Adjuvant valproate therapy for patients with suspected mixed-depressive features

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Abstract

Objective: Mixed-depressive features imply an occult bipolarity and might be linked to resistance to antidepressant therapy and a higher risk of suicide. Currently, there is no consensus about or any clinical guidelines available for this ill-defined clinical entity. The aim of this study was to assess the effectiveness, safety, and tolerability of mood stabilizers, such as valproate, for adjuvant therapy in patients suspected of having mixed-depressive features.

Methods: This retrospective observational study reviewed medical records of psychiatric outpatients attended by the author from 2008 to 2013. Patients who presented with inadequately treated, long-lasting atypical depressive- and/or anxiety-spectrum symptoms, and who started adjuvant valproate therapy for the first time in their course of treatment, were identified. Patient demographics, clinical profiles, treatment responses, and treatment-emergent adverse events (AEs) were examined in detail.

Results: A total of 22 patients (7 men and 15 women) ranging in age between 25 and 78 years were treated with valproate 100–1250 mg/day and observed for 3–60 months. The majority exhibited much or moderate improvement, and only four showed a limited response. During follow up, 12 continued adjuvant valproate, 3 were intermittent users, and 3 quit after no apparent response; 4 experienced an aggravation of symptoms after discontinuation but were stabilized soon after reinstitution. AEs were reported by 12 patients and 4 stopped valproate for intolerability despite improvement.

Conclusion: Adjuvant valproate therapy seems to be a promising approach to treating patients who manifest atypical neurotic or mood disorders with subthreshold bipolarity at a dosage around the lower end of that used to treat full-syndromal bipolar disorders.

Keywords: adjuvant therapy, bipolarity, depressive-mixed states, mixed-depressive features, valproate

Introduction

It has been suggested that mixed-depressive features, or depressive-mixed states, imply an ‘occult’ bipolarity [Benazzi, 2008a]. Unrecognized bipolarity has been regarded as a contributor to treatment-resistant depression [Correa *et al.* 2010], and ignorance about agitating symptoms in depressive patients might result in elevated suicide rates if treated with antidepressants alone [Akiskal *et al.* 2005; Koukopoulos *et al.* 2005]. Under-rated hypomanic-like symptoms, such as psychomotor agitation, irritability, hostility, talkativeness, racing thoughts, increased goal-directed or risky activities, and distractibility, might also render these patients at a higher risk for a manic

switch if they are treated with antidepressants without the concomitant use of mood-stabilizing agents [Benazzi, 2007; Liu *et al.* 2009; Rybakowski, 2012].

Mood stabilizers are expected to be effective for these ‘subthreshold’ affective symptoms in the same way that they work in bipolar disorders [Benazzi, 2007; Hantouche *et al.* 2005]; however, there is no consensus about the concept of mixed-depressive features among experts in bipolar and affective disorders [Benazzi, 2008b; Koukopoulos *et al.* 2005; Koukopoulos and Sani, 2014], and this is relatively new to psychiatrists practicing in community settings [Schneck, 2009]. Currently,

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only limited, yet supportive, evidence for adjuvant valproate therapy for bipolar depression has been reported [Ghaemi *et al.* 2007], but no guidelines are available for treating depressive-mixed states [Vieta and Valenti, 2013].

In the outpatient clinics of a university-based hospital and its community branch, the author identified a group of patients who presented with atypical depression and/or anxiety symptoms, usually characterized by increased emotional reactivity, impulsivity, episodic agitation, hyperactivity, pressured speech, frequent conflicts with others, or being over-conscientious about any “unjust” happenings around him or her, along with prolonged and excessive rumination about events that aroused negative feelings. The majority of these patients had been treated with antidepressants, however, only a minimal or no response was seen. Therefore, low-dose adjuvant valproate therapy was employed to ameliorate these suspected mixed-depressive features. Some patients showed rapid improvement at their first return visit, usually 1–2 weeks after starting adjuvant valproate therapy, but not all reported positive experiences with this approach. The aims of this study were to scrutinize the effectiveness, treatment-emergent adverse events (AEs), and tolerability of this approach, and to provide insights into the treatment of mixed-depressive features with adjuvant valproate therapy.

Methods

A retrospective, case-series observational study was performed by reviewing patient medical records at the National Taiwan University Hospital (NTUH) and the Bei-Hu Branch of NTUH. All the medical records of outpatients seen consecutively by the author from January 2008 to June 2013 were screened, and the records of those whose clinical characteristics fulfilled the criteria of this study were examined in detail. This work was approved by the NTUH Research Ethics Committee.

The inclusion criteria were: (a) patients with mixed-depressive features, such as psychomotor agitation, irritability, hostility, talkativeness, racing thoughts, increased goal-directedness, increased risky activity, distractibility, and increased emotional reactivity; (b) patients who received adjuvant valproate therapy prescribed by the author for the first time in the course of their illness; (c) patients who had been treated for their

depressive- or anxiety-spectrum disorders for a substantial period of time prior to the initiation of adjuvant valproate; (d) patients who had been followed up for at least 3 months after the initiation of adjuvant valproate, although not necessarily under continuous valproate therapy since initiation of this agent. The exclusion criteria were: (a) patients with a diagnosis of bipolar I or bipolar II disorder prior to their first visit to the clinic; (b) patients with a diagnosis of a major psychosis, such as schizophrenia, schizoaffective disorder, delusional disorder, or organic brain syndrome; (c) patients who had previously received valproate treatment for seizures or other medical/neurological disorders; (d) patients who had previously received lithium or other mood stabilizers for treatment of their affective symptoms.

Patients' clinical profiles, including demographic characteristics, key clinical presentations suggesting mixed-depressive features, previous clinical diagnoses, previous pharmacotherapy, estimated duration of unremitted mixed-depressive features, dose of adjuvant valproate, treatment-emergent AEs suspected of being related to valproate, and duration of follow up were recorded in detail. Patients' treatment responses were estimated as much improved, moderately improved, minimal/no change, and worsened. Patients' comments about their subjective feelings, if any, after taking valproate were also carefully appraised and selectively presented in this paper with the patients' confidentiality and anonymity rigorously protected.

Results

A total of 23 patients met the inclusion criteria. One did not take valproate for fear of the side effects listed on the pharmacy's supplementary instructions and was excluded. Thus 22 (7 men and 15 women), ranging in age between 25 and 78 years (mean $\pm$ standard deviation [SD]: 51.7 ± 13.4), were identified (Table 1). Based on the main clinical manifestations, their diagnoses were approximately grouped into depressive-spectrum disorders (10), anxiety-spectrum disorders (5), adjustment disorders with mixed anxiety and depression (5), and psycho-physiological disorders (2).

The key clinical features that prompted the author to consider adjuvant valproate were grouped into five categories: (a) psychomotor agitation: feeling that it was difficult to curb

Table 1. Summary of subjects' demographic and clinical profiles.

Case	Age	Gender	Previous diagnosis	Key previous pharmacotherapy	Duration of symptoms	Effective dose [mg/day]	Adverse events	Follow up (months)	Improvement
1	58	F	Psychophysiological disorder, insomnia	SSRI	> 3 years	100	Dry mouth	12	Moderate
2	55	F	Adjustment disorder with mixed emotion	SSRI	2 years	500	Headache	18	Much
3	78	M	Anxiety disorder	SSRI	3 years	500		24	Moderate
4	60	M	Recurrent depressive disorder	SNRI, TCA	> 3 years	1000		30	Much
5	54	M	Dysthymia, intermittent explosive disorder	SSRI, SNRI, AP	> 5 years	500	Dry mouth	6	Moderate
6	40	F	Dysthymia	TCA, AP	3 years	250		15	Much
7	64	F	Anxiety disorder	SSRI	> 5 years	125	Flattened emotion	8	Much
8	66	F	Depressive disorder	SNRI	> 5 years	500		24	Moderate
9	65	F	Adjustment disorder with mixed emotion	SSRI, AP	> 5 years	500	Joint pain	10	Much
10	60	F	Psychophysiological disorder, insomnia	BZD, hypnotics	2 years	500	Hair loss	36	Much
11	44	F	Adjustment disorder with OC symptoms	BZD, hypnotics	1 year	500		18	Moderate
12	54	F	Depressive disorder	SSRI	2 years	500		6	Minimal
13	53	M	Dysthymia	SSRI	2 years	750		60	Moderate
14	43	F	Panic disorder	SSRI	1 year	100*	Bitter taste	36	No
15	32	M	Dysthymia	SNRI	1 year	1250		24	Moderate
16	26	F	Dysthymia	SSRI	1 year	500*	Skin rash	60	Minimal
17	25	M	Social phobia	SSRI	> 3 years	500		60	Much
18	58	M	Depressive disorder with OC symptoms	TCA	> 5 years	100	Dizziness	6	Much
19	62	F	Anxiety disorder with dissociative symptoms	SSRI	2 years	500		3	Much
20	46	F	Depressive disorder with paranoid symptoms	SSRI + AP	5 years	250	Flattened emotion	36	Moderate
21	51	F	Adjustment disorder with mixed emotion	SSRI	2 years	250*	Headache	6	No
22	41	F	Adjustment disorder with mixed emotion	SSRI, bupropion	3 years	500	Mildly elevated liver enzymes	36	Moderate

* The dosage when the patient stopped valproate for intolerable adverse events.

AP, antipsychotic; BZD, benzodiazepine; OC, obsessive compulsive; SNRI, serotonin norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressants.

impatience, impulsivity, intrusiveness, agitation, and frequently on the verge of losing control; (b) irritability/hostility: episodic tantrums triggered by trivial events, frequent quarrels, friction, conflicts, sometimes with verbal aggression/threatening, even physical aggression, and feeling regretful after acting out exaggerated emotional reactivity; (c) increased talkativeness: being talkative, complaining, nagging, critical, argumentative, and pressured in speech; (d) racing thoughts: excessive ruminations about negative feelings related to recent irritating events, having trouble with sleep or somatic discomfort while being overwhelmed by mixed thoughts such as anger, revenge, regret, guilt, loss, or ambivalence; (e) emotional lability: being very sentimental with excessive tearfulness when left alone, feeling criticized, feeling abandoned, or very sensitive to changes in the weather. Each patient had symptoms in at least two categories, while many of them had symptoms in more than two categories. These symptoms were on and off, usually lasting for at least 1 year, some for longer than 5 years or even to the point 'as far back as I can remember, I always ran into trouble due to my emotional problems'.

Prior to the initiation of adjuvant valproate, the majority of patients (20/22) had received antidepressants, primarily selective serotonin reuptake inhibitors, but some serotonin norepinephrine reuptake inhibitors, tricyclic antidepressants, or bupropion; many also used benzodiazepines/hypnotics and several received very low-dose antipsychotics. They either had inadequate responses or were intolerant of these treatments, including one who experienced a manic switch that prompted the use of valproate. The remaining two patients received only benzodiazepines and hypnotics. The starting dose of valproate ranged from 100 mg/day to 250 mg/day and the endpoint dose ranged from 100 mg/day to 1250 mg/day (mean $\pm$ SD: 490.8 $\pm$ 284.7). Some patients used it only as needed, especially those who used only 250 mg/day or less. Treatment-emergent AEs were sporadic; these included dry mouth, headache, dizziness, hair loss, skin rash, joint pain, bitter taste, mildly elevated liver enzymes, and "too flattened in emotional reactions".

Based on observation periods ranging from 3 months to 5 years, 9 of the 22 experienced much improvement, 9 felt moderately improved, 4 had limited responses (including 2 early discontinuations related to suspected treatment-emergent

AEs). During follow up, 12 patients continued adjuvant valproate on a regular basis, 4 stopped it because of intolerable AEs despite improvement, 3 used it only as needed once they felt improved, and 3 quit with no apparent response; 4 became unstable soon after discontinuing valproate but were stabilized again soon after reinstitution, 6 were able to decrease the dosage of their previously used benzodiazepines or hypnotics. Those who were regularly administered valproate had blood levels of valproic acid ranging from 23 μ g/ml to 75 μ g/ml (mean $\pm$ SD: 50.3 $\pm$ 17.8). The one patient with mildly elevated liver enzyme levels had no progression of impaired liver function during follow up and stayed well while treated with adjuvant valproate.

Discussion

To the best of my knowledge, this was the first case series reporting adjuvant valproate therapy in a group of patients with suspected mixed-depressive features. These patients received a relatively low dose of valproate and the majority of them showed at least moderate improvement. Patients and/or their key family members reported that their long-lasting emotional over-reactivity and affective symptoms were apparently diminished soon after the administration of valproate. Of those patients who were responsive to treatment, several showed symptoms that worsened once they stopped adjuvant valproate and regained stability after resuming valproate. Many have been followed up for several months and even years, and the responses seem to be substantial. Such a temporality in response suggests its effect on mood regulation to be plausible.

Around half of the patients stayed on this therapy for its long-term benefits, while some of them opted to use it only as needed. They recognized its mood stabilization effect to be superior to that of their previous regimens. Interestingly, two patients stopped valproate because they felt that their "normal" emotional reactivity was "excessively diminished", although both showed moderate improvement in affective symptoms. One of these patients complained that "it's weird after taking the medicine. I don't feel as happy when I see a sunny day and don't feel as gloomy when it is raining as I used to". The other claimed that "after taking the medicine, I lost my acuity in appraising classical music when I was sitting in a theatre listening to a performance which I would have gotten much more thrilled about before". Both opted

to try other agents instead. This observation suggests that valproate was able to diminish the amplitude of a patient's emotional reactivity, although it was not necessarily welcomed by all of them.

Although the mechanism by which valproate is effective as a mood stabilizer is still uncertain, its function in enhancing the inhibitory actions of gamma aminobutyric acid and reducing the excitatory actions of glutamate might explain its clinical utility [Stahl, 2013]. In this study, such mechanisms seem to explain why there were modulating effects on patients' excessive or exaggerated emotional reactivity. In real-world practice, the major challenge while trying to employ this adjuvant therapy is how to identify correctly patients who might benefit from this approach [Vieta and Valenti, 2013], as the clinical manifestations of so-called mixed-depressive features may overlap with several psychiatric syndromes as well as temperamental characteristics [Benazzi, 2008a; Koukopoulos and Sani, 2014; Maina *et al.* 2010]. Interestingly, the symptoms of 'emotional lability' identified in this case series were similar to 'mood reactivity' and 'interpersonal rejection sensitivity' as described by the historical term 'atypical depression'. The proposed criteria for mixed depression by Koukopoulos and Sani, also included 'mood lability and marked emotional reactivity' [Koukopoulos and Sani, 2014]. Thus this category of symptoms might be an important identifier in addition to previous descriptors that generally included only hypomanic-like symptoms.

The major limitations of this study were that patients' clinical states and treatment responses were not evaluated by a tool-based clinical assessment. The five 'categories' of symptoms suggesting mixed-depressive features were not derived by statistical measures but were a clinical observation pending further validation. A family history of bipolar disorder was not extensively checked while it has been reported to be a strong predictor of the validity of mixed depression [Benazzi, 2008b]. In addition, there is often a bias toward favorable outcomes in an open-label add-on trial. The strengths of this study were that all patients were observed by a single psychiatrist who used similar standards to examine each patient's clinical features and treatment response, and the detailed descriptions of features suggesting depressive-mixed states will be useful in identifying candidates for this adjuvant therapy.

In summary, this case series suggested that adjuvant valproate therapy might be helpful to mitigate affective and behavioral symptoms suggesting subthreshold bipolarity with a dosage at the lower end of the recommended dose range for full-syndromal bipolar disorder or epilepsy. Even when given at a relatively low dose, AEs were not uncommon and should be monitored carefully. A fine-tuned approach is recommended to accommodate tolerability while trying adjuvant valproate, and perhaps a symptomatic treatment approach, using it only as needed, can also be considered. Finally the tolerability, safety, and efficacy of valproate for treating putative subthreshold bipolarity need to be justified by more large-scale, prospective, well-designed clinical trials.

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Conflict of interest statement

The author has served as a speaker and received honoraria from Astra-Zeneca, Eli Lilly, Janssen-Cilag, Otsuka, Pfizer, and Sanofi.

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