

CLINICAL AND THERAPEUTICAL ASPECTS OF BIPOLAR DISORDER: THE SWITCH ON DEPAKINE CHRONO® FROM OTHER VALPROATE TREATMENTS – RETROSPECTIVE DATA COLLECTION

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Abstract

Bipolar disorder is one of the most frequent and severe psychiatric disorder. Sodium valproate proved its efficacy in both manic episodes treatment and in relapses prevention. The primary objective was the assessment of the reasons for switching from another form of valproate on Depakine Chrono® in current medical practice in patients with bipolar disorder (BPD). The study was an open-label, uncontrolled, non-randomized, multicenter, retrospective and non-interventional study. The clinicians included patients with BPD treated for at least 3 months with Depakine Chrono®, after switching from other forms of valproate medication. The main switch reasons from other valproate treatments to Depakine Chrono® in BPD patients were: efficacy in 82.6% of the cases, compliance in 68.4%, and adverse events in 53% of them, taken into account separately or in combination. The overall treatment outcome after 3 months of Depakine Chrono® treatment was a consistent improvement in terms of efficacy, adverse events and compliance. The results of this study are similar with data from the literature, though this retrospective research presents some limitations. Future directions for research are necessary in order to optimise the treatment of patients with BPD with or without associated co-morbidities.

Rezumat

Tulburarea bipolară este printre cele mai frecvente și severe afecțiuni psihice. Valproatul de sodiu și-a dovedit eficacitatea atât în episoadele maniacale, cât și în prevenirea recăderilor. Obiectivul primar al acestui studiu a fost evaluarea motivelor trecerii de la o altă formă de valproat la Depakine Chrono® în practica medicală curentă, la pacienții cu tulburare bipolară (TBP). Studiul a fost *open-label*, necontrolat, ne-randomizat, multicentric, retrospectiv și non-intervențional. Au fost incluși pacienți cu TBP tratați cel puțin 3 luni cu Depakine Chrono®, după schimbarea altor forme de valproat. Motivele principale ale utilizării Depakine Chrono® la pacienții cu TBP au fost: eficacitatea în 82,6% din cazuri, complianța la 68,4% și efectele adverse la 53% dintre pacienți, separate sau în combinație. Rezultatul după 3 luni de tratament cu Depakine Chrono® a fost o îmbunătățire considerabilă în ceea ce privește eficacitatea, efectele adverse și complianța. Rezultatele studiului prezentat sunt comparabile cu rezultate similare din literatură, deși această cercetare retrospectivă prezintă unele limitări. Sunt necesare noi direcții în cercetare, pentru optimizarea tratamentului pacienților cu TBP cu sau fără co-morbidități asociate.

Keywords: bipolar disorder, pharmacological therapy, valproate

Introduction

Bipolar disorder (BPD) represents one of the most severe psychiatric illnesses, which can significantly interfere with the overall functioning and, if improperly treated, has a negative impact on patients' life quality. Once diagnosed, it is extremely important to start and continue with the best treatment [1]. The treatment of bipolar disorder is a difficult challenge due to the recurrent, episodic, and heterogeneous nature of the disease [2, 3]. Among the main objectives, there are: the treatment of acute depression, of manic episodes, but also the prevention of the depressive or manic relapses [4, 5].

Valproate, a salt of valproic acid, is a well-established anti-epileptic medication also commonly used in the acute and chronic management of bipolar illness [6, 7]. Sodium valproate proved its efficacy in both manic episodes treatment and in relapses prevention, and is considered as a first line option, along with other mood stabilisers or antipsychotics [8, 9]. In bipolar disorder, valproate was studied almost exclusively as valproate hemisodium. Since there are relatively few studies available in the literature concerning the use of Depakine Chrono® in bipolar disorder, the present study intends to bring new data for clinicians.

Materials and Methods

This was an open-label, uncontrolled, non-randomized, multicentre, retrospective, and non-interventional study. The study took place between July 2007 and November 2009. The study population included male or female patients, over the age of 18 years old, diagnosed with bipolar disorder according to the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM IV) [10], treated for at least 3 months with Depakine Chrono[®] after switching from another treatment with valproate medication. The exclusion criteria were according to the Summary of Product Characteristics [11]. All the patients included have signed an informed consent prior their participation in the study. An ethical committee approved the study protocol, accordingly local regulations.

The primary objective of this study was the assessment of the reasons for switching from another form of valproate to Depakine Chrono[®] in current medical practice in patients with bipolar disorder, as well as the evaluation of the outcome of this switch, after 3 months of treatment with Depakine Chrono[®].

The secondary objective was the evaluation of the prescribed doses of Depakine Chrono[®] and associated medication in current medical practice.

Results and Discussion

A number of 1670 patients with BPD were included in this study. For these patients demographic data,

diagnosis of BPD, age at onset, presence of alcohol and substances co-morbidities, reasons for switch from other valproate treatments, dose regimen of Depakine Chrono[®] during the 3 months of treatment, concomitant therapies and switch outcome, were collected retrospectively. Descriptive statistics were used to analyse data and characterise the study results.

Demographic characteristics

In the study there were included 656 male patients and 997 female patients. The mean age of the patients was of 46 years in male, respectively 45 years in the female group. Almost 20% of the patients had other concomitant disorders or relevant medical history.

Diagnosis

Bipolar disorder type I was present in more than half of the patients (55.2%). Bipolar disorder type II was diagnosed in 27% of the total number of patients, while 61% from the group had cyclothymic disorder and 11.7% had bipolar disorder not otherwise specified (NOS).

Higher percentages of female patients were included in every diagnosis category.

Alcohol and substance abuse

We analysed the frequency of alcohol and substance abuse in each category. We observed that 10.1 % of males from the entire group and only 3.2% of females had concomitant alcohol abuse, while 1.9% of males and 2.8% of females had other substances abuse (different types of drugs) (Table I).

Table I

Frequency of alcohol abuse by diagnosis and gender

Diagnosis		Number of patients	Percentage %
Bipolar disorder I	Male	100	6.1%
	Female	29	1.8%
Bipolar disorder II	Male	43	2.6%
	Female	16	1.0%
Cyclothymic disorder	Male	14	0.8%
	Female	3	0.2%
Bipolar disorder NOS	Male	10	0.6%
	Female	4	0.2%
Total	Male	167	10.1%
	Female	52	3.2%
			13.3%

Almost 60% (58.9%) of the patients with co-morbid alcohol abuse were having the diagnosis of bipolar disorder type I, with similar percentages in male (59.9%) and female patients (55.8%). Regarding substance abuse, the highest percentage of patients presenting this co-morbidity was also registered in the bipolar disorder type I group - 62.0% of patients with substance abuse presenting BPD I - with a higher

percentage in the female category (63.0%), compared to male patients with bipolar disorder type I (59.4%). Regarding the overall alcohol and substance abuse, the percentage of patients with co-morbid alcohol abuse was almost three times higher than the one of patients with substance abuse: 13.3% had alcohol abuse *versus* 4.7% with substance abuse (Table II). The percentage of males with co-morbid alcohol abuse from the entire group was five times higher

than the one of females having the same co-morbidity (25.5% in males *versus* 5.2% in females). In terms of substance abuse, similar percentages

were observed in both gender categories (4.9% from all male patients and 4.6% from all female patients).

Table II

Frequency of substance abuse by diagnosis and gender

Diagnosis		Number	Percentage %
Bipolar disorder I	Male	19	1.2%
	Female	29	1.8%
Bipolar disorder II	Male	5	0.3%
	Female	10	0.6%
Cyclothymic disorder	Male	4	0.2%
	Female	4	0.2%
Bipolar disorder NOS	Male	4	0.2%
	Female	3	0.2%
Total	Male	32	1.9%
	Female	46	2.8%
			4.7%

Table III

History (number of years) of bipolar disorder before enrolment

Diagnosis	Age of onset of bipolar disorders	Number	Percentage %
Bipolar disorder I	< 1 year	41	2.5%
	> 5 years	526	31.8%
	1-5 years	302	18.3%
	Unspecified	43	2.6%
Bipolar disorder II	< 1 year	16	2.0%
	> 5 years	229	13.9%
	1-5 years	181	11.0%
	Unspecified	20	1.2%
Cyclothymic disorder	< 1 year	16	1.0%
	> 5 years	47	2.8%
	1-5 years	35	2.1%
	Unspecified	3	0.2%
Bipolar disorder NOS	< 1 year	7	0.5%
	> 5 years	96	5.8%
	1-5 years	85	5.1%
	Unspecified	6	0.3%
Total	< 1 year	80	4.9%
	> 5 years	898	54.3%
	1-5 years	603	36.5%
	Unspecified	72	4.4%

Regarding the number of years from the onset of bipolar disorder since the inclusion in this study, there are some differences between the four diagnosis categories. In bipolar disorder I the average of disease before enrolment was about 11 years, in bipolar disorder II and bipolar disorder NOS the average was approximately 9.5 years, similar in both groups. Regarding cyclothymic disorder, the average number of years before inclusion in this study was approximately eight.

There were no differences between genders, in each diagnosis category. The highest percentage in each diagnosis category was observed in patients diagnosed with bipolar disorder for more than 5 years before inclusion in this study, while the lowest percentages were registered in patients who had the disorder for less than one year, at enrolment (Table III).

Age of onset

Up to 90 percent of bipolar disorder patients were diagnosed before the age of 20, although the illness

may start in early childhood or as late as in the 40's and 50's. An equal number of men and women develop bipolar disorder and it could be found in all ages, race, ethnic groups and social classes [4].

The mean age of bipolar disorder onset was evaluated during this study. As seen in Table IV, the total mean age of the patients when they received their first diagnosis was of 36.24 years for

males and of 35.28 years for females. The analysis also showed that bipolar disorder I installed approximately two years earlier in the female sub-group, while the onset of cyclothymic disorder and bipolar disorder NOS was approximately two years earlier in the male sub-group. No major differences between mean age of onset of bipolar disorder II, in both male and female sub-group were observed.

Table IV

Diagnosis	Gender	Mean age of bipolar disorder onset
		Mean (years)
Bipolar disorder I	Male	35.65
	Female	33.21
Bipolar disorder II	Male	37.44
	Female	37.58
Cyclothymic disorder	Male	37.80
	Female	39.83
Bipolar disorder NOS	Male	35.47
	Female	37.89
Total	Male	36.24
	Female	35.28

Table V

Patients' mood at the switch moment to Depakine Chrono®

	Depressive (%)	Euthymic (%)	With rapid cycles (%)	Dysphoric mania (%)	Euphoric mania (%)	Hypomania (%)
Bipolar disorder I	30.3	5.6	3.9	24.4	21.0	14.9
Bipolar disorder II	52.2	2.7	4.7	11.9	9.2	19.3
Cyclothymic disorder	39.6	0.0	20.8	6.9	13.9	18.8
Bipolar disorder NOS	42.6	6.2	8.2	21.5	7.7	13.8

Patients' mood at the switching moment to Depakine Chrono® from another mood stabiliser was assessed. As seen in Table V, the highest percentages were registered in patients presenting depressive mood in the moment of the mood stabiliser switch, in all four diagnosis categories. Almost one third of the patients with bipolar disorder type I presented depressive mood, more than a half of those diagnosed with bipolar disorder type II had depression, while similar percentages of patients (approximately 40%) with cyclothymic and bipolar

disorder NOS presented the same mood. Table VI shows the main reasons of switching to Depakine Chrono® from another mood stabiliser, in the four diagnosis categories. More than 40% of all patients had switched due to compliance, adverse effects and efficacy reason all together. A percentage of 20% of all patients, switched to Depakine Chrono® due to efficacy alone, while lower percentage was registered in patients whose reason for switching was compliance (7.7%) or adverse effects (6.4%).

Table VI

Reason for switching to Depakine Chrono® on each diagnosis category

Reason for changing treatment	Diagnosis				Total
	Bipolar disorder I	Bipolar disorder II	Cyclothymic disorder	Bipolar disorder NOS	
Compliance	5.2%	1.5%	0.2%	0.7%	7.7%
Adverse effects	3.9%	1.4%	0.1%	0.9%	6.4%
Efficacy	11.7%	4.6%	0.5%	3.5%	20.2%
Compliance and adverse effects	0.6%	0.7%	0.0%	0.1%	1.4%
Compliance and efficacy	8.9%	5.7%	1.0%	1.9%	17.5%
Compliance, adverse effects and efficacy	22.6%	12.5%	4.1%	4.6%	43.8%
Efficacy and adverse effects	1.9%	0.6%	0.2%	0.3%	3.0%

Total	54.9%	27.0%	6.2%	12.0%	100.0%
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Figures below describe the main reasons for switching from another mood stabiliser to Depakine Chrono[®], in each diagnosis category. Compliance, adverse effects and efficacy all together were by far the most common reasons for switching in all four categories, with percentages ranging from 38% in bipolar disorder NOS and 66% in cyclothymic disorder.

Efficacy alone was another important reason for treatment changing, being the second reason in patients with bipolar disorder I and bipolar disorder NOS, and the third reason in bipolar disorder type II and cyclothymic disorder. Compliance and efficacy together were also of great importance when changing the current treatment in all bipolar disorders observed (Figure 1).

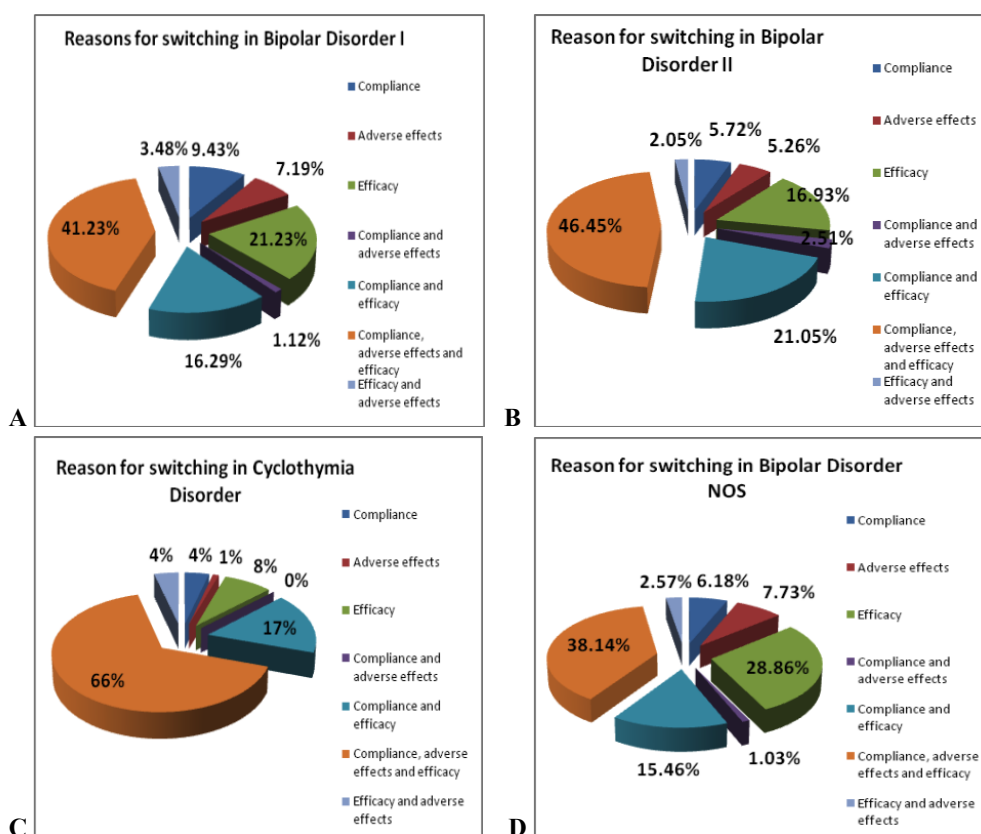


Figure 1.

Reasons for treatment change to Depakine Chrono[®] by the type of illness (A. Bipolar Disorder I; B. Bipolar Disorder II; C. Cyclothymic Disorder; D. Bipolar Disorder NOS)

Patients were treated with different doses of Depakine Chrono[®], depending on their status at the time of the treatment switch. The doses ranged from 150mg/day to 2000 mg/day. Lower doses of Depakine Chrono[®] were prescribed for patients with cyclothymic and bipolar II disorders, while the highest daily doses were used for the treatment of the patients with bipolar disorder type I.

Table VII

Mean doses mg/day of Depakine Chrono[®] prescribed for patients taken into study

	Mean	N	Std. Deviation
Baseline	1042.45	1669	411.950
End of study	1032.86	1669	411.990

The mean dose of Depakine Chrono[®] decreased during the 3 months of treatment period, from 1042.45 mg to 1032.86 mg, while the daily intakes number remained almost unchanged (around 15% of the patients once, 65% twice and 18% three-times daily).

In this study, different associations between Depakine Chrono[®] and other psychotropics were analysed. Clinicians used associations between Depakine Chrono[®] and antipsychotics (typical and atypical), antidepressants, anxiolytics, hypnotics, or other mood stabilisers. The most common associations were: olanzapine (N = 316), quetiapine (N = 199), amisulpride (N = 199), risperidone (N = 59), sertraline (N = 39) and escitalopram (N = 35).

Most of the patients were much or moderately improved after the 3 months of treatment with

Depakine Chrono[®] with respect to the main reasons of changing other valproate treatment (Table VIII).

Table VIII

Switch outcome-efficacy, compliance and adverse events (N = 1670)

	Efficacy		Compliance		Adverse events	
	Number of patients	Percentage %	Number of patients	Percentage %	Number of patients	Percentage %
Much improved	1166	69.8	887	53.1	604	36.2
Moderately improved	194	11.6	191	11.4	183	11.0
Unchanged	19	1.1	64	3.8	98	5.9
Minimally worse	1	.1	1	.1	1	.1
Total	1380	82.6	1143	68.4	886	53.1

The results of the study offer descriptive information about the patients included. More than half of the patients presented bipolar disorder type I, while smaller percentages from the group had cyclothymic disorder and bipolar disorder NOS.

Approximately 10% of males from the entire group and only 3% of females had concomitant alcohol abuse, while even lower percentage had substance abuse, in both gender categories. Regarding the overall alcohol and substance abuse, the percentage of patients with co-morbid alcohol abuse was almost three times higher than the one of patients with substance abuse. The percentage of males with co-morbid alcohol abuse from the entire group was five times higher than the one of females having the same co-morbidity.

The main switch reasons from other valproate treatments to Depakine Chrono[®] in BPD patients were: efficacy in 82.6% of the cases, compliance in 68.4% and adverse events in 53% of them, taken into account separately or in combinations. After 3 months of Depakine Chrono[®] treatment, the improvement in terms of efficacy, adverse events and compliance was higher or moderate.

Moreover and, most probably, related to the improved efficacy, compliance and tolerability, the mean daily dose of Depakine Chrono[®] was decreased significantly by the physicians during the 3 months of the treatment period.

Conclusions

The findings of our research are comparable with the results from literature, mainly regarding the relationship of bipolar disorders with alcohol and substance abuse, being known the fact that bipolar disorder is frequently associated with a high risk of comorbidities, such as substance abuse, personality disorders, anxious disorders or eating disorders [12].

There are some aspects of this study (such as the fact that it was uncontrolled, non-randomized, retrospective and non-interventional, along with the absence of specific rating scales in the assessment of the efficacy of Depakine Chrono[®]) that limit its results. Future directions for research are necessary in order to optimise the treatment of the patients with bipolar disorders with or without associated co-morbidities.

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