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ORIGINAL PAPER

Adjunctive valproate in panic disorder patients with comorbid bipolar disorder or otherwise resistant to standard antidepressants: a 3-year "open" follow-up study

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Abstract The aim of the study was to report on the clinical utility of naturalistic adjunctive treatment with valproate (VPA) in a group of panic disorder (PD) patients with comorbid bipolar disorder (BD) or otherwise resistant to antidepressants. The hypothesis was that these patients might not respond because of coexisting low-grade mood instability and adjunctive VPA treatment might ameliorate PD symptoms. A group of 47 patients with lifetime comorbid BD ($n = 35$, 74.5%) or otherwise resistant to antidepressants ($n = 12$, 25.6%), from a population of 326 consecutive outpatients with PD-Agoraphobia evaluated and treated at the Psychiatric Institute of the University of Pisa from 1991 to 1995, and followed for a period of 3 years. All patients were evaluated at baseline and at least every 2 months by means of an intensive interview including semi-structured and structured instruments (SCID, Life-Up, and Panic Disorder/Agoraphobia Interview). Mean dosage was 687 (SD = 234) mg/day (min 400, max 1,500 mg/day). Adjunctive treatment with VPA was well tolerated by all subjects, and there was no treatment interruption because of side effects or adverse events. All antidepressants-resistant subjects and 31 of 35 (88.6%) patients with bipolar comorbidity achieved symptomatological remission. During the observation period, 7 (58.3%) among resistant subjects and 17 (48.6%) of bipolar patients had a relapse of panic disorder after remission. Survival analysis of remission durations and onset relapses for PD and Agoraphobia did not show significant differences between the two groups. Relapses of Agoraphobia were less frequent and more delayed than those for panic. According to the results, VPA seems to be an effective and a well-tolerated adjunctive treatment in PD patients who were resistant to antidepressant therapy or had BD in comorbidity. The results of the study support the hypothesis of resistance to antidepressant treatment being related to mood instability.

Keywords Valproate · Resistant panic disorder · Comorbid panic disorder

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Introduction

Clinical studies of patients with panic disorder (PD) report comorbidity rates of bipolar disorder (BD) varying from 13 to 23% [1–4], while among bipolar subjects PD shows prevalence rates ranging from 10 to 80% [4–9]. Several studies have suggested that BD and PD may share the same familial and genetic basis [10]. A follow-up study [10] has found a high prevalence of PD in 57 families with high rates of BD. Only the families with high risk for PD showed a linkage with markers on the long arm of chromosome 18. In a study on first-degree relatives ($n = 966$)

of probands with BD type I ($N = 192$) and schizoaffective disorder, bipolar type ($N = 11$), the same authors [11] found that 90% of subjects with PD also had a mood disorder; moreover, PD occurred in 17% of relatives with recurrent mood disorders, versus 3% of relatives without mood disorders. These data support the hypothesis that BD is a risk factor for PD, and PD may be an index of genetic heterogeneity in BD; it is also likely that PD in bipolar families may represent an alternative expression of BD.

Patients with BD and comorbid PD typically have a more severe symptomatology with an early onset and higher risk for somatic disorders as well as higher rates of mixed states and suicidality [4–9]. As for treatment response, a history of panic attacks in BD patients appears to be associated with poorer outcome for BD [12, 13], which would require the use of multiple drugs [12].

No information is available on the influence of BD comorbidity on the course and the treatment response of PD. Anxiety disorders are routinely treated with antidepressants, which not infrequently trigger hypomanic or mixed episodes in subjects with a bipolar diathesis [13–16]; on the other hand, the administration of some antimanic agents, especially typical [17, 18] and atypical [19, 20] antipsychotics, may worsen phobic-anxious symptoms.

Because of the wide clinical overlap and frequent comorbidity between PD and BD, the treatment of PD with anticonvulsants has been proposed, especially in resistant cases to standard treatments [21, 22].

Valproate (VPA) is the most studied anticonvulsant in anxiety disorders. Roy-Byrne [26] reported on a patient with panic attacks and non-specific EEG anomalies in left temporal lobe; VPA was effective during a one-year follow-up. Subsequently, an open 7-week study of VPA in 10 PD patients [23] showed a statistically significant improvement evaluated by the Clinical Global Impression Scale (CGIS), the Hamilton Anxiety Rating Scale (HARS), and the Hopkin's Symptom Checklist-90 scores. VPA was used at a maximum dosage of 2,250 mg/day and significant improvement was observed especially with regard to panic attacks and anticipatory anxiety, whereas phobic anxiety did not show significant variations. This study suggests that PD is likely a heterogeneous disorder within which there is a subpopulation of patients that might be responsive to VPA.

The only double-blind, placebo-controlled study of VPA [24] was done on 12 PD patients who had interrupted benzodiazepine treatment; after a 6-week trial, all patients reported a significant improvement at the CGI severity and improvement in the frequency and severity of panic attacks and in all somatic and psychic anxiety scores. In a 6-week open study [25], VPA was administered at a mean dosage of 1,130 mg/day to 12 PD patients, and a moderate improvement of the number of panic attacks and of general anxiety levels in 3 subjects and marked improvement in 9 patients was observed. The drug was well tolerated and in no case treatment interruption was necessary because of side effects. The improvement appeared to be maintained in an extension of the study to 6 and to 18 months. Keck et al. [29] have also reported on 16 patients with PD treated with VPA a reduction of 50% of panic attacks and a significant reduction of generalized anxiety in 10 patients, whereas 6 reached full remission.

Efficacy of VPA has also been tested in the prevention of panic attacks after infusion of sodium lactate in "sensitive" subjects. VPA was able to block lactate induction of panic attacks in 10 patients out of 12; moreover, 71% of subjects showed a reduction of the weekly frequency of panic attacks greater than 50%, and 43% of patients had a full remission of anxious symptoms [26]. Finally, VPA was effective in an open observation on 13 patients with panic attacks that were associated to frequent mood swings of both polarities and were refractory to standard treatments [27].

The aim of the present study is to report on the clinical utility of VPA in PD patients with comorbid BD or otherwise resistant to antidepressants.

Method

Hypothesis

In the present study, we have analyzed the data concerning the naturalistic adjunctive treatment with VPA in a group of outpatients with PD and lifetime comorbid BD—but in remission at the moment of the enrollment—or who had not responded to standard treatment with antidepressants after a period ranging from 8 to 12 weeks. Our starting hypothesis, based on the available literature and the preliminary clinical experience, was that these patients might not respond because of coexisting mood instability. Instability of mood may be low grade or "subclinical", which corresponds to the symptomatological pattern defined as "soft" bipolar spectrum [28]. The cooccurrence of mood instability may indeed worsen PD and induce resistance to antidepressants.

Patients

The sample comprised 47 subjects from a population of 326 consecutive outpatients with PD-Agoraphobia evaluated and treated at the Psychiatric Institute of the University of Pisa from 1991 to 1995, and followed for a period of 3 years. All patients received open adjunctive VPA in combination with antidepressants; 35 (74.5%) had lifetime comorbid BD, type II, according to DSM-III R criteria and 12 (25.6%) had not responded to antidepressant therapy.

PD-Agoraphobia represented the main diagnosis for all patients and the primary reason for which they sought help at our outpatient department. At the moment of the inclusion in the study, none of the 35 patients with comorbid BD, type II, were suffering from major depressive episode or hypomania and none of them met criteria for rapid cycling or mixed state. In all these patients, the course and the severity of the PD-agoraphobic symptomatology seemed to be independent from the presence of major mood episodes.

The mean age of our sample at the time of admission into the study was 34.1 (SD 11.2), and 61.7% of patients were females ($n = 29$); Agoraphobia was present in 39 subjects (83.0%). Mean age at onset, duration of illness, severity of PD and of Agoraphobia, impairment of general adaptation, and the frequency of other comorbid anxiety disorders and alcohol abuse are reported in Table 1.

This study is one of the research protocols from the Pisa-San Diego Collaborative Clinical Research Program on the long-term characteristics of mood and anxiety disorders. Inclusion criteria for the present protocol were as follows: (1) a history of spontaneous panic attacks; (2) a diagnosis of PD with or without Agoraphobia according to DSM-III-R criteria; (3) absence of severe physical and laboratory abnormalities; (4) absence of current psychotic disorders (last 6 months). All patients gave informed consent for their participation in the study.

All patients were evaluated by the senior Italian psychiatrists on the project (GP and CT) in face-to-face interviews to ensure that admission criteria were met. Presence of a current or past history of mood or other anxiety disorders (lifetime comorbidity) was not considered as exclusion criteria, to ensure the selection of patients that covered the full range of the clinical universe applying for treatment; additionally, this allowed us to consider the various evolutionary stages of PD.

Table 1 Clinical features of 47 panic disorder patients treated with valproate

Age, mean (SD)	34. 1 (11.2)
Gender, female, *n* (%)	29 (61.7)
Agoraphobia, *n* (%)	39 (83.0)
Age at onset, mean (SD)	27.1 (9.9)
Duration of illness(months), mean (SD)	85.5 (110.5)
Life-up severity score at baseline, mean (SD)	
Panic disorder	3.3 (1.0)
Agoraphobia	3.1 (1.2)
General adjustment (GAS)	66.2 (11)
Comorbidity, *n* (%)	
Bipolar II	35 (74.5)
Generalized anxiety	10 (21.3)
Social phobia	10 (21.3)
Obsessive–compulsive dis.	6 (12.8)
Alcohol abuse	4 (8.5)

Data collection

An intensive face-to-face interview that consisted of structured and semi-structured components was used to collect data. The interview lasted approximately 1 h at baseline, and half an hour in subsequent visits. The interviews were done by residents with extensive clinical experience in the diagnosis and treatment of anxiety disorders. Each interviewer underwent a training program in the use of the interview instruments that included direct observation of experienced interviewer and interrater trials. The interviewers were not involved in treatment decisions that were entrusted to an independent clinician. Each patient was evaluated by the same interviewer.

At baseline, patients were evaluated by means of the Structured Clinical Interview for Diagnosis (SCID) [35], the Panic Disorder/Agoraphobia Interview [29], and the Longitudinal Interview Follow-up Examination (Life-up) [30]. Life-up has been designed to be administered every 6 months; however, as accuracy is duly enhanced by shorter intervals, it can be administered more frequently, according to the specific design of a given study. In our study, it was administered during the periodic visits every 2 months or at shorter intervals, as dictated by clinical necessity. Patients who interrupted the study were contacted at the end of the 3 years of follow-up and evaluated by means of a semi-structured interview, widely utilized in the World-Wide Upjohn Follow-up Study [31]. The interview lasted 30–40 min and was carried out face-to-face or by phone.

Instruments

The main instrument for diagnostic evaluation was the Panic Disorder-Agoraphobia Interview. This instrument is subdivided into different sections:

(1) Demographic characteristics, based on the Adult Demographic and Personal Inventory (ADPI) [32];
(2) Family history of anxiety, mood and other disorders in first degree relatives, based on Winokur's approach as incorporated into the Family History version of the Research Diagnostic Criteria [33].
(3) Personal history of the patient using the first panic attack as the primary anchoring point. Once the period of the first panic attack was described, the number of years preceding and following this event was reviewed with particular focus on the

symptomatological characteristics of PD, the course of the illness and comorbidity with other mental disorders.

(4) Affective temperaments according to Akiskal and Mallya [34] criteria and avoidant and dependent personality disorders according to DSM-III-R criteria, the former now shown to have good reliability and internal consistency in the TEMPS-clinical interview version [34], and the latter based on the corresponding sections of the Structured clinical Interview for DSM III-R Personality Disorder (SCID-II) [35].

Follow-up was accomplished through the use of the Longitudinal Interview Follow-up Examination (Life-up). This is a semi-structured interview and rating system for assessing the longitudinal course of psychiatric disorders in sufficient detail to enable researchers to date individual episodes of any psychiatric disorder and thus to provide the basis for precise calculation of time to recovery, length of ensuing wellness intervals, and time to subsequent relapse or recurrence. The instrument consists of different sections geared to assess psychopathological features, obtain history for psychiatric treatment and psychosocial functioning, as well as that for non-psychiatric medical illness. Finally, the LIFE provides a global assessment scale according to which the overall health and functioning of the patients are indicated. PD and Agoraphobia severity is recorded week–by-week on a score scale ranging from 1 to 6. According to this instrument, "remission" is defined as a period of 8 weeks during which patients with PD have no attacks, though sometimes they may feel on the verge of an acute attack. "Recurrence" is defined as a period of at least 4 weeks during which patients have one or more panic attacks per day, or a persistent fear of them. For Agoraphobia, "remission" is defined as the absence of avoidance for a period of 8 weeks, while "recurrence" defines a period of at least 4 weeks, during which avoidance is present. Also depression and (hypo)mania were evaluated week-by-week on a score scale ranging from 1 to 6. For both these pictures, remission is defined as a period of 8 consecutive weeks during which the score is 1 or 2 (respectively, absence of symptoms or 1 or more symptoms but with a slight interference in everyday adjustment; i.e. mild insomnia or decreased need to sleep). While in short-term controlled studies quantitative parameters are usually utilized in order to establish the efficacy of a drug, in long-term naturalistic designs more general indexes, such as remission and relapse, are utilized to describe the course of a disorder under pharmacological treatment.

Drop-out Interview was the last instrument used. This instrument is specifically designed to explore symptoms, disability, help seeking, and medications after the end of the study and in the last year [31]. After the registration of the reasons of interruption, such as remission, inefficacy of the treatment, side effects, distance to the clinic, onset of other medical diseases, etc., the course of the illness was investigated. In this way, remissions and recurrences throughout the period from the interruption of the study to the moment of the interview were recorded. Moreover, drugs that had been taken during that period were registered.

Treatment management

Clinicians involved in the treatment decisions and management were independent from the raters. Patients were assigned to pharmacological treatment with imipramine ($n = 17$, 36.2%), clomipramine ($n = 15$, 31.9%), or paroxetine ($n = 15$, 31.9%). In the first years of the study, tricyclic antidepressants (TCAs) represented the best known antipanic agents and for this reason they have been widely employed in our patients. Subsequently, the acquisition of the antipanic properties of paroxetine [36] has prompted the use of this new compound in the outpatients enrolled in the follow-up study. Only since 1995 paroxetine emerged in our experience as a viable first line intervention drug for PD-Agoraphobia. Initially, paroxetine was prescribed to patients judged less severe. Subsequently, paroxetine was also prescribed to those subjects for whom TCAs were contra-indicated, as well as in those who had shown a jitteriness syndrome or a supersensitivity to anticholinergic side effects. The initial dose was of 10 mg for imipramine or clomipramine and 10 mg for paroxetine. Dosage was gradually increased (10 mg every two days for TCAs and 5 mg every 4 days for paroxetine) to a maximum of 300 and 40–50 mg, respectively. The treating clinician could raise or lower the dose, without a fixed time schedule, depending upon the individual patient's clinical state or side effects.

At baseline, for those patients who were taking benzodiazepines (BDZ) a gradual tapering was scheduled. Subsequently, the administration of BDZ was allowed only occasionally when absolutely unavoidable. Moreover, when comorbidity with BD was present, the use of mood stabilizers was allowed.

Valproate (VPA) was used as an adjunctive treatment at the beginning of the observation, when lifetime comorbidity with bipolar disorder was found ($n = 35$, 74.5%), or when a patient with some affective instability, but not a full diagnosis of mood disorder, showed a partial response to antidepressants ($n = 12$, 25.6%), after a period of treatment ranging from 8 to 12 weeks. The initial dose of VPA was of 300 mg/day, and the treating clinician could raise or lower the dose, depending upon the individual patient's

clinical state or side effects. The mean dosage was 687 (SD = 234) mg/day (min 400, max 1,500 mg/day).

Statistics

Statistical comparisons between patients with resistant PD and PD + BD were conducted by means of t-test and chi-square analysis for continuous and categorical variables, respectively. Kaplan–Maier survival analysis was utilized to define the relationship between PD course (length of periods free from the illness and number of recurrences) and the presence of comorbid BD or resistance to antidepressants.

Results

Adjunctive treatment with VPA was well tolerated by all subjects and nobody had to interrupt treatment because of side effects or adverse events. Twenty-six subjects (55.3%) remained in the study for the entire 3-year follow-up study, 8 (17%) interrupted treatment since they deemed further contacts with the clinic unnecessary because of symptomatological remission, whereas in 5 cases (10.6%), suspension of treatment was related to treatment inefficacy. For the remaining 8 (17%) subjects, there was no information about treatment interruption, since they could not be traced at the end of the follow-up period.

Among the 47 patients who received VPA treatment, all subjects who were resistant to antidepressants and 31 of 35 (88.6%) subjects with bipolar comorbidity achieved symptomatological remission, as defined according to Life-up criteria. During the observation period, 7 (58.3%) among the resistant subjects and 17 (48.6%) of the bipolar patients had a relapse of panic disorder after remission. The mean number of recorded relapses was 2.05 (SD = 1.0). Mean duration of relapses in resistant patients and in bipolar subjects was 28.6 (SD = 27.4) and 31.4 (SD = 20.0) weeks (P = NS), respectively. None of these patients developed major depressive or hypomanic episodes during the period of observation.

Survival analysis of remission durations for PD and Agoraphobia did not show significant differences between the two groups (Figs. 1, 2), even if panic remission was quicker than the one of Agoraphobia. No significant difference was found as regards the onset of relapses for PD and Agoraphobia during follow-up (Figs. 3, 4). Relapses of Agoraphobia were less frequent and more delayed than those for panic.

The comparison between subjects with resistant PD and those with bipolar comorbidity did not show any significant differences as regards PD severity, Agoraphobia severity, and the impairment of general adaptation (Table 2). As regards possible response predictors, no specific relationship was observed between the PD course (duration of remissions and number of relapses) and the presence of comorbid BD or of resistance to antidepressants.

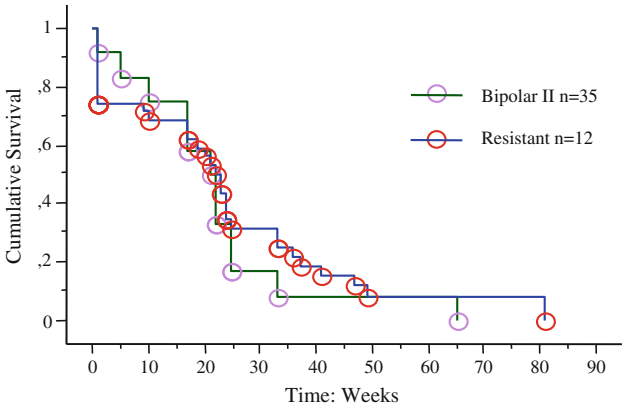

Fig. 1 Kaplan–Maier survival curves for remission times of panic disorder in two groups of PD patients

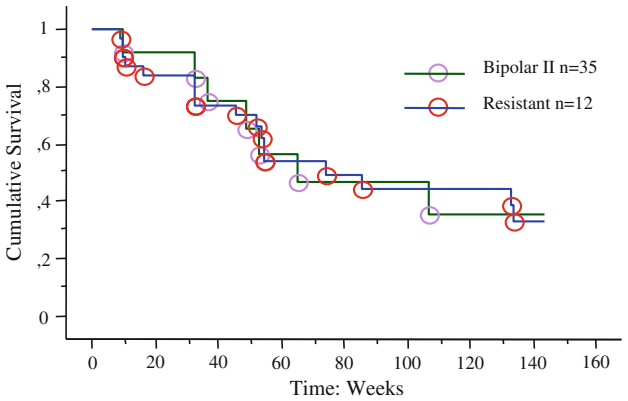

Fig. 2 Kaplan–Maier survival curves for relapse times of panic disorder in two groups of PD patients

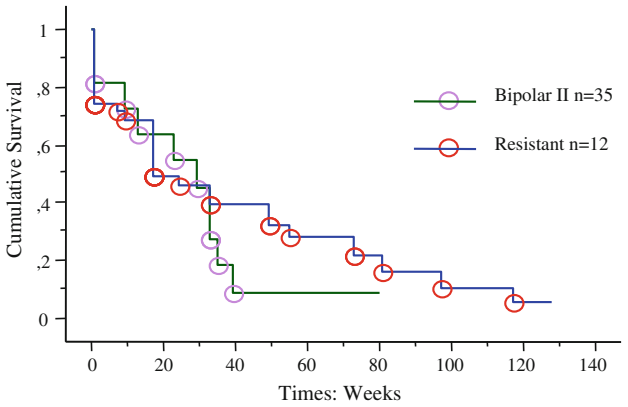

Fig. 3 Kaplan–Maier survival curves for remission times of agoraphobia in two groups of PD patients

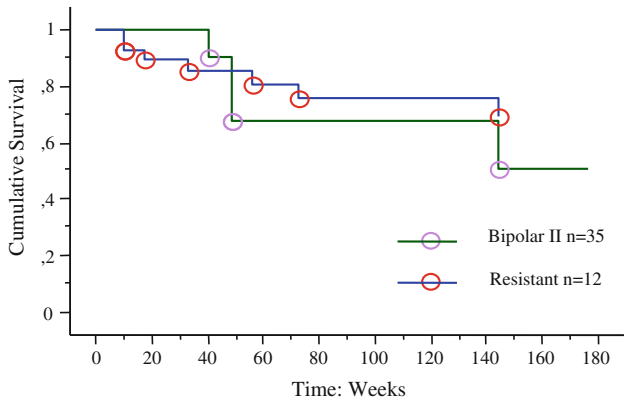

Fig. 4 Kaplan–Maier survival curves for relapse times of agoraphobia in two groups of PD patients

Table 2 Symptomatology in 47 patients with PD resistant (PD) or comorbid with bipolar disorder (PD + BD)

	PD [12]	PD + BD [24]
Life-up severity scores at baseline, mean (SD)*		
PD	3.3 (.8)	3.3 (1.0)
Agoraphobia	3.1 (1.4)	3.1 (1.2)
General adjustment	68.3 (10.3)	65.5 (11.3)

* All comparisons statistically non-significant

Discussion

Limited information is available on the therapeutic strategies of patients with PD resistant to standard treatments or comorbid with BD. Nonetheless, these forms of panic-agoraphobic syndrome cannot be deemed negligible, as PD is reported to be refractory to standard treatments in percentages ranging from 20 to 40% (57), while a growing number of epidemiological and clinical observations indicate that the cooccurrence of PD and BD is far from a rare finding [7, 9, 12, 37–41].

According to our study, VPA seems to be an effective and well-tolerated adjunctive treatment in PD patients who were resistant to antidepressant therapy or had lifetime BD comorbidity. Specifically, adjunctive treatment with VPA was effective in more than 90% of our patients, who achieved a complete remission of PD. The relapse percentages with VPA treatment were 58.3% for antidepressants-resistant PD patients and 48.6% for bipolar-PD subjects, respectively, over a 3-year observation.

In comparison to other studies, where VPA was used as a monotherapy, in our sample quite satisfying results were obtained by relatively low dosages (600–700 mg/day). As regards tolerability and safety, the results of our study indicate that VPA did not show clinically significant side effects or negative interactions. No patients interrupted the pharmacological treatment because of side effects or intolerance.

Results appear to be consistent with the other observations about short-term efficacy of VPA in the treatment of PD [23–26]. Our study represents the only existing observation that evaluated the course of the symptoms over a whole 3-year period utilizing very conservative definition criteria for remission and relapse. However, it is not a simple task to demonstrate the efficacy of VPA as an adjunctive treatment when used in a naturalistic setting and in combination with other sometimes-inhomogeneous treatment regimens.

Unfortunately, no information from controlled studies is available about this subject. All available observations were essentially drawn from open studies and, as noted earlier, the only existing controlled trial was conducted in a limited case series of patients who interrupted benzodiazepine treatment after achieving symptom remission [24].

In a more speculative vein, we hypothesized that the patients with PD and lifetime comorbid BD might not respond to standard antidepressant treatments because of a cooccurring mood instability although at a subclinical level. No patient developed major depression or (hypo)-manic episodes during the whole period of observation. By the way, we should stress that in our sample bipolar comorbidity was represented at a low level of severity: PD/Agoraphobia was the main diagnosis at the first observation, for which patients were seeking help; still, at the first evaluation mood appeared balanced and comorbidity with BD, type II, was only lifetime. Among previous studies, only the investigation by Beatz and Bowen [27] was aimed to evaluate the efficacy of VPA in PD patients, who had mood swings and were refractory to standard treatments. The results of our study are consistent with the conclusions of these authors and are consistent with the hypothesis of resistance to antidepressant treatment being related to subclinical mood instability [27, 42]. In our study, indeed, the observed response to VPA seems to be unrelated to the possible effect on major affective episodes even in patients with comorbid bipolar II disorder. Obviously, the relationship between refractoriness to standard treatments and mood instability needs to be further investigated with specific instruments focusing on “soft bipolarity” [43, 44].

Of course, our study has several limitations. Even if the size of our sample was remarkably greater than the one of previous studies, our results will have to be confirmed in larger samples. One of the main limitations has been the lack of control group. However, the likelihood of placebo effect or spontaneous remissions having a significant effect must be deemed quite low, taking into account the duration of the observation and the fact of all patients having a chronic, long-lasting, continuous, treatment-resistant course of the illness.

Overall, the results of our study give strength to the hypothesis that VPA may play a significant role in the adjunctive treatment of PD, when the disorder is associated to BD or appears to be resistant to standard treatments. It has been remarked that the cases of PD with bipolar comorbidity—and, more generally, the cooccurrence of multiple mental disorders—often are not included in the controlled studies, *notwithstanding* their remarkable frequency and importance in clinical practice. On the other hand, controlled clinical studies often are not feasible in bipolar spectrum disorders, because of several factors, such as severity of symptomatology, impairment of insight, impulsive changes of consent, and the difficulty of setting outcome criteria and evaluating changes of clinical status because of the frequent mood swings. In these situations, information from open studies, case series and observations from naturalistic settings acquire a fundamental importance to evaluate the possible efficacy of a treatment and create meaningful guidelines for choices in routine clinical practice.

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