GABAPENTIN (GBP) VERSUS VALPROATE (VPA) AS AN ADJUNCT TO NEUROLEPTICS IN THE TREATMENT OF ACUTE MANIC SYMPTOMS

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INTRODUCTION

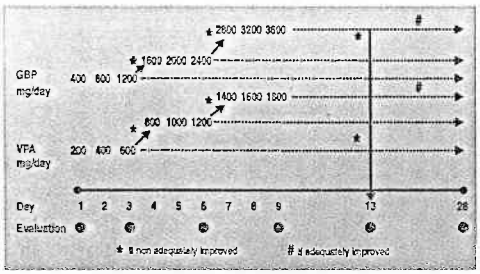
GBP is an anticonvulsant marketed as add-on therapy for partial epilepsy. Soon after GBP introduction in the USA market, a few reports of its use as an add-on anti-manic or mood stabilizer agent were published. GBP resulted effective in reducing manic symptoms in a percentage of patients varying between 64 and 78%, at doses as high as 4800 mg/day, but generally below 3600 mg/day. Interestingly, this action was evident in the first 1-4 weeks of therapy and was associated to few and mild side effects, like somnolence, short-term memory disturbances and ataxia, which tended to spontaneously resolve reducing the dose or within a few days of therapy. The published reports yielded promising results, but the interpretation of the therapeutic role of GBP in mania was difficult because the drug was always associated to a wide range of other agents, whose dose was not maintained unchanged during the study. The objective of our study was to assess the efficacy and safety of GBP versus VPA in adjunct to a fixed dose of neuroleptics (NL) in patients hospitalized because of an outburst of acute manic symptoms.

METHODS

This was an open-label, comparative study of GBP versus VPA, in add-on to NL, in patients with acute manic symptoms.

Study Design

Patients hospitalized for acute manic symptoms were evaluated for eligibility and randomly assigned to receive GBP or VPA in adjunct to a fixed dose of NL. GBP was titrated in three days to 1200 mg/day and VPA to 600 mg/day. If the patient had not achieved a satisfactory response, the dose could be increased up to a maximum of GBP 3600 mg/day or VPA 1800 mg/day. Patients with a good response were dismissed from hospital on day 13, with a schedule for NL tapering.



Inclusion Criteria

- Gender: Males and females
- Age: > 18 years
- Diagnosis: Bipolar Disorder, Schizo-affective Disorder, Schizophrenia
- Symptoms at entry: Mean score of the BPRS Items No. 6, 21 and 23 between 5 and 7
- Informed consent

Exclusion Criteria

- Medications: Current lithium therapy, Previous use of GBP or valproate
- Other diseases: Renal insufficiency, Chronic active hepatitis

Evaluation criteria

Principal efficacy criterion:

- Decrease in the score at the three BPRS items considered for inclusion.

Secondary efficacy criteria:

- Responder rate = % of patients with a mean score of the three items ≤ 2
- Total BPRS score at the end of the visit versus baseline
- Score at the subsets of BPRS rating psychotic (items 6, 9, 10, 11, 12, 13, 14, 15, 24), neurotic (items 1, 2, 19, 20), depressive (items 3, 4, 5, 16, 17, 18), and manic (items 7, 8, 21, 22, 23) symptoms
- Time to improve.

Safety criteria:

- Side effects were collected at every visit.

Concomitant NL therapy

A standard NL therapy was given to all the patients at the time of hospitalization. The preferred NL used was Haloperidol, at a dose of 0.14 mg/kg/day.
At day 13, if a marked improvement in manic symptoms was observed, the patients was dismissed from hospital and it was instructed to gradually halve the dose of NL in the two following weeks.

RESULTS

Twenty-four patients were enrolled, twelve in each group, and all terminated the study.

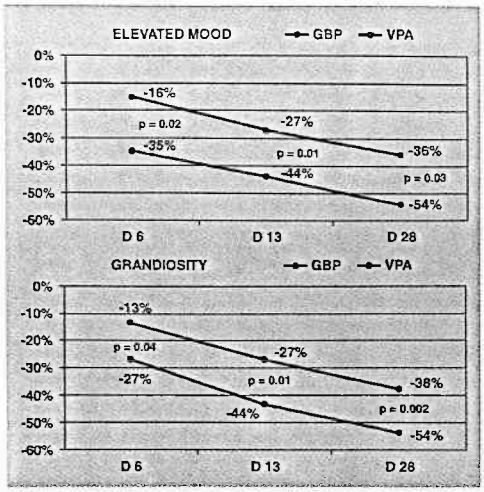
Demographics and baseline patients characteristics

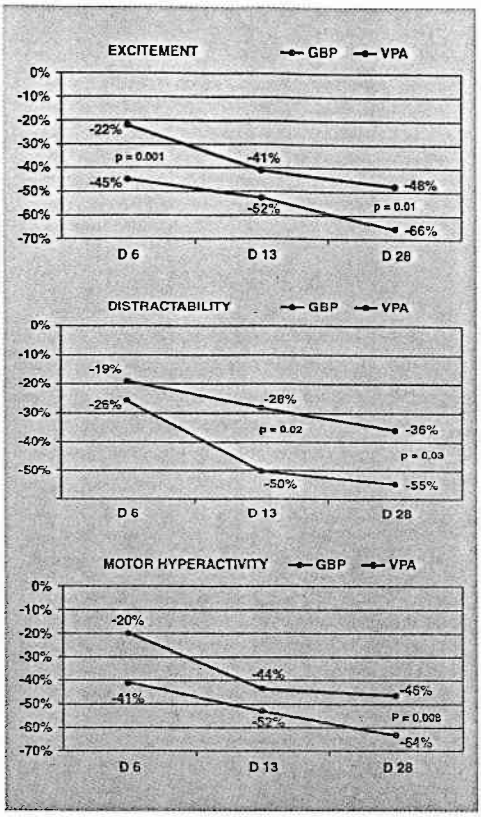
CHARACTERISTIC	GBP GROUP (N = 12)	VPA GROUP (N = 12)	P VALUE
Sex			
• Male	8	4	NS
• Female	4	8	
Age (mean ± SD)	46.5 ± 14.7	43.3 ± 14.9	NS
Diagnosis (DSM IV code)			
• Bipolar Disorder (296.40)	5	6	
• Schizoaffective Disorder (295.70)	6	4	NS
• Schizophrenia (295)	1	2	
BPRS			
• Total Score (mean ± SD)	80.2 ± 12.4	85.8 ± 8.7	NS
• Items 6 ,21, 23 (mean)	5.6	5.4	NS
• Psychotic subset (mean)	3.1	3.6	NS
• Neurotic subset (mean)	4.1	4.3	NS
• Depressive subset (mean)	1.6	2.1	NS
• Manic subset (mean)	5.2	4.9	NS

Efficacy

CHARACTERISTIC	GBP GROUP (N = 6)	VPA GROUP (N = 6)	P VALUE
Dose mg/day (mean ± SD)	1500 ± 542.7	900 ± 328.6	
Dose to improve:			
· Minimal (no increase) (No. pts)	9	7	NS
· Need to increase	3	5	
Responders at last visit (N and %)			
· yes	7 (58.3)	1 (8.3)	0.03
· no	5 (41.7)	11 (91.7)	
Mean decrease in score at BPRS 6, 21, 23 items (value and %)	-3.6 ± 1.0 (64.5)	-2.6 ± 0.6 (48.4)	0.01
Mean decrease in total BPRS score (value and %)	-41.3 ± 16.0 (50.5)	-30.2 ± 5 (35.4)	0.04
Mean decrease in psychotic subset (value and %)	-1.5 ± 0.7 (47.2)	-1.3 ± 0.3 (36.5)	NS
Mean decrease in neurotic subset (value and %)	-2.3 ± 0.9 (53.9)	-1.5 ± 0.5 (35.4)	0.03
Mean decrease in depressive subset (value and %)	-0.4 ± 0.6 (18.0)	-0.4 ± 0.5 (15.9)	NS
Mean decrease in manic subset (value and %)	-3.1 ± 0.8 (59.5)	-2.0 ± 0.4 (41.6)	0.02

Decrease over time in the single manic subset items





All five items of the BPRS manic subset decreased significantly more in the GBP group than in the VPA group.

Tolerability

A total of 9 side effects were reported by 5 patients in the GBP group and 14 side effects by 7 patients in VPA group. The table lists the side effects in the different groups.

	GBP	VPA
• **Sedation**	3	4
• **Hypersomnia**	2	3
• **Ataxia**	1	3
• **Nausea**	1	2
• **Hypotension**	2	2

CONCLUSIONS

In this study, GBP and VPA were both effective in controlling symptoms of acute mania, when added to a standard dose of NL.
In GBP group the time to reach a satisfactory improvement was shorter, and the mean decrease in BPRS score, both total score and the score of 2 (neurotic and manic) of the 4 subsets measuring different symptomatological dimensions, was significantly greater than in VPA group.
These data must be considered with great caution and every definite conclusion about a difference between the two drugs is not possible because of the small sample of patients, however it is interesting that all the scores variations were in the same direction and tended to indicate a superiority of GBP over VPA.
This open label study, which is the first to compare GBP and [illegible] litions, conf [illegible] anage-men [illegible]

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