EFFICACY AND TOLERABILITY OF GABAPENTIN (GBP) VERSUS VALPROATE (VPA) AS ADD-ON THERAPY 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.

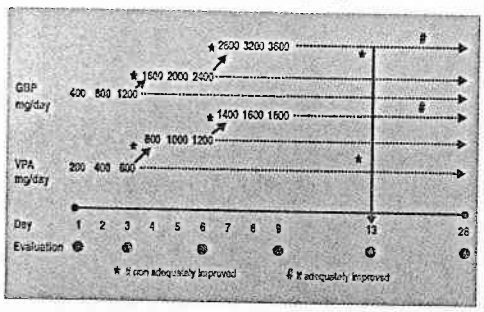
The published reports yielded promising results, but the interpretation of the therapeutic role of GBP in mania was difficult because the drug was always associated to a wide range of other agents, whose dose was not maintained unchanged during the study. The objective of our study was to assess the 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 vas 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, Schizoaffective 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

Twelve patients were enrolled, six in each group, and all terminated the study.

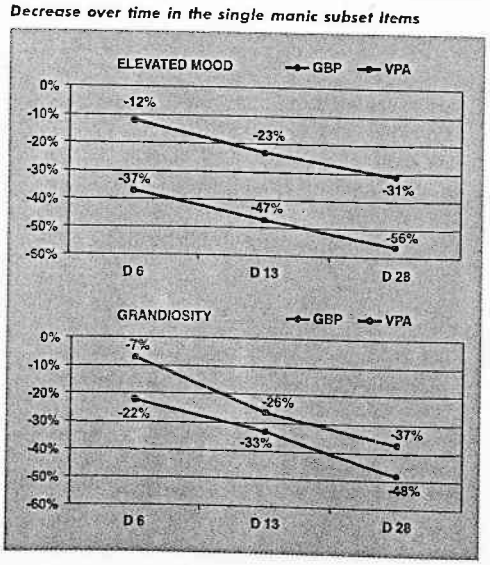
Demographics

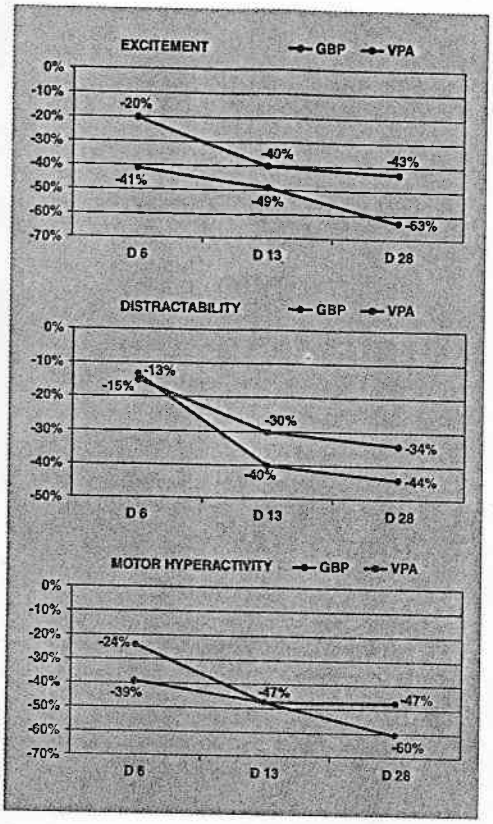
CHARACTERISTIC	GBP GROUP (N = 6)	VPA GROUP (N = 6)	P VALUE
Sex			
• Male	5	1	NS
• Female	1	5	
Age (mean ± SD)	43.0 ± 14.1	43.2 ± 14.9	NS
Diagnosis (DSM IV code)			
• Bipolar Disorder (296.40)	1	2	NS
• Schizoaffective Disorder (295.70)	4	2	
• Schizophrenia (295)	1	2	

Efficacy

CHARACTERISTIC	GBP GROUP (N = 6)	VPA GROUP (N = 6)	P VALUE
Dose mg/day (mean ± SD)	1400 ± 489.9	900 ± 328.6	
Dose to improve:			
• Minimal (no increase) (No. pts)	5	3	NS
• Need to increase	1	3	
Time to improve			
• 3 days	5	3	NS
• 6 days	1	3	
Responders at last visit (N and %)			
• yes	3 (50.0)	1 (16.7)	NS
• no	3 (50.0)	5 (83.3)	
Score at BPRS 6, 21, 23 items Mean decrease ± SD (%)	−3.3 ± 0.8 (61.5)	−2.6 ± 0.8 (47.9)	NS
Total BPRS score Mean decrease ± SD (%)	−34.8 ± 12.5 (45.0)	−29.7 ± 6.1 (34.8)	NS
Psychotic subset Mean decrease ± SD (%)	−1.3 ± 0.5 (41.7)	−1.2 ± 0.2 (35.9)	NS
Neurotic subset Mean decrease ± SD (%)	−2.3 ± 1.1 (51.6)	−1.5 ± 0.6 (35.2)	NS
Depressive subset Mean decrease ± SD (%)	−0.1 ± 0.5 (0.6)	−0.6 ± 0.5 (24.1)	NS
Manic subset Mean decrease ± SD (%)	−2.7 ± 0.5 (55.6)	−1.9 ± 0.6 (38.4)	0.03

Decrease over time in the single manic subset items





Tolerability

Two patients in the GBP group and 4 patients in VPA group reported side effects.

GBP

- Somnolence
- Somnolence and ataxia

VPA

- Somnolence, nausea, ataxia
- Ataxia, nausea, hypotension
- Somnolence
- Somnolence and ataxia.

CONCLUSIONS

In this study, GBP and VPA were equally effective in controlling 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 the 4 subsets measuring different symptomatologic dimensions, was slightly greater than in VPA group. However there was no statistically significant difference between groups, apart from the decrease in the subset of BPRS scoring manic symptoms.

When analysing the score of the five items of the manic subset over time, *"Elevated Mood"* and *"Excitement"* items decreased more substantially and more rapidly in the GBP group than in the VPA group, suggesting a prompter action of the drug on these symptoms. Also the *"Motor Hyperactivity"* item was at the limit of significance, in favour of GBP.

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 score 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 VPA under controlled and standardised conditions, confirms that GBP has a therapeutic role in the management of the acutely manic patients.