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Original Research Article

AN OPEN COMPARATIVE AND RANDOMIZED STUDY ON VALPROATE'S EFFECT IN THE LONG-TERM TREATMENT OF BIPOLAR DISORDERS VERSUS LITHIUM CARBONATE AND CARBAMAZEPINE

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Abstract

Bipolar disorder is a chronic disorder, with a large diversity range of clinical manifestations that affects around 1% of total population around the world. **Objective**: Evaluation of differences in efficacy between Sodium Valproate and Lithium Carbonate and Carbamazepine in maintenance treatment of patients with bipolar disorder during a 2 years follow-up period. **Design**: an open comparative and randomized study. **Setting**: UHC Tirana "Mother Teresa", Psychiatric Service, Emergency Ward **Participants**: A total of 235 inpatient and outpatient, diagnosed with bipolar disorder I and II (at least two mood episodes) based on DSM-IV-TR. **Main Outcome measures**: Time survival analyses to any events (relapse/recurrence) for entire population in study, comparing three separated groups (n=60) valproate (Vp) versus lithium (Li) versus carbamazepine (Cbz). **Results**: Cumulative survival of Vp was 26% higher than Cbz (p=0.001) and 4.3% than Li (p=0.4304). The mean survival time for Vp was 35 +/- 7% higher than Cbz and 10 +/- 6% higher than Li, while median time for Vp was respectively 53 +/- 7% and 14 +/- 13% higher than Cbz and Li groups. Hazard ratio of Cbz has been 108.5% higher than Vp (B=0.735, p=0.001), for Li was 20.4% higher than Vp (B=0.186). Concerning the predictors: Vp was more effective than Li in non-classic BD I (p=0.031), also superior to Li in mixed, rapid cycling subtypes and in co-morbidities. Vp was more effective than Cbz in classic BD-I (p=0.0312). **Conclusions:** Vp is significantly more effective than Cbz in long-term treatment of BD, Vp is superior than Li in non-classic form of BD.

Key words: Bipolar disorder, Comparative and Randomize study, survival analysis Kaplan Meier, mood stabilizer.

Introduction:

Bipolar disorder is a lifelong condition. It runs an unpredictable course of ups and downs especially after the first episode. When left untreated, these ups and downs can be devastating. Recovering from bipolar disorder doesn't happen overnight (1, 2, 3, 4, 5). As with the mood swings of bipolar

disorder, treatment has its own ups and downs, especially when patients suffer from psychiatric or physical co-morbidity. Some subtypes of BD such as rapid cycling, mix episodes with psychotic features or influenced by significant life stressors are associated with high risk for suicidal behavior (6, 7, 8, 9,10). During the course of life bipolar disorder might change and worsened its clinical presentation which reveals the need to reconsider the treatment strategies. Because everyone responds to medication differently, the doctors may have to try several different medications before they find one that reach remission (12).

Aim: Effect's comparison of Sodim Valproate versus Lithium and Sodium Valproate versus Carbamazepine in long term treatment of patients with Bipolar Disorders.

Main Objective - clinical viewpoint: To measure the effect's difference between Sodium Valproate and Lithium Carbonate as well as between Sodium Valproate and Carbamazepine in long term treatment of patients with bipolar disorders. **Main Objective - statistical aspects:** To measure the survival time to relapse/recurrence between Sodium Valproate and Lithium Carbonate as well as between Sodium Valproate and Carbamazepine in long term treatment of patients with bipolar disorders. **Specific Objective**: a. To measure the survival time and reveal the difference of survival time to relapse/recurrence in long term treatment of bipolar patients with Sodium Valproate, Lithium Carbonate and Carbamazepine. b. To measure the mean and median time survival in long term treatment of bipolar patients with Sodium Valproate, Lithium Carbonate and Carbamazepine. **Null Hypothesis**: **Vp-Li:** There is no difference in the effect between Sodium Valproate and Lithium Carbonate; **Vp-Cbz:** There is no difference in the effect between Sodium Valproate and Carbamazepine. **Alternative Hypothesis: Vp-Li:** There is a difference in the effect between Sodium Valproate and Lithium Carbonate. **Vp-Cbz:** There is a difference in the effect between Sodium Valproate and Carbamazepine.

Method and Material

General Aspects

This is an open comparative and randomized longitudinal prospective clinical trial with parallel groups and a pre-randomized treatment phase. It was aimed to differentiate the effect of Sodium Valproate versus standard medications such as lithium carbonate and carbamazepine traditionally used in bipolar patients. This is a prospective study with three parallel comparison groups (each group n=60). The study was performed chronologically during September 2000 –June 2004. Patients were selected according to DSM-IV criteria for bipolar disorder and required a long-term treatment (n=235), both sexes, in age interval 19-65 years, presented to Psychiatric Service, Emergency Ward (UHC "Mother Teresa" Tirana). All of them with more than two mood episodes during the time prior to our study, and severity levels from moderate to severe according to standard rating scales CGI 4-7, GAF, HAMD-RS and MRS. All patients underwent a comprehensive psychiatric and physical examination to exclude all possible organic illness.

Inclusion criteria: Patients 19–65 years old, with classical bipolar I disorder (recent manic and depressive episode without psychotic features); non-classical bipolar I dpisorder (recent manic and depressive episode with psychotic features); bipolar I disorder mix-episode, bipolar I disorder rapid cycling type, bipolar II disorder with recent depressive episode or hypomania; bipolar II disorder rapid cycling type; bipolar I and II disorder with moderate to severe gravity, with at least two episodes (in order to require long-term treatment); with or without treatment prior to the study.

Exclusion criteria: patients with not otherwise specified bipolar disorder, mood disorder due to other medical conditions,

cyclothymic disorder, mild bipolar I and II disorders or in partial remission, and pregnant women or those during lactation period.

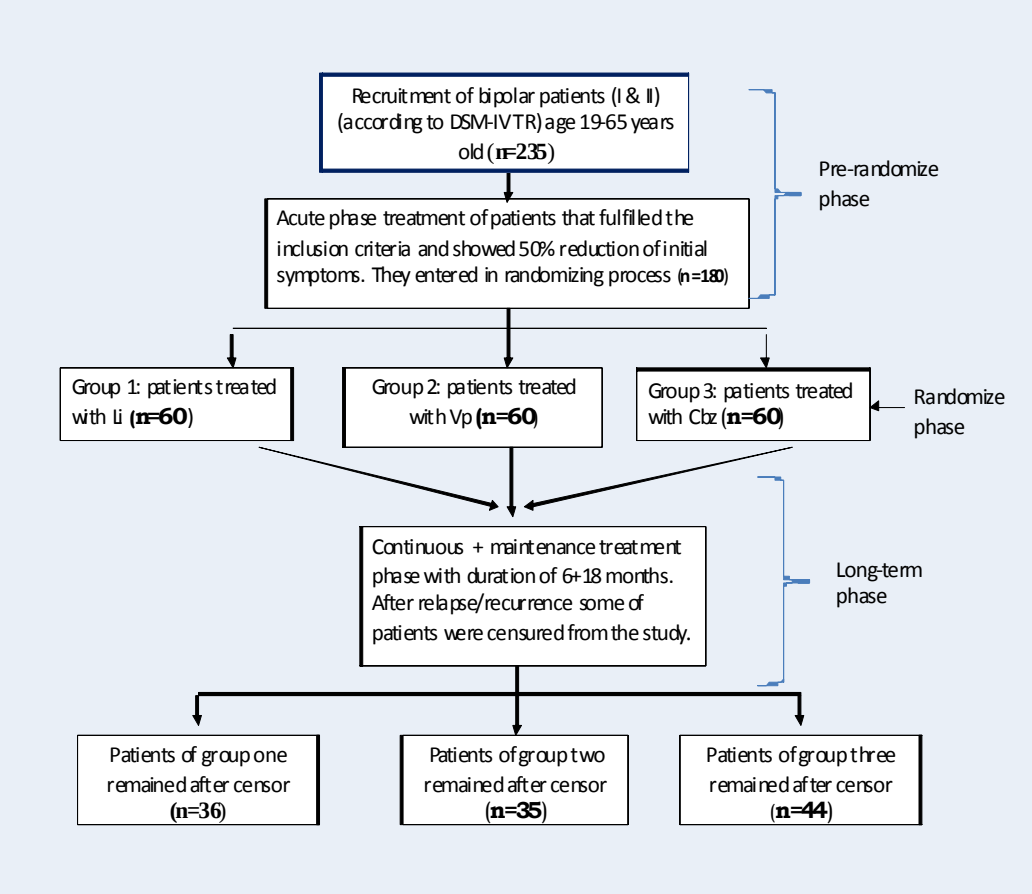


Fig.1. Flow chart of study methodology

Sample size of 180 patients is defined to assure a study power of ≥ 80% (α = 0,05) to reveal 20% absolute improvement (change) of survival to any relapse or recurrence (Fig.1).

Assessment during the *acute phase* is done every 2 weeks, using clinical evaluation and rating scales as follows: CGI – clinical global improvement and index of efficacy (13) GAF (14), HAMD (15) and MRS (16). All the patients that resulted with CGI efficacy index of 4-5 (cut-off) and CGI improvement of 2-3 (cut-off) entered to the next phase. The main treatment was one of the mood stabilizer Li, Cbz or Vp. Meanwhile the additional treatments were decided upon the type and the gravity of the episode and were used antipsychotics, antidepressants, anxiolytics or combo therapy. The doses were carefully attended based on local treatment guidelines and the drug plasmatic levels were carefully monitored. The duration of this phase was 2-8 weeks. If a patient resulted with CGI efficacy index of 4-5 (cut-off) and CGI improvement of 2-3 (cut-off) and 50% symptoms reduction were considered as potential case for randomization. From the initial total number of 235 patients (recruited during open phase) it resulted that 180 of them fulfilled the criteria to enter in randomizing process (158 with bipolar I disorder and 22 with bipolar II) (fig2). Even in this phase all of patients gave their written consent.

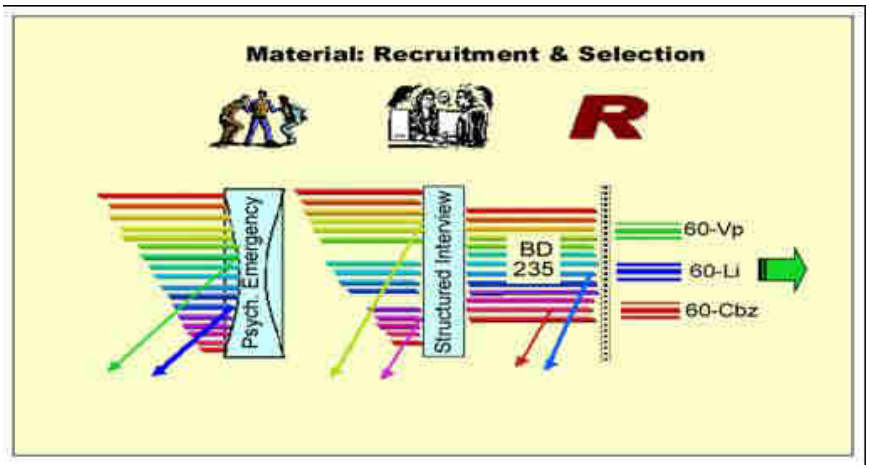


Fig. 2. Recruitment process and selection phases

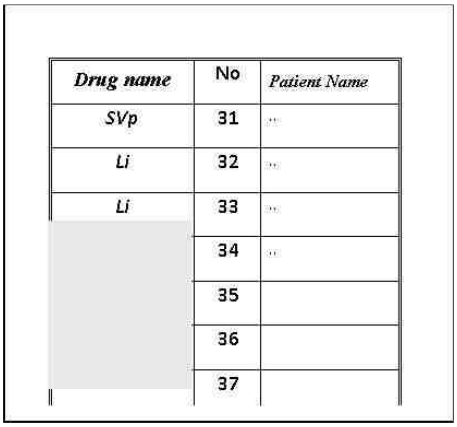
Randomization and Treatment Continuous Phase

Continuous treatment phase started when the positive response was achieved for all patients and it lasted 6 months. This was a crucial phase of the study as it implicates two fundamental moments of it: The initial time of the continuous phase, considered as the randomizing time which coincides with null time (t0). Assignment of randomized drugs in the study.

Randomizing criteria*:*

Inclusion criteria: patients that benefited from acute phase treatment; patients resulted with moderate gravity of mood episode and with assessment outcomes MRS >16, HAMD-RS>18, GAF<60, were directly randomized.

Exclusion criteria: patients that did not fulfill the criteria of a positive treatment response within 8 weeks; patients with physical illness or side effects during acute phase, patients that did not accept to continue the trial after the randomization (after learning the new drug that randomly happened to be his/her new treatment alternative).



Drug name	No	*Patient Name*
SVp	31	,,
Li	32	,,
Li	33	,,
	34	,,
	35	
	36	
	37	

Fig. 3 Randomized list with hidden drug name

Main treatments for the patients during the *long-term phase* (continuous + maintenance) included Vp, Li and Cbz. That phase lasted 24 months or 104 weeks since from the randomizing moment. *Continuous phase* of the treatment starts when is achieved the positive outcome from the acute phase and lasts till 6 months. During this phase, the

assessment is performed every 2 months. Patients that relapsed, discontinued the treatment or lost to follow-up were excluded from the study. *Maintenance phase* (prophylactic) extends from the end of continuous phase till the end of follow-up period, which lasted 18 months. The study phases are demonstrated graphically in fig.4.

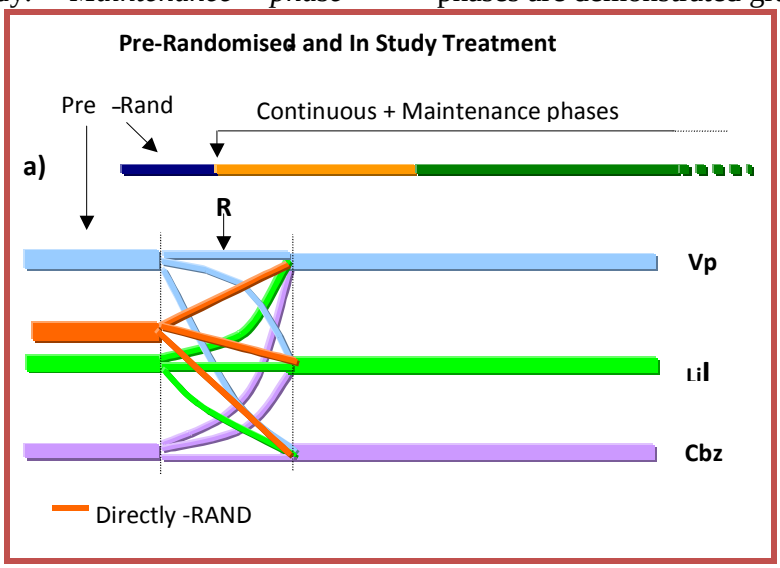


Fig .4 Treatment pre-and after randomized procedure

Statistical analysis

Survival analysis is the method used in this study. Survival analysis is generally defined as a set of methods for analyzing data where the outcome variable is the time until the occurrence of an event of interest (17, 18). In survival analysis, subjects are usually followed over a specified time period and the focus is on the time at which the event of interest occurs. Time-to-event is a clinical course duration variable for each subject having a beginning and an end anywhere along the time line of complete study (19, 20). The event of interest in our study is the time to relapse, recurrence or censure. Censure event is considered the time of second unregistered event (did not happened any new mood episode during the study period) [21, 22]. The results evaluation in survival analysis uses the Cumulative Probability of Survival also called the Survival Function (S(t)), in any time during the study as well as in median time which is time to survival for half of the sample. Results were expressed as mean ± standard deviation (SD). Data was analyzed using the IMB, SPSS statistics version 10. A p value <0.05 was considered as statistically significant. Results were expresses using Cumulative Survival: S(t); Standard Error]: Cumulative Events; Number Remaining.

Eligibility:

Genders eligible for study: Both

Safety: Patients were voluntary involved in the study. In this study, all the aspects related to safety are taken into consideration and are clearly included in patient's written consent.

Declaration of interest: None

Results:

Demographic characteristics of sample in the study were as follows: majority of the sample were females (55%), the age-group distribution in each of the groups is dominated by 25-45 years old.

The majority of the population was married. The education level and work position was distributed as follows (table 1).

Table 1. Demographic characteristics of population in study

Education Level	%	**Work position**	%
high school	57.8%	Unemployed	58.3%
college degree	11.1%	Employed	32.8%.

Clinical characteristics distribution of the population of 180 patients was as follows (table 2)

Table 2. Clinical characteristics for three groups in study

			Diagnosis						Total
			Classic BP-I	Non-Classic BP-I	Mix BP-I	Rapid Cycling BP-I	Type II BP	Rapid Cycling BP-II	
Treatment groups	CBZ	No	23	13	14	4	4	2	60
		% Total	12.8%	7.2%	7.8%	2.2%	2.2%	1.1%	33.3%
	LI	No	21	16	13	2	6	2	60
		% Total	11.7%	8.9%	7.2%	1.1%	3.3%	1.1%	33.3%
	DVP	No	20	13	13	6	7	1	60
		% Total	11.1%	7.2%	7.2%	3.3%	3.9%	.6%	33.3%
Totali		No	64	42	40	12	17	5	180
		% Totali	35.6%	23.3%	22.2%	6.7%	9.4%	2.8%	100.0%

The distribution of two major group diagnosis of bipolar disorder was classic bipolar disorder 36.1% and non-classic bipolar disorder 63.9%.

Table 3. Number of mood episodes in three groups in study

			Group-no Episode		Total
			2-5 episodes	> 5 episodes	
Treatment groups	CBZ	No	53	7	60
		% Total	29.4%	3.9%	33.3%
	LI	No	51	9	60
		% Total	28.3%	5.0%	33.3%
	DVP	No	47	13	60
		% Total	26.1%	7.2%	33.3%
Total		No	151	29	180
		% Total	83.9%	16.1%	100.0%

The patient's distribution for each group based on number of previous episodes was 83.9% those with 2-5 episodes and 16.1% with more than 5 episodes.

Co-morbidity was found in 34.4%, the presence of stressors was found in 56.7% of the sample.

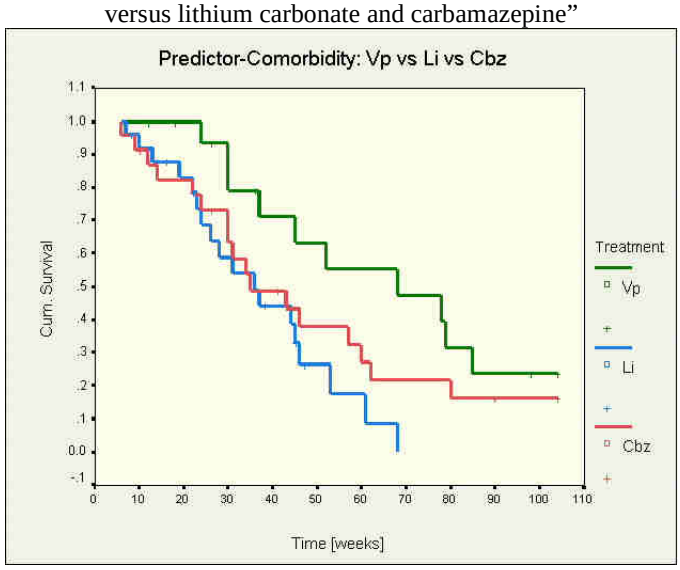


Fig. 5. Co-morbidities as predictor in three treatment groups

Survival analysis for the group in treatment with Cbz during follow-up time the time relapse/recurrence (in weeks) is showed in the table 4. For this group, total number of patient was 60, censored were 16 (26.67%) and events were encountered 44 times. The S(t) value and value of SE in 104-th week is calculated using interpolation method based on respective values in 80-th week and 90-th week.

Table 4. Mean and median time for three groups in study

		Time to survival	Standard Error	Confidence interval 95%
Cbz	**Mean:**	54	4	(47 - 62)
	Median	51	6	(40 - 62)
Li	**Mean:**	66	4	(57 - 75)
	Median	68	9	(51 - 85)
Vp	**Mean:**	73	4	(66 - 81)
	Median	79	9	(62 - 96)

Survival analysis for the group in treatment with Li during follow-up time the time relapse/recurrence (in weeks) is showed in the table 4. For this group, total number of patient was 60, censored were 24 (40.00%) and events were encountered 36 times. The S(t) value and value of SE in 104-th week is calculated using interpolation method based on respective values in 84-th week and 94-th week.

Survival analysis for the group in treatment with Vp during follow-up time the time relapse/recurrence (in weeks) is showed in the table 4. For this group, total number of patient was 60, censored were 25 (41.67%) and events were encountered 35 times. The S(t) value and value of SE in 104-th week is calculated using interpolation method based on respective values in 80-th week and 90-th week.

The comparison of survival time between three groups included in the study Vp-Li-Cbz clearly demonstrated the superiority of sodium valproate versus carbamazepine and a slight superiority versus lithium carbonate (Fig 6).

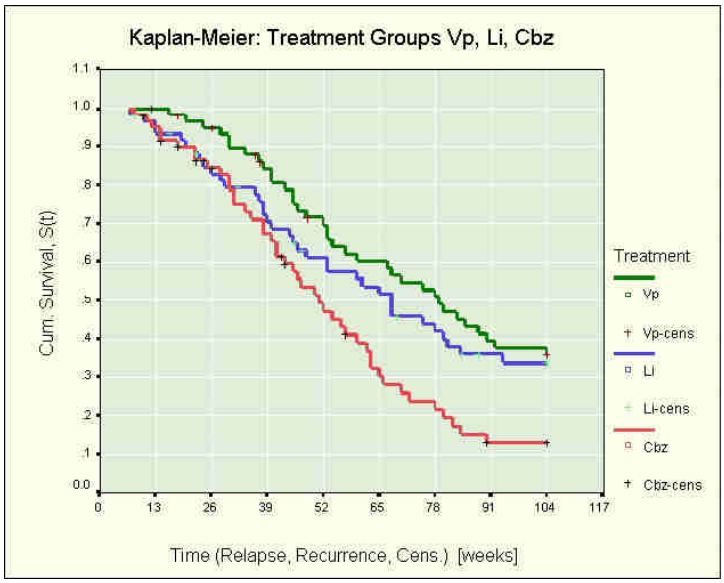


Fig 6. Time to relapse/recurrence/censored for three groups in study

Discussion

This is the first clinical study in our country that compares the effect of Vp versus Li e Cbz in long term treatment of bipolar disorder and among fewer studies found in literature that compares the effect of those three medications.

In prophylactic treatment with Cbz we found survival to relapse and/or recurrence 9.71%. In literature for the survival of patient treated with Cbz are described different times: Keck et al (2002) ≤ 25% in a year period [23], Hartong et al (2003) found a survival time in Cbz group 32% in two years period [24], Denicoff et al (1997) found a survival time in Cbz group 4% in a year period [25] and Solomon et al (2000] found 47% in a year period [39]. **The result of Solomon (47%) is in accordance with our result for the same time period (47, 13%, in 52nd week).**

The survival in two years for the group treated with Li was 31.36%; the mean time to survival was 66 weeks (SD=4) and the median time to survival was 68 weeks (SD=9). Solomon et al (2000) found a very interesting result for survival time that was 33% as a mean value of several clinical trials that used Li as maintenance therapy for 2 years. Our result of 31.36% resembles to the mean value resulted from many other studies. Based on this accordance we can deduct the integrity of our study.

Based on literature from the studies with a timeframe of one year we have found different survival results: around 40% from Bowden et al (2000), 30% from Tondo et al (1998) [31], 29% from Mc Manamy et al [26], 11% from Denicoff et al (1997), while our result in one year is 57% (52nd week, in survival table of treatment with Li or the point over the survival curve in 52nd week). The survival value found from our study is similar to that of Bowden et al (cited as a study with rigorous methodology and randomization) but is higher than survival results in a year from other studies [27]. Nevertheless, the low value of Denicoff' study (11% in a year period) it is referred the survival until the occurrence of relapse/recurrence only of manic episode (it uses different measures to the results) (40).

Regarding the survival in long term treatment with Vp, we found a survival to relapse/recurrence 35.7% in 2 years, with a mean time 73 weeks (DS=4), with median time 79 weeks (DS=6). After reviewing the literature, we found those results: Bowden et

al (2000) 41% in one year; Keck et al (2002) 25% in one year which are considered lower values compared with our results of 69.5%.

Difference in effect between groups:

Comparing the effects of group treated with Vp with group treated with Li we found a curious result: "there is no statistically significant difference on survival to relapse/recurrence between patients treated with Vp and Li", which is in accordance with the literature, e.g.; Lambert & Venaud (1992) [28], Solomon et al (1997) [29], Hirchfeld et al (1999) [30] and Bowden et al (2000) (Wilcoxon $\chi 2=3.54$, $p = 0.06$) [27]. The difference found in our study between Vp and Li groups is statistically insignificant ($p>0.05$). Li group has a hazard rate 20,4% higher than Vp group (Cox regression).

A similar difference in effect given in hazard rate was found in other studies 20% Lambert & Venaud (1992), 22% Bowden et al (2000) and 22% Macritchie et al (2002) [32] with a remarkable superiority of Vp versus Li. Based on similarity of those results, we are confident in accepting the assertion of other authors specially Lambert & Venaud and Bowden on the superiority of Valproate's effect versus Lithium in prophylactic treatment of bipolar spectrum disorders.

From the comparison of Vp-Cbz group and Li-Cbz group resulted a statistically significant difference as follows:

Vp-Cbz pair: survival time 26% higher for Vp ($p=0.0010$), with a mean time 35% and median time 53% higher for Vp, while hazard rate for patients treated with Cbz is 108,5% higher ($p=0.001$).

Li-Cbz pair: survival time 21,6% higher for Li ($p=0.0256$), with a mean time 22% and median time 30% higher for Li, while hazard rate for patients treated with Cbz is 64.7% higher ($p=0.028$).

This result is confirmed by verification of null hypothesis: Breslow and Log-rank, in comparison Li-Cbz: Breslow test is more sensitive for short period of time, but with no statistically significant difference ($p=0,121$), while the Long-rank test is more sensitive for longer periods of time, with a statistically significant difference ($p=0,025$). A similar result is found from McManamy [26], Post [34] and Grunze et al [35].

The superiority of Vp versus Li in bipolar I disorder (mixed episode) is confirmed from many studies Bowden et al (2000), Swann (1992) [36], Calabrese et al (2003) [33], Kusumakar et al (1997) [38].

Regarding the side effects that became reason for treatment discontinuation in each group we found that Li and Cbz had similar results respectively 10% and 11.7%, while Vp only 5%.

We found to have very few patients that discontinued treatment for other reasons that were 2.8% from the entire sample. Two of them from Cbz group discontinued the treatment during the 24^{th} and 26^{th} week as result of negative compliance, two others discontinued treatment during 37^{th} week from ovarian cysts, and one woman discontinued medication during 12^{th} week from pregnancy. Overall 2,8%(n=5) of the patients were lost from follow-up, three of them from Li group and each of two others from Vp group (in 18^{th} week) and Cbz group (in 57^{th} week).

Such results suggest that a considerable number of bipolar patients do not respond to treatment with lithium and a large proportion of bipolar patients with rapid cycling or classical bipolar illness are prone to Cbz resistance.

Conclusions

Sodium valproate is an effective mood stabilizer, with a good tolerability for long term treatment of bipolar patients. Sodium valproate has almost the same or slightly superior effect compared to lithium carbonate in long term treatment of bipolar disorders and superior to carbamazepine when used as monotherapy in long term treatment of bipolar disorders. Sodium valproate is superior to lithium carbonate in long term treatment of non-classical bipolar disorders (bipolar I mixed type, bipolar

rapid cycling and bipolar disorders associated with comorbidities.

Lithium carbonate is superior to sodium valproate and carbamazepine in long term treatment of classical bipolar disorder. Sodium valproate has got a tendency to be superior to lithium carbonate and carbamazepine in prevention of depressive episodes occurrence and has the same effect with lithium in prevention of mania/hypomania episodes. Carbamazepine after the first year of treatment is found to have a reduction of efficacy earlier than two other medicaments (Vp and Li).

We are confident in giving the recommendation that considering the whole of our results on the effectiveness of three drugs in study for bipolar disorder as follows:

- Sodium valproate and lithium carbonate are the first best choice in long treatment of bipolar disorder
- Carbamazepine is an alternative choice for the same therapeutic reasons.

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