# Lithium and Valproate Treatment of Pathological Gambling: A Randomized Single-Blind Study

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***Objective:*** The aim of the present study was to evaluate the efficacy and safety of lithium and valproate in nonbipolar pathological gamblers.

***Method:*** Forty-two subjects with DSM-IV–defined pathological gambling entered a 14-week single-blind trial with lithium (N = 23) or valproate (N = 19). A total of 15 subjects on lithium treatment and 16 patients on valproate treatment completed the 14-week protocol.

***Results:*** At the end of the 14-week treatment period, both the lithium and the valproate groups showed significant ($p < .01$) improvement in mean score on the Yale-Brown Obsessive Compulsive Scale modified for pathological gambling. This improvement did not significantly differ between groups. Fourteen (60.9%) of the 23 patients taking lithium and 13 (68.4%) of the 19 patients taking valproate were responders based on a Clinical Global Impressions-Improvement score of much or very much improved.

***Conclusion:*** Findings from the present study suggest the efficacy of both lithium carbonate and valproate in the treatment of pathological gambling. This is the first controlled trial of the efficacy of mood stabilizers in pathological gambling. A double-blind, placebo-controlled trial is required to confirm these findings.

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Pathological gambling is an impulse-control disorder characterized by persistent and recurrent maladaptive patterns of gambling behavior.[1] Pathological gambling is relatively common, with a reported prevalence of 1.6% among U.S. adults and an even higher prevalence among younger populations.[2] Due to an increase in access to legalized gambling in Italy, our group recently found that approximately 6% of frequenters of a discotheque in Florence, Italy, had a score on the South Oaks Gambling Screen corresponding to a probable diagnosis of pathological gambling.[3]

Pathological gambling is chronic and progressive and is associated with a 20% rate of suicide attempt.[4] Substance abuse, obsessive-compulsive disorder (OCD), anxiety disorders, attention-deficit/hyperactivity disorder, and depressive disorders are highly comorbid with pathological gambling, and several reports suggest that these conditions share a pathophysiologic substrate with pathological gambling.[5] There is a phenomenological link between pathological gambling and OCD,[6] and, as is seen in OCD, there is evidence of serotonin dysfunction in pathological gambling.[7–9]

Studies have been performed on the efficacy of serotonin reuptake inhibitors (SRIs) in patients with pathological gambling. Such studies were initially motivated by the conceptualization of pathological gambling as an obsessive-compulsive spectrum disorder.[6] A single positive result was obtained with clomipramine in the treatment of a 31-year-old woman with a 12-year history of pathological gambling.[10] In a short-term, single-blind trial with fluvoxamine, 7 of the 10 subjects were considered to be responders with a significant reduction in gambling urge and gambling behavior. However, fluvoxamine seemed to exacerbate gambling behavior and mood symptoms with dysphoric elation in 2 of the 3 nonresponders.[11] A recent 16-week, double-blind, placebo-controlled trial with fluvoxamine demonstrated a greater degree of improvement in both gambling urge and gambling behavior after long-term treatment with fluvoxamine as compared with placebo.[12]

The core psychopathologic features of pathological gambling are mixed: impulsive features (arousal), compulsive

features (anxiety reduction), addictive features (symptoms of withdrawal), and features associated with bipolar disorder such as urges, pleasure seeking, and the reduction of judgment capability related to an unrealistic appraisal of one's own abilities.

The problematic categorization of pathological gambling and other impulse-control disorders not elsewhere classified and their relationship with bipolar disorder have been comprehensively reviewed by McElroy et al., who suggest that "impulsivity and bipolarity (or mania) are related."[13(p229)] The clinical features of pathological gambling resemble those of bipolar disorder, and the comorbidity between pathological gambling and bipolar disorder has been estimated to be approximately 30%.[14] Although previous studies have demonstrated the effectiveness of both lithium carbonate[15] and valproate[16–21] in various impulse-control disorders, there are no methodologically sound trials with mood stabilizers in pathological gambling. A placebo-controlled study with carbamazepine in a single case of chronic pathological gambling found significant clinical benefits of carbamazepine at a dosage of 600 mg/day.[22] Lithium was found to be effective in treating 3 pathological gambling patients with bipolar features.[23]

The current study investigated the efficacy and safety of monotherapy with lithium and valproate in a 14-week, single-blind trial in pathological gamblers. Patients with comorbid gambling behavior and bipolar disorder were excluded from the enrollment, after the problem of differential diagnosis as indicated in DSM-IV criteria was considered.[1(p617)]

## METHOD

Seventy-three subjects with pathological gambling recruited through media information were assessed for entry into the study. Gambling was described as a hygiene problem, and our institute was named as a research and therapeutic center on gambling. Diagnoses were obtained through the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I).[24] Twenty-five patients were excluded from the study because of comorbid or principal diagnosis of current alcohol or drug addiction, bipolar disorder, schizophrenia, schizoaffective disorder, or an organic illness. Six patients refused to enter the study, refused any pharmacologic treatment, and accepted only psychotherapeutic help. Forty-two patients (32 male, 10 female) with pathological gambling (DSM-IV) entered a 14-week single-blind study of lithium or divalproex sodium treatment. All of the subjects gave oral and written consent to participate in our Institutional Review Board–approved study. The mean ± SD age of the subjects studied was 31.6 ± 4.9 years.

Baseline clinical ratings and medical and laboratory evaluations, including physical and neurologic examinations, complete blood count, liver and thyroid function tests, electrolytes, electroencephalogram, and electrocardiogram, were conducted, and patients with abnormal results on any of these tests were excluded from the study, as were patients with positive urine drug screens and patients with focal neurologic abnormalities. At the time of enrollment, each patient was randomly assigned to 1 of the 2 14-week standardized treatments of lithium carbonate or divalproex sodium. The ratings were made under blind conditions by a psychiatrist independent evaluator, and patients, who were not blinded to which medication they were taking, were instructed to make no mention of medication or side effects to the independent evaluator.

### Dosing Schedules

The dosing schedules were as follows. Group 1 received 600 mg/day of lithium carbonate for days 1 through 4 and 900 mg/day for days 5 through 9, then was titrated to 1200 mg/day according to tolerability (assuming plasma lithium levels < 1.0 mEq/L). Blood lithium level was monitored once a week, starting at baseline. Group 2 received 600 mg/day of divalproex sodium for days 1 through 5, then was titrated to 1500 mg/day according to tolerability. Blood valproate level was monitored once a week to achieve plasma levels of drug between 50 and 100 mg/mL.

The titration of medication was adjusted according to clinical conditions and plasma drug levels, but the clinical independent rater remained blind to the adjustment. The occurrence of severe side effects, lack of compliance (missing more than 3 consecutive doses of the drug), and withdrawal of patient consent were criteria for premature discontinuation from the study. No other medications, including psychoactive agents, were administered during the study.

### Assessment

Patients were assessed with the South Oaks Gambling Screen (SOGS)[25] at enrollment. The Yale-Brown Obsessive Compulsive Scale modified for pathological gambling (PG-YBOCS),[26] which evaluates the severity of gambling, the Mania Rating Scale (MRS),[27] and the Hamilton Rating Scale for Depression (HAM-D)[28] were administered at baseline and every 2 weeks until the end of the study. Overall severity and improvement were assessed with, respectively, the Clinical Global Impressions-Severity of Illness scale (CGI-S)[29] (1 = not ill to 7 = extremely ill) and the Clinical Global Impressions-Improvement scale (CGI-I)[29] (1 = very much improved, 4 = no variation, and 7 = very much worsened).

### Data Analysis

Intent-to-treat analysis was used for repeated measures. Student t tests, paired t tests, and 1-sample analyses were performed where appropriate to assess the significance of

**Table 1. Demographic and Clinical Characteristics at Baseline of Pathological Gambling Subjects Assigned to Lithium or Valproate Treatment[a]**

| Characteristic | All Subjects (N = 42) | Lithium Group (N = 23) | Valproate Group (N = 19) |
|---|---|---|---|
| Age, y | 31.6 (4.9) | 30.1 (4.2) | 32.5 (4.6) |
| Gender, N | 32M, 10F | 17M, 6F | 15M, 4F |
| Age at onset, y | 19.6 (5.2) | 19.4 (5.6) | 19.1 (5.3) |
| SOGS score | 15.3 (1.8) | 15.8 (1.5) | 14.6 (2.1) |
| PG-YBOCS | 21.6 (6.3) | 22.3 (5.9) | 20.7 (6.8) |
| HAM-D (total score) | 10.6 (3.7) | 10.8 (3.7) | 10.3 (3.9) |
| MRS (total score) | 9.2 (3.8) | 9.4 (3.5) | 8.8 (4.2) |
| CGI-S | 4.8 (1.0) | 4.9 (1.1) | 4.6 (1.0) |

[a]Values are expressed as mean (SD) except for gender. Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness, HAM-D = Hamilton Rating Scale for Depression, MRS = Mania Rating Scale, PG-YBOCS = Yale-Brown Obsessive Compulsive Scale modified for pathological gambling, SOGS = South Oaks Gambling Screen.

**Table 2. Clinical Measures at the Beginning and End of Treatment in Pathological Gamblers Assigned to Lithium or Valproate Treatment[a]**

| | Lithium Group (N = 23) | | Valproate Group (N = 19) | |
|---|---|---|---|---|
| Scale | Beginning | End | Beginning | End |
| PG-YBOCS | | | | |
| Urges/thoughts score | 10.4 (3.7) | 6.5 (3.1)[b] | 9.7 (3.7) | 7.3 (2.9)[c] |
| Behavior score | 11.9 (3.7) | 8.6 (3.4)[d] | 11.0 (2.9) | 7.0 (3.1)[e] |
| Total score | 22.3 (5.9) | 15.1 (4.0)[b] | 20.7 (6.8) | 14.3 (4.1)[c] |
| CGI-S | 4.9 (1.1) | 2.5 (0.9)[b] | 4.6 (1.0) | 2.3 (0.7)[c] |
| HAM-D (total score) | 10.8 (3.7) | 8.6 (3.8) | 10.3 (3.9) | 7.9 (4.2) |
| MRS (total score) | 9.4 (3.5) | 7.2 (3.6) | 8.8 (4.2) | 7.8 (3.9) |

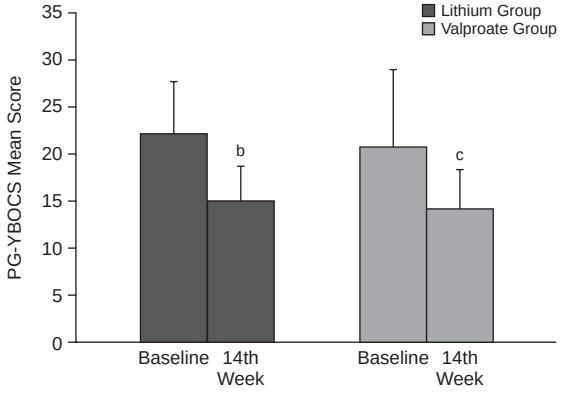
[a]Values are expressed as mean (SD). Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness, HAM-D = Hamilton Rating Scale for Depression, MRS = Mania Rating Scale, PG-YBOCS = Yale-Brown Obsessive Compulsive Scale modified for pathological gambling.
[b]From baseline (paired t); df = 22, p < .01.
[c]From baseline (paired t); df = 18, p < .01.
[d]From baseline (paired t); df = 22, p < .05.
[e]From baseline (paired t); df = 18, p < .05.

differences between groups, with alpha set at p < .05, 2-tailed. Parametric tests were utilized for variables with interval unit of measurement and for the normal distribution of the data. Data were analyzed using an SPSS-PC package (SPSS, Chicago, Ill.).

## RESULTS

Of the 42 enrolled subjects, 19 (45.2%) were married, 8 (19.0%) were divorced, and 15 (35.7%) were single. Twelve (28.6%) were left-handed, and 30 (71.4%) were right-handed. Preferred types of gambling (patients could choose more than 1 type) were horse races (N = 18), video poker (N = 26), lotto/numbers (N = 12), cards (N = 10), sports (N = 5), and stocks/bonds (N = 6). Comorbid diagnoses included past depressive episodes (N = 7), past alcohol or drug abuse (N = 23), past panic disorder (N = 15), past OCD (N = 9), antisocial personality disorder (N = 8),

**Figure 1. Mean (+ SD) PG-YBOCS Scores at Baseline and at the End of Treatment in Patients Treated With Lithium (N = 23) or Valproate (N = 19)[a]**




[a]Abbreviation: PG-YBOCS = Yale-Brown Obsessive Compulsive Scale modified for pathological gambling.
[b]From baseline: paired t = 3.05, df = 22, p < .01.
[c]From baseline: paired t = 3.98, df = 18, p < .01.

and other impulse-control disorders (N = 16). Demographic and baseline clinical characteristics of the patients assigned to each treatment group are summarized in Table 1. There were no significant between-group differences in age, gender, age at onset, duration of the disorder, SOGS score, or PG-YBOCS total score.

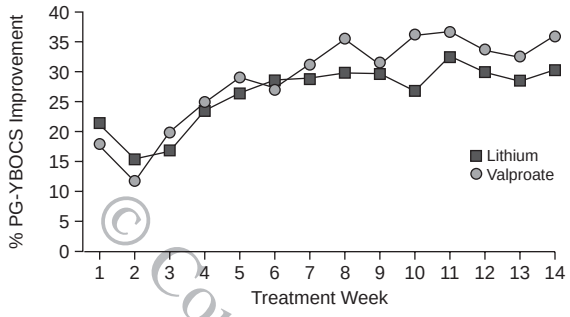
Eight (34.8%) of the 23 subjects taking lithium and 3 (15.8%) of the 19 subjects taking valproate dropped out of treatment. Six subjects taking lithium and 2 taking valproate were dropped from the study because of noncompliance. Two subjects taking lithium and 1 subject taking valproate dropped out due to an intolerance of side effects. A total of 15 subjects taking lithium and 16 patients taking valproate completed the 14-week protocol.

The mean lithium dose was 795.6 ± 261.5 mg/day, and the mean valproate dose was 873.7 ± 280.1 mg/day, including dropouts. The mean blood drug levels at the 14th week (including the last levels monitored in the dropouts) were 0.8 ± 0.1 mEq/L for lithium and 71.9 ± 14.0 mg/mL for valproate.

Table 2 shows the scores for the clinical variables at the beginning and at the end of the treatment period for each group. At the end of the 14-week treatment period, both the lithium (30.1%; t = 3.05, df = 22, p < .01) and the valproate (35.9%; t = 3.98, df = 18, p < .01) groups showed significant mean percentage improvement on PG-YBOCS score, but the improvement difference between groups was not statistically significant. Figure 1 shows the mean PG-YBOCS scores at baseline and at the end of the treatment in patients treated with lithium or valproate.

Both groups showed an early response at the end of the first week of treatment. This response reached statistical significance at week 1 for the lithium group (paired t = 2.41, df = 22, p < .05). We observed a reduction of

**Figure 2. Mean Percentage Improvement on PG-YBOCS in Patients Treated With Lithium (N = 23) or Valproate (N = 19)[a]**




[a]Abbreviation: PG-YBOCS = Yale-Brown Obsessive Compulsive Scale modified for pathological gambling.

improvement following week 1 in both groups, and significant improvements were seen again only after week 4. Figure 2 shows the percentage PG-YBOCS mean improvement during the 14-week treatment period for each group.

CGI-S score was significantly reduced in both groups when the scores at the 14th week and at baseline were compared (see Table 2). The mean CGI-I score at the 14th week was 2.8 ± 1.0 (vs. null value of 4: t = 5.61, df = 22, p < .01) for the lithium group, and 2.5 ± 0.8 (vs. null value of 4: t = 7.64, df = 18, p < .01) for the valproate group. Twelve (52.2%) of the 23 patients initially enrolled on lithium treatment and 11 (57.9%) of the 19 enrolled on valproate treatment reached a CGI-I score of very much or much improvement in the fourth week of treatment. Fourteen (60.9%) of the 23 patients on lithium treatment and 13 (68.4%) of the 19 patients on valproate treatment were considered to be responders (score of very much or much improved on the CGI-I) by the 14th week (end of the study). Comparison at baseline and the end of the trial between patients with and without a past history of substance abuse revealed no difference in outcome after treatment (mean PG-YBOCS score in patients with a history of substance abuse: baseline, 22.7 ± 5.6; end of trial, 14.0 ± 4.4; mean PG-YBOCS score in patients with no history of substance abuse: baseline, 20.3 ± 6.9; end of trial, 14.9 ± 4.7; difference between groups: baseline, t = 1.19, df = 40, NS; end of trial, t = 0.62, df = 40, NS).

## CONCLUSION

Both mood stabilizers (lithium and valproate) demonstrated efficacy in the treatment of pathological gambling in this randomized, single-blind, 14-week treatment study. The mean SOGS score was 15.3 for all subjects (see Table 1). This score suggests severe addictive gambling behavior when one takes into account that the scores for this instrument range from 0 to 20 and "problem gambling" is defined as a score of 5 or higher. The lithium and valproate subgroups did not differ in severity of pathological gambling behavior, and both groups of subjects had a severe level of gambling-related pathology. Significant and persistent improvements were seen after week 4. Compared with baseline values, endpoint PG-YBOCS total score and subscores were significantly reduced for both the valproate (mean percentage of total PG-YBOCS improvement: 35.9%) and lithium groups (mean percentage of total PG-YBOCS improvement: 30.1%) (see Figures 1 and 2). Twelve (52.2%) of the 23 patients initially randomly assigned to lithium and 11 (57.9%) of the 19 randomly assigned to valproate reached a CGI-I score of much or very much improved in the fourth week of treatment. Responders (scoring "much improved" on the CGI-I) included 14 (60.9%) of the 23 patients taking lithium and 13 (68.4%) of the 19 taking valproate at the 14th week (end of the study). The initial transient response observed at the end of the first week in both groups and reaching statistical significance for lithium could be interpreted as a strong early placebo effect. Such an effect has previously been reported in patients with impulsive disorders and pathological gambling.[14] Improvement on both outcome measures that persisted throughout the course of the 14-week trial starting at week 4 suggests that this is not merely a placebo response. However, the lack of a placebo-controlled group is to be considered a limitation of the study, and long-term placebo and nonspecific treatment effects cannot be excluded.

Lithium has been used for many years to treat disorders frequently associated with pathological gambling such as bipolar mood shifts, mood instability, and impulsivity. The findings of this extensive single-blind study are consistent with previous reports on the efficacy of lithium carbonate in pathological gambling with comorbid bipolar features.[23] The efficacy of valproate in a behavioral addiction, such as pathological gambling, is also consistent with the reported efficacy of this drug in the treatment of bipolar disorder with comorbid addictions.[30] Mood stabilizers have shown antiaggressive and anti-impulsive effects in other populations.[30] Such effects have been observed in open and double-blind trials of borderline subjects,[20,21] in a double-blind study of youth with explosive temperament and mood lability,[17] and in studies of impulsive aggressive patients with personality disorders[18] and concomitant substance abuse.[31] Therefore, a specific "anti-impulsive" action of mood stabilizers can be hypothesized. We cannot consider the reduction of gambling urges and behaviors to be a consequence only of mood improvement, as the scores on the HAM-D and MRS scales were reduced only slightly in value (see Table 2). Furthermore, because patients with bipolar disorder were excluded from the present study, reductions in gambling urge cannot be directly accounted for by the effects of lithium and valproate on mood instability. While we agree that valproate and lithium can have an impact on mood consistent with reports by McElroy[32] in

intermittent explosive disorder, this effect was not significant (see Table 2), and since we excluded bipolar patients in this sample, this effect is clinically less relevant than the actions on urge-related symptomatology.

The clinical courses of improvement for lithium and valproate are similar, but fewer patients taking valproate dropped out of the study. Differences in sociodemographic characteristics of the sample do not explain slight differences in response. Our sample was composed of subjects with a long-term history of pathological gambling (the mean duration of illness was 10 years) and with several previous episodes or chronic behavior.

Since none of the patients received psychosocial or supportive therapies during the trial, the findings of this study do not reflect an interaction between medication and psychosocial treatment.

The experience of the "urge" in pathological gambling represents a potential overlap between pathological gambling and the spectrum of bipolar clinical disorders. This experience is difficult to define and may overlap with a mixed episode in a subclinical manner, yet be undetectable by standardized instruments and criteria. Therefore, it may be necessary to adopt a new, more subtle instrument and set of criteria that include a broader definition of a mixed episode, such as the criteria recently proposed by Cassidy et al.[33] Unfortunately, even with such new criteria, symptoms of a soft bipolar condition, such as irritability and mood lability, may be difficult to distinguish from the effects of acute and chronic substance abuse[23] and from the so-called "urge" of behavioral addiction.

The addiction cycle has been described as having 3 components: preoccupation-anticipation, binge-intoxication, and withdrawal–negative affect.[34] Addiction, to substances or behaviors, is not a static phenomenon; different components constitute a cycle or cycles of ever-growing pathology.[35] It is possible that in a behavioral addiction such as pathological gambling, drugs with different mechanisms of action (e.g., lithium and valproate) could interfere in different clinical phases or at different levels of the dysfunction. Medication seems to be effective in reducing several dimensions of pathological gambling thought and behavior, and this effect could be mediated through several different pathways. Influences at the level of the decision-making process, delay of reward, and pathological gambling compulsive behavior[36] could mediate the clinical effect of mood stabilizers.

In addition, the effectiveness of lithium and valproate in pathological gambling could be dependent on different mechanisms of action. The efficacy of lithium supports the hypothesis that medications acting on the serotonergic system invoke a therapeutic response in pathological gambling. In interpreting the efficacy of valproate, its amplitude of activity with its wide spectrum of clinical effectiveness and range of mechanisms of action should be considered.

Valproate causes a potentiation of GABAergic activity, affects enzymes related to tricarboxylic acid, affects sodium channels, and has an inhibitory effect on the high-frequency firing of neurons.[37] It is possible that changes in other neurotransmitters (such as increases in the levels of norepinephrine, dopamine, and serotonin documented in several brain regions after chronic treatment or a decrease in norepinephrine and serotonin in the hypothalamus)[38] are secondary to the changes in GABAergic neurotransmission.

The mechanism of action of valproate in bipolar disorder may be similar to that of lithium. Valproate, like lithium, may stimulate glutamate release and inositol 9(1,4,5)-trisphosphate accumulation as reported in a study conducted on mouse cerebral cortical slices, though through a different mechanism.[39] The efficacy of valproate in pathological gambling could be related to any of these mechanisms of action. These mechanisms could ameliorate pathological gambling by acting on different neurobiological aspects of addiction. Because another potential beneficial effect of valproate is related to its anxiolytic action,[40] comorbidities for anxiety disorders should be assessed in future investigations.

Of the initial sample of 73 patients, 25 were excluded for comorbid conditions, 6 refused drug treatment, and 1 1 dropped out. Eight of the dropouts were treated with lithium, and 3 were treated with valproate. The findings of this study may not be applicable to non–treatment-seeking gamblers or to noncompliant, difficult-to-treat patients. An integrated psychosocial setting may be necessary to enhance compliance.

The conclusions that can be drawn from this study are limited by its single-blind design, its small sample size (especially since the sample was divided into 2 treatment groups), and the characteristics of the sample. Alcohol and substance abusers were excluded from the sample, yet alcohol and substance abuse are highly comorbid with pathological gambling. Ideally, these subjects should be included to test the effectiveness of mood stabilizers in the treatment of pathological gambling.

The SCID was used in the present study to determine the absence of a comorbid bipolar disorder. The validity of this assessment is questionable, as there is much debate over the accuracy of the SCID in detecting bipolar disorder, and, in particular, bipolar II disorder. The use of this instrument may have biased the sample by including bipolar II patients in the study. Future research could instead assess patients based on criteria for the so-called "bipolar spectrum" disorders.[13,41,42] This approach could be helpful in identifying pathological gamblers who may be appropriate for treatment with mood stabilizers.

The long-term outcome of gambling addiction in subjects under pharmacologic treatment has not been exhaustively studied. While there remains a controversy around the definition of impulsive and addictive symptoms and their differentiation from compulsive and craving

symptoms, a full discussion is outside the range of this article.

While the existence of an "addiction memory" and its importance in relapse occurrence and maintenance of learned addictive behavior have been recently proposed,[43] follow-up studies using lithium and valproate to treat pathological gambling with a duration greater than that considered in the present study could provide useful information on the course of gambling addiction and its response to treatment. The percentage of left-handed subjects in the sample was elevated at 28.6%. It is possible that potential influences of hemispheric imbalance with right hemisphere dysfunction, a so-called "gourmand syndrome,"[44,45] could play a peculiar role in influencing this impulsive behavior.

Despite the limitations of this study, the results suggest the efficacy of both lithium carbonate and valproate in the treatment of pathological gambling. Further placebo-controlled studies with mood stabilizers in pathological gambling should be performed to confirm these promising preliminary results.

*Drug names:* carbamazepine (Tegretol and others), divalproex sodium (Depakote), fluvoxamine (Luvox and others).



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