significant differences and the results here should be interpreted cautiously due to the small sample size. In conclusion, these post hoc analyses suggest that adjunctive brexpiprazole has comparable efficacy in reducing depressive symptoms in patients with MDD with irritability compared with the patients with MDD without irritability.

AUTHOR DISCLOSURE INFORMATION

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Affective Recurrences in Bipolar Disorder After Switching From Lithium to Valproate or Vice Versa
A Series of 57 Cases

To the Editors:

For many years lithium was the only mood stabilizer (MS) in common use, and it is still the first choice in the preventive treatment for bipolar disorder (BD).[1] However, there are many safety and tolerability concerns such as cognitive impairment, weight gain, dermatological reactions, and renal or thyroid dysfunction that can lead to the use of lithium being stopped.[2] A higher risk of recurrences even after many years of clinical stability is associated with the discontinuation of

lithium,[3,4] and, in case of rapid discontinuation, recurrences increase sharply soon after.[5]

When lithium is tapered off, an alternative MS should be started. Among MSs, valproate represents a first-line treatment for BD.[6] Nevertheless, evidence for its effectiveness in comparison with lithium remains sparse. In the BALANCE study, lithium was more effective than valproate in preventing recurrences. Combined therapy was also not more effective than lithium alone.[7] Similar findings emerged from an observational cohort study with links to nationwide registers of patients with BD in psychiatric hospital settings who were treated with valproate or lithium.[8] Taken together, these results seem to indicate that lithium is superior to valproate in the maintenance treatment of BD. However, there is a lack of data regarding the efficacy of valproate in patients who discontinue maintenance treatment with lithium, and the same applies for patients switching from valproate to lithium.

Thus, we compared the recurrence rates in patients with BD who switched from lithium to valproate and vice versa. Moreover, we analyzed any correlation between the baseline characteristics of the patients and occurrence of mood episodes after the treatment switch. We considered patients in the euthymic phase (for at least 8 weeks, based on clinical judgment), either responders to monotherapy with lithium (Li-R) or valproate (Va-R), and requiring change of MS for any reason with the exception of lack of efficacy. Patients were excluded based on having the following: main diagnosis other than BD, concomitant severe/unstable neurological or physical diseases, history of nonresponse to lithium or valproate, any safety/tolerability concerns to valproate for patients in current treatment with lithium and vice versa.

No attempt was made to influence decisions regarding the study treatments, and patients received care as per usual. The aims of the study and study procedures were thoroughly explained to potential participants who gave their oral consent before participation.

At the study entry, Li-R were prescribed valproate and Va-R were prescribed lithium. Within 4 weeks, the serum levels of both valproate and lithium were adjusted to comply with the therapeutic range (valproate, 50–100 μg/L; lithium, 0.5–0.8 mmol/L). The previous MS was gradually discontinued. Each patient was followed-up for an 18-month period. Patients were assessed monthly in the first 6 months, then every 3 months thereafter. In addition, all patients were informed to contact their psychiatrists every time they experienced a worsening of symptoms.

We compared demographic and clinical characteristics between the two patient groups by way of χ^2 in the case of categorical variables and analysis of variance (F) in the case of continuous variables. A LogReg analysis was then conducted to assess any relationship between characteristics of the patients-independent variables: sex, age, type of BD, age at onset, duration of illness, previous MS (lithium or valproate), duration of treatment with previous MS, stop motivation, and reduction time of previous MS-and presence/absence of a recurrent episode of BD (dependent variable).

Fifty-seven patients participated in the study. Of those, 33 were Li-R and 24 were Va-R. Before lithium or valproate monotherapy, most of the subjects typically received varying combinations of MSs, antidepressants, antipsychotics, and benzodiazepines as indicated by changing clinical requirements. No relevant differences emerged from the history of the subjects of the 2 groups in terms of response to previous treatments. All baseline demographic and clinical characteristics of the patients are shown in Table 1.

The most common adverse events leading to discontinuation of MS treatment were tremors (30%), renal dysfunction (15%), and hypothyroidism (9.0%) in the Li-R group, whereas weight gain (29.2%), elevated liver enzymes (20.8%), hair loss (12.5%), and sexual side effects (12.5%) occurred in the Va-R group.

The mean discontinuation time of MS treatment was 5.0 ± 3.3 and 3.6 ± 2.2 months, respectively, for Li-R and Va-R (F = 3.21; P = 0.79).

During the 18-month follow-up period, a BD recurrence was observed in 14 (42.4%) of Li-R and 4 (16.7%) of Va-R (χ^2 = 4.267; P = 0.048). As shown in Table 1, no significant differences in terms of characteristics of recurrences were detected between the 2 groups.

The LogReg analysis showed that none of the baseline characteristics of the patients were significantly associated with the BD recurrences with the exception of the duration of treatment with previous MS (B = 0.129; Wald = 4.658; P = 0.031).

DISCUSSION

It is known that the discontinuation of MS (especially lithium) leads to a high risk of

TABLE 1. Baseline Characteristics, Recurrence Rates After MS Switching, and Clinical Characteristics of Mood Episodes: Comparison Between Li-R and Va-R

	Li-R	Va-R	Statistics		
	n = 33	n = 24	F/χ^2	*df*	*P*
Sex, n (%)					
Male	19 (57.6)	12 (50)	0.571	1	0.601
Female	14 (42.4)	12 (50)			
Age, mean ± SD, y	47.61 ± 9.34	45.75 ± 10.48	0.495	56	0.485
Diagnosis, n (%)					
BD I	15 (45.5)	7 (29.2)	0.212	1	0.275
BD II	18 (54.5)	17 (70.8)			
Age at onset, mean ± SD, y	25.42 ± 4.95	29.13 ± 5.27	7.346	56	0.009
Illness duration, mean ± SD, y	21.88 ± 10.22	16.63 ± 11.37	3.338	56	0.073
Treatment duration, mean ± SD, y	7.27 ± 5.70	5.56 ± 4.16	1.553	56	0.218
Stop motivation, n (%)					
Adverse effects	29 (87.9)	18 (75.0)	8.150	2	0.017
Patient desire	4 (12.1)	1 (4.2)			
Pregnancy planning	0 (0)	5 (20.8)			
Recurrence rate, n (%)	14 (42.4)	4 (16.7)	4.267	1	0.048
Recurrence type, n (%)					
Mania/hypomania	8 (24.2)	3 (12.5)	0.417	1	1.000
Depression	6 (18.2)	1 (4.2)			
Specifiers, n (%)					
Mixed features	5 (15.1)	3 (12.5)	0.163	1	0.275
Psychotic symptoms	3 (9.1)	0 (0)	0.310	1	1.000
Time to recurrence, mean ± SD, mo	9.93 ± 5.24	5.75 ± 4.50	2.081	17	0.168
Suicide attempts, n (%)	5 (15.1)	0 (0)	0.160	1	0.278
Hospitalization, n (%)	9 (27.3)	3 (12.5)	0.688	1	1.000
Compulsory treatment	5 (15.1)	1 (4.2)	0.505	1	1.000

recurrence in patients with BD. Accordingly, we found a higher rate of affective recurrences after the MS switch in Li-R than in Va-R (42.4% vs 16.7%; $P = 0.048$). The slow tapering of lithium allegedly delayed the time to recurrence in Li-R (10 months on average) compared with Va-R (6 months on average), although there were no statistically significant differences neither in terms of the reduction time of the previous MS nor in terms of the length of time to recurrence. Previous studies showed that the risk of a BD recurrence increased up to 70% in the first year after lithium discontinuation, even after many years of clinical stability.[4] Particularly, a study on BD patients with a good response to lithium maintenance (of at least 5 years) showed that 62% of them had a recurrence in the first year after discontinuation.[9] In light of these data, it can be argued that, for BD patients discontinuing lithium treatment, valproate confers a mild protective effect against recurrences compared with no MS treatment: approximately 40% of recurrences instead of 60% to 70%, as found by the abovementioned studies. On the other hand, switching from valproate to lithium seems useful in terms of the risk of recurrences: only 16.7% of patients had a recurrence during the follow-up period. This finding could be explained by the superior efficacy of lithium over valproate in the long-term treatment of BD, as stated by the literature on this topic[7,8] and confirmed in a recent study comparing lithium, valproate, olanzapine, and quetiapine as maintenance monotherapy for BD.[10]

Most recurrences in our study were (hypo) manic episodes. Likewise, other studies found a prevalence of manic episodes after MS discontinuation.[11] Although without statistically significant differences, recurrences in the Li-R group appeared more severe than those in the Va-R group. There was a higher frequency of psychotic symptoms, hospitalizations, and compulsory treatments. In addition, 15.1% of those in the Li-R group attempted suicide after MS switching compared with none from the Va-R group. These data are consistent with those of the study by Baldessarini and colleagues[5] showing an increase of suicidal risk in the first year off lithium.

The recurrence rates in Li-R and Va-R should be considered in light of 2 noteworthy differences in the baseline characteristics of the 2 groups. First, the age at onset of BD was lower in the Li-R than in the Va-R group. Together with a trend toward longer illness duration, nonsignificantly longer treatment duration, and proportion of BD type I diagnosis, it could mean that patients in the Li-R subgroup had more severe BD. In particular, a lower age at the onset of BD has shown to be related to more frequent manic episodes with psychotic symptoms, a short duration of euthymic phases, and a higher risk of suicide attempts.[12] Thus, the higher rate of recurrences in Li-R could depend on the higher severity of BD in this group.

Second, pregnancy planning was one of the reasons for treatment discontinuation only in the Va-R group. Because valproate should be stopped in women who are planning to become pregnant, this baseline difference between Li-R and Va-R was expected. Furthermore, no women became pregnant in the follow-up period. Thus, the baseline difference in reasons for treatment discontinuation should not be considered as a potential bias.

The regression analysis showed that the only variable significantly associated with BD recurrences was the duration of previous MS treatment: the longer the period of maintenance treatment with MS, the higher the risk of BD recurrences when it is discontinued. The interpretation of this finding should consider the length of the treatment duration of Li-R (7.2 years) compared to Va-R (5.5 years). Furthermore, this difference could become statistically significant in a larger sample of patients. However, this result could indicate that the long duration of treatment with MSs has no protective effects against recurrences once the treatment is replaced for any reason.

In conclusion, our results suggest that the risk of recurrence after a long period of mood stability is higher in cases of switching from lithium to valproate than vice versa, although this difference appears to be related more to the duration of MS treatment than to the type of drug being switched.

These findings should be considered in light of the several limitations of the study: the sample size was rather small; bias due to confounding factors cannot be excluded, in particular the two subgroups could be not comparable in terms of illness severity, history of past medications, intercurrent medical illnesses, and reason for medication discontinuation; and the definitions of euthymic phase and recurrence were based on clinical judgment. Furthermore, no systematic assessments of compliance to treatments were conducted, with the exception of periodic evaluations of plasma levels of MS according to the clinical practice.

In summary, the high risk of recurrences of BD in patients who need to discontinue MSs warrants further analyses to provide clinicians with more robust information on treatment options.

AUTHOR DISCLOSURE INFORMATION

The authors declare no conflicts of interest.

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Baclofen-Related Mania
Lower Threshold for Bipolar Patients?

To the Editors:

Baclofen, a prototypic γ-amino butyric acid type B receptor agonist that has been in use for more than 50 years for treating spasticity, has recently emerged as a promising pharmacotherapy for treatment of alcohol dependence.[1] Initial open and randomized controlled trials have shown the efficacy of 30 mg/d of baclofen on alcohol craving, intake, and relapse prevention.[2] Higher doses of baclofen, that is, more than 100 mg/d, have also been used off-label.[3] Baclofen-related disinhibition and mania have been reported in a small number of patients being treated for spasticity and dystonia[4–7] as well as alcohol use disorders.[3,8,9] The doses have varied from 30[5] to 270 mg/d[9] of baclofen, and more than half of the reported cases are in those with a pre-existing bipolar I disorder. We report a case of baclofen-related mania in a patient with bipolar II disorder at a relatively low dose of 20 mg/d. We have applied the Naranjo algorithm[10] for establishing causality.

Mr A, a 47-year-old man, presented to our psychiatry outpatient services with complaints of sadness of mood, easy fatiguability, disturbances in sleep and appetite, and decreased self-esteem for the past 2 months. Symptoms fulfilled the criteria for major depression. Around 15 years ago, the patient had a depressive episode of similar severity that lasted for 2 to 3 months and improved on taking some medications. Three years ago, the patient had an episode characterized by euphoria, increased goal-directed activity, overfamiliarity, increased self-esteem, and decreased need for sleep for 2 to 3 weeks, but there was no socio-occupational dysfunction reported. He was started on divalproex 250 mg/d, and thereafter, these symptoms subsided. When improved, his compliance became poor. Mr A had another 2 to 3 such episodes in the past 3 years on the same medication. He was consuming alcohol for the last 19 to 20 years, and a dependent pattern was established for the last 6 to 7 years. Approximately 2 years ago, he reduced both the amount and frequency. He was also using clonazepam 0.25 to 0.5 mg/d for the past 15 years without which he would have sleep disturbances and restlessness. He had never used any other drug of abuse and was never on any other psychotropic medication. To confirm the possibility of bipolar disorder, mood disorder questionnaire[11] was applied and he screened positive for the same. As the history revealed episodes of major depression and hypomania, a diagnosis of bipolar II disorder was kept. During the initial period of assessment and management, divalproex 250 mg was continued. The patient continued alcohol intake in the same pattern but stopped clonazepam on his own.

It was suspected that his hypomanic/manic episodes were possibly linked with alcohol intake as increase in alcohol intake usually preceded these episodes. However, the patient desired to consume alcohol occasionally, continued to take approximately 10 to 20 grams of alcohol per day for 3 to 4 days a week, and reported having moderate to severe degree of craving. In view of this, baclofen 20 mg/d was started. On the second day of starting baclofen, Mr A experienced racing of thoughts, appeared extremely cheerful, energetic, confident, boisterous, and argumentative, and had decreased need for sleep. On mental state examination conducted after a week of onset of symptoms, he was euphoric, distractible, with increased psychomotor activity, and had increased self-confidence and self-esteem. Mr A described the new drug (baclofen) as a "wonder drug." The Young Mania Rating Scale (YMRS) score was 19. He was taking divalproex 250 mg/d with good compliance during this time and had not consumed alcohol since baclofen was started a week ago. He was not using any other drug of abuse and was neither on any other psychotropic medication. Baclofen was withheld, and after 2 days, all the manic symptoms (increased self-confidence, increased energy, and decreased need for sleep) disappeared and the YMRS score dropped to 0. For another 2 weeks, the patient again had depressive symptoms. Divalproex was increased to 750 mg/d with complete resolution of symptoms, and the patient has been euthymic for the last 8 months. To retrospectively assess the role of baclofen in the occurrence of the manic symptoms presented by Mr A, we used the Naranjo algorithm, which found baclofen's imputability to be "probable" (Table 1).

Baclofen-related mania and disinhibition have been reported in less than half a dozen cases,[3–9] but a validated instrument for establishing psychopathology and causality was used in only one of these cases.[3] We used the mood disorder questionnaire to establish bipolarity in the index case, besides documenting the manic symptoms by using the YMRS. Most importantly, we used the Naranjo algorithm to establish causality and confirmed the findings of Geoffroy et al.[3] It may be argued that because the mood episodes in bipolar disorder are

TABLE 1. Probability of ADR of Baclofen Using Naranjo Algorithm in the Index Case

Sr.	Item	Answer	Score
	Are there previous conclusive reports on this reaction?	Yes	+1
	Did the adverse events appear after the suspected drug was given?	Yes	+2
	Did the adverse reaction improve when the drug was discontinued or a specific antagonist was given?	Yes	+1
	Did the adverse reaction appear when the drug was readministered?	Not done	0
	Are there alternative causes that could have caused the reaction?	No	+2
	Did the reaction reappear when a placebo was given?	Not done	0
	Was the drug detected in any body fluid in toxic concentrations?	Not done	0
	Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	Yes	+1
	Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	No	0
	Was the adverse event confirmed by any objective evidence?	Yes	+1
Total score			Score = 8

Scoring: ≥9 indicates definite ADR; 5–8, probable ADR; 1–4,possible ADR; 0, doubtful ADR.
ADR indicates adverse drug reaction.