be associated with more profound or linger depressive phases and clear increase in tardive dyskinesia.
Further studies are necessary to evaluate the effectiveness of ECT.

LITERATURE CITED

1- Harrison's

2- American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 4th ed. Washington, DC: American Psychiatric Association; 1994.

3- Craddock N, et al. Mathematical limits of multilocus models: the genetic transmission of bipolar disorder *.Am J Hum Genet* 1995; 57: 690-702.

4- Pettigrew JD, Miller SM. A 'sticky' interhemispheric switch in bipolar disorder? *Proc R Soc Lond B Biol Sci* 1998; 265(1411): 2141-8.

5- McInnes LA, et al. A complete genome screen for genes predisposing to severe bipolar disorder in two Costa Rican pedigrees *.Proc Natl Acad Sci USA* 1996; 93(23):13060-5.

6- Freimer NB, et al. Genetic mapping using halotype, association and linkage methods suggests a locus for severe bipolar disorder (BPI) at 18q22-q23(letter). *Nat Genet* 1996; 12: 436-441.

7- Ginns EI, et al. A genome-wide search for chromosomal loci linked to bipolar affective disorder in the Old Order Amish(letter).*Nat genet* 1996; 12(4): 431-435

8- Baron M. Genetic linkage and bipolar affective disorder: progress and pitfalls. *Mol Psychiatry* 1997; 2: 200-10.

9- Berrettini WH, et al. Chromosome 18 DNA markers and manic-depressive illness: evidence for a susceptibility gene. *Proc Natl Acad Sci USA* 1994; 91: 5918-21.

10- Stine OC, et al. Evidence of linkage of bipolar disorder to chromosome 18 with a parent-of-origin effect. *Am J Hum Genet* 1995; 56: 1384-94.

11- Pauls DL, et al. Linkage analyses of chromosome 18 markers do not identify a major susceptibility locus for bipolar affective disorder in the Old Order Amish. *Am J Hum Genet* 1995; 57: 636-43.

12- Straub RE, et al. A possible vulnerability locus for bipolar affective disorder on chromosome 21q22.3. *Nat Genet* 1994; 8: 291-6.

13- Adams LJ, et al. A susceptibility locus for bipolar affective disorder on chromosome 4q35 . *Am J Hum Genet* 1998; 62: 1084-1091.

14- Blackwood DHR, et al. A locus for bipolar affective disorder on chromosome 4p. *Nat Genet* 1996; 12: 427-30.

15- Gutierrez B, et al. Association analysis of the catechol O-methyltransferase gene and bipolar affective disorder. *Am J Psy* 1997; 154: 113-115.

16- Kelsoe JR, et al. Possible locus for bipolar disorder near the dopamine transporter on chromosome 5. *Am J Med Gen* 1996; 67: 533-540.

17- Parsian A, Todd RD. Genetic association between monoamine oxidase and manic-depressive illness: comparison of relative risk and halotype relative risk data. *Am J Med Gen* 1997; 74: 475-479.

18- Young LY, Koda-Kimble MA. Applied Therapeutics: The Clinical Use of Drugs. 6th edition. Vancouver, WA; 1996.

19- Silverston T, Romans S. Long term treatment of bipolar disorder. *Drugs* 1996; 51(3): 367-82.

20- Symmonds RL, Kendell RE. Lithium and the changing incidence of mania. *Psychol Med* 1981; 11: 521-30.

21- Dickson WE, Kendell RE. Does maintenance lithium therapy prevent recurrences of mania under ordinary clinical conditions ?*Psychol Med* 1986; 16: 521-30.

22- Tohen M, Waternaux CM, Tsuang MT. Outcome in mania in a 4-year prospective follow-up of 75 patients utilizing survival analysis. *Arch Gen Psychiatry* 1990; 47: 1106-11.

23- Harrow MGJF, Grossman LS, Meltzer HY. Outcome in mania disorders: a naturalistic follow-up study. *Arch Gen Psychiatry* 1990; 47: 665-71.

24- Winokur G, et al. A prospective follow-up of patients with bipolar and primary unipolar affective disorder. *Arch Gen Psychiatry* 1993; 50: 457-65.

25- Baldessarini RJ, et al. Effects of the rate of discontinuing lithium maintenance treatment in bipolar disorders .*J Clin Psychiatry* 1996; 57(10): 441-8.

26- Baldessarini RJ, et al. Reduced morbidity after gradual discontinuation of lithium for bipolar I and II disorders: a replication study .*Am J Psychiatry* 1997; 154(4): 551-3.

27- Tremont G, Stern RA. Use of thyroid hormone to diminish the cognitive side effects of psychiatric treatment. *Psychopharmacol Bull* 1997; 33(2): 273-80.

28- Aagaard J, Vestergaard P. predictors of outcome in prophylactic lithium treatment: a 2-year prospective study .*J Affect Disord* 1990; 18: 259-66.

29- Suppes T, Baldessarini RJ, Faedda GL. Risk of recurrence following discontinuation of lithium treatment in bipolar disorder. *Arch Gen Psychiatry* 1991; 48: 1082-8.

30- Emilien G, et al. Lithium compared to valproic acid and carbamazepine in the treatment of mania: a statistical meta-analysis. *Euro Neuropsychopharmacol* 1996; 6(3): 245-52.

31- Dardennes R, et al. Comparison of carbamazepine and lithium in the prophylaxis of bipolar disorders: a meta-analysis .*Br J Psychiatry* 1995; 166: 378-81.

32- Simhandl C, Denk E, Thau K. The comparative efficacy of carbamazepine and lithium on remission from affective illness. *Br J Psychiatry* 1993; 150: 180-2.

33- Post RM, et al. Carbamazepine prophylaxis in refractory affective disorders: a focus on long-term follow-up. *J Clin Psychopharmacol* 1988; 10: 318-27.

34- Pope Hg, et al. Valproate in the treatment of acute mania. *Arch Gen Psychiatry* 1991; 48: 62-8.

35- Freeman TW, et al. A double-blind comparison of valproate and lithium in the treatment of acute mania. *Am J Psychiatry* 1992; 149: 108-11.

36- Bowden CL, et al. Effect size of efficacy measures comparing divalproex, lithium and placebo in acute mania. *Depress Anxiety* 1997; 6(1): 26-30.

37- Hayes SG. Long term valproate prophylaxis in refractory affective disorder. *Ann Clin Psychiatry* 1992; 4: 55-63.

38 - Bowden CL. Dosing strategies and time course of response to antimanic drugs. *J Clin Psychiatry* 1996; 57 suppl 13: 4-8.

39- Noaghlius S, Narayan M, Nelson JC. Divalproex treatment of mania in elderly patients. *Am J Geriatr Psychiatry* 1998; 6(3): 257-62.

40- Bowden CL. New concepts in mood stabilization: evidence for the effectiveness of valproate and lamotrigine. *Neuropsychopharmacology* 1998; 19(3): 194-9.

41- Martinez JM, Russell JM, Hirschfeld RM. Tolerability of oral loading of divalproex sodium in the treatment of acute mania. *Depress Anxiety* 1998; 7(2): 83-6.

42- Bowden CL, et al. Relation of serum valproate concentration to response in mania .*Am J Psychiatry* 1996; 153(6): 765-70.

43- Chou J, et al .Neuroleptics in acute mania: a pharmacoepidemiologic study .*Ann Pharmacother* 1996; 30: 1396-8.

44- Naylor G, Scott C. depot injections for affective disorder. *Br J Psychiatry* 1980; 136: 105.

45- Lowe M, Batchelor D. Depot neuroleptics and manic depressive psychosis. *Int Clin Psychopharmacol* 1986; 1 suppl 1: 53-62.

46- Prien RF, Potter WZ. NIMH workshop report on treatment of bipolar disorder. *Psychopharmacol Bull* 1990; 26: 409-27.

47- Ahlfors UG, et al. Flupenthixol decanoate in recurrent manic depressive illness: a comparison with lithium .*Acta Psychiatr Scand* 1981; 64: 226-37.

48- Adler L, et al. Acute inpatient treatment of manias. Effects of independent variables on neuroleptic dosage and length of stay .*Nervenarzt* 1996; 67(3): 235-43.

49- Esparon J, et al. Comparison of the prophylactic action of flupenthixol with placebo in lithium-treated manic depressive patients .*Br J Psychiatry* 1986; 148: 723-5.

50- White E, Cheung P. Silverston T. Depot antipsychotics in bipolar affective disorder. *Int Clin Psychopharmacol* 1993; 8: 119-22.

51- Littlejohn R, Leslie F, Cookson J. Depot antipsychotics in the prophylaxis of bipolar disorder. *Br J Psychiatry* 1994; 165: 827-9.

52- Gelenberg AJ, Hopkins HS. Antipsychotics in bipolar disorder .*J Clin Psychiatry* 1996; 57 suppl 9: 49-52.

53- Howland RH. Induction of mania with serotonin reuptake inhibitors .*J Clin Psychopharmacol* 1996; 16(6): 425-7.

54- Sanchez M, et al. Clinical experience with electroconvulsive therapy at the Instituto Mexicano de Psiquiatria. *Arch Med Res* 1996; 27(3): 339-43.

55- Banazak DA. Electroconvulsive therapy: a guide for family physicians. *Am Fam Physician* 1996; 53(1): 273-8.

56- Chamberlain E, Tsai GE. A glutamatergic model of ECT-induced memory dysfunction .*Harv Rev Psychiatry* 1998; 5(6): 307-17.

57- Kusumakar V, et al. Treatment of mania, mixed state, and rapid cycling. *Can J Psychiatry* 1997; 42 suppl 2: 79-86.

58- Sajatovic M, Gerhart C, Semple W. Association between mood-stabilizing medication and mental health resource use in the management of acute mania. *Psychiatr Serv* 1997; 48(8): 1037-41.

59- Steffens DC, Krishnan KR. Decision model for the acute treatment of mania. *Depress Anxiety* 1996-97; 4(6): 289-93.

60- Suppes, et al. Treatment algorithm use to optimize management of symptomatic patients with a history of mania. *J Clin Psychiatry* 1998; 59(2): 89-97.

61- Small JG, et al. Comparison of therapeutic modalities for mania. *Psychopharmacol Bull* 1996; 32(4): 623-7.

62- Solomon DA, et al. Lithium plus valproate as maintenance polypharmacy for patients with bipolar I disorder: a review. *J Clin Psychopharmacol* 1998; 18(1): 38-49.

63- Granneman GR, et al. Pharmacokinetic interactions and side effects resulting from concomitant administration of lithium and divalproex sodium. *J Clin Psychiatry* 1996; 57(5): 204-6.

64- Zarate CA, Tohen M, Baraibar G. Combined valproate or carbamazepine and electroconvulsive therapy. *Ann Clin Psychiatry* 1997; 9(1): 19-25.

65- Jha AK, Stein GS, Fenwick P. Negative interaction between lithium and electroconvulsive therapy- a case control study. *Br J Psychiatry* 1996; 169(6): 794.

66- Gay C, Olie JP. Lithium et alternatives a la lithotherapie .*Encycl Med Chir, Psychiatrie* 1999; 37-860-D-10: 10p.

67- Creed F, et al. Predicting length of stay in psychiatry .*Psychol Med* 1997; 27(4): 961-6.