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Original Article

Gabapentin in the acute treatment of refractory bipolar disorder

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Background: Gabapentin, a new anti-epileptic agent, has been anecdotally reported to be effective in the treatment of mania. We systematically assessed the response rate in bipolar patients being treated adjunctively with gabapentin for manic symptoms, depressive symptoms, or rapid cycling not responsive to standard treatments.

Method: Twenty-eight bipolar patients experiencing manic (n = 18), depressive (n = 5), or rapid-cycling (n = 5) symptoms inadequately responsive to at least one mood stabilizer were treated in an open fashion with adjunctive gabapentin. Illness response was assessed using the Clinical Global Impression Scale modified for bipolar disorder (CGI-BP). A 'positive response' was operationalized as a CGI response of much or very much improved.

Results: Fourteen of the 18 (78%) treated for hypomania or mania had a positive response to a dosage range of 600–3600 mg/day. Patients with hypomania responded fastest, with a positive response achieved in 12.7 ± 7.2 days. Patients with classic mania had a mean time to positive response of 25 ± 12 days, and in patients with mixed mania it was 31.8 ± 20.9 days. All of the five patients treated for depression had a positive response within 21 ± 13.9 days. Only one of five patients with rapid cycling had a positive response. Gabapentin was well tolerated by all patients, with the most common side-effect being sedation.

Conclusions: Gabapentin appears to have acute anti-manic and anti-depressant properties as an adjunctive agent for refractory bipolar illness. Prospective double-blind studies are needed to further delineate its acute efficacy when used as monotherapy and its prophylactic efficacy as monotherapy or in conjuction with other mood stabilizers.

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Given the efficacy of the anti-convulsants, carbamazepine and divalproex sodium in the treatment of patients with bipolar disorder, considerable interest has been generated in the potential usefulness of the newer anti-epileptic agents (1) One such new agent, gabapentin (Neurontin), has been available in the US since 1993 and is now FDA approved for adjunctive treatment of refractory partial epilepsy (2–6). Although its mechanism of anti-epileptic action is unknown, gabapentin is a GABA analog not directly active at GABA receptors that has been postulated to exert its anti-convulsant effects by modulation of inhibitory (GABA) and excitatory (glutaminergic) amino acids (7, 8). This is of potential relevance to the treatment of bipolar illness, as the anti-manic action of divalproex sodium has been hypothesized to be due, in part, to its GABAergic activity (1), and GABA deficits have been reported in depression (9).

Gabapentin also has a favorable pharmacokinetic profile. It is not protein bound or hepatically metabolized and is renaly excreted. There are few interactions with other medications, including divalproex sodium and carbamazepine (10, 11). Gabapentin has a wide therapeutic index, is gener-

ally well tolerated, is not associated with adverse hematologic or hepatic effects, and does not require routine serum concentration or blood monitoring.

Preliminary reports suggest a role for gabapentin in bipolar illness. They suggest possible anti-manic (12–15), anti-depressant (15, 16), and anti-cycling (12, 14, 15, 17–20) properties: We thus sought to further evaluate the efficacy of gabapentin in the treatment of bipolar disorder.

Methods

Subjects

Twenty-eight patients (both in- and out-patients) with DSM-IV Bipolar I (n = 23) or II (n = 5) disorder were treated in an open fashion with gabapentin at one of the four US centers of the Stanley Bipolar Network. Demographic and clinical characteristics of this group are shown in Table 1. Patients were treated adjunctively with gabapentin for hypomania/mania, depression, or rapid cycling that was inadequately controlled with at least two prior trials of standard pharmacotherapy. In all cases, gabapentin was added to an already existing pharmacologic regimen that was ineffective at controlling the patients' symptoms, and prior medication regimens were not changed during the assessment period of the efficacy of add-on gabapentin. Of the 28 patients, 18 were treated for hypomania/mania, five for depression, and five for rapid cycling. In the rapid-cycling patients, treatment was initiated when they were euthymic. Informed consent was obtained for each patient prior to a trial with gabapentin.

Patients were followed prospectively, seen weekly to monthly by their treating physicians, and rated for improvement by a separate study clinician every 2 weeks using the Clinical Global Impression Scale (21) modified for bipolar disorder (CGI-BP) (22). The CGI-BP was developed to be able to capture improvement scores for different aspects of the illness (e.g., mania, depression, and overall illness). Raters across sites were trained in the use of CGI-BP, with good inter-rater reliability across the sites using the CGI (ICC range, 0.92–0.93). A positive response to gabapentin was operationalized as a CGI-BP score of 1 or 2 (much or very much improved). For patients with rapid cycling, life chart data of the patients' course over 6 months to 1 year prior to the initiation of gabapentin was compared to life chart data in the year after gabapentin treatment was initiated.

At the initiation of the gabapentin trial, data were systematically recorded regarding concurrent mood-stabilizing medications that were not sufficient for affective symptom resolution (Table 1). The length of the gabapentin add-on trial, as well as the time to positive response and dose at the time of positive response, were recorded for each patient. Specific side-effects were noted and characterized as mild, moderate, or severe.

Statistics

Statistical analyses consisted of descriptive statistics.

Table 1. Demographic and clinical characteristics of bipolar sample

	Total (n = 28)	Hypomania/mania (n = 18)	Depression (n = 5)	Rapid cycling (n = 5)
Age	39 ± 5	–	–	–
n (%) male	10 (36)	–	–	–
n (%) with BPI	23 (82%)	17 (94%)	4 (80%)	2 (40%)
n (%) with BPII	5 (18%)	1 (6%)	1 (20%)	3 (60%)
Adj meds at gabapentin trials				
Li		3	–	–
Li + anti dep		–	3	–
Li + DVPX		5	–	–
Li + CBZ		3	–	–
Li + verapamil		1	–	–
DVPX		1	–	–
DVPX + anti dep		–	2	1
DVPX + CBZ		1	–	2
DVPX + verapamil		1	–	–
DVPX + anti psypsychotic		2	–	2
DVPX + benzodiazepines		1	–	–

Table 2. Dosages of and time to respond to adjunctive gabapentin in positive responders

Treated for	Medication dosage range at positive response	n (%) positive response (CGI 1 or 2)	Days to positive response	Total length of trial responders (days)	Total length of trial in non-responders (days)
Mania, classic (n = 3)	1800 ± 1081 (900–3000)	3 (100%)	25 (12.0 ± 13–37)	255 ± 287.1	N/A
Mania, mixed (n = 9)	1722 ± 1081 (300–3600)	5 (56%)	31.8 ± 20.9 (12–63)	251.2 ± 315	33.3 ± 16.7
Hypomania (n = 6)	1875 ± 1209 (900–3600)	6 (100%)	12.7 ± 7.2 (7–27)	80 ± 87.4	N/A
Depression (n = 5)	1200 ± 1081.7 (300–2400)	5 (100%)	21 ± 13.9 (5–35)	246.7 ± 306.2	N/A
Rapid cycling (n = 5)	1500 ± 1076 (600–3000)	1 (25%)	39[a]	274.0[a]	120 ± 119.54

[a] Represents one patient.

Results

A total of 18 patients were being treated for mania/hypomania: 12 were manic (nine mixed, three classic) and six were hypomanic. Five were being treated for depression. An additional five patients with rapid cycling were started on a medication trial of gabapentin when euthymic. Gabapentin was added to a pre-existing mood stabilizer regimen, including lithium and anti-depressants (venlafaxine, SSRIs, stimulants; n = 3), lithium and divalproex sodium (DVPX; n = 5), lithium and carbamazepine (n = 3), lithium and verapamil (n = 1), DVPX monotherapy (n = 1), DVPX and anti-depressants (n = 3), DVPX and carbamazepine (n = 3), DVPX and verapamil (n = 1), DVPX and anti-psychotics (n = 4), DVPX and benzodiazepines (n = 1) (Table 1). In all cases, gabapentin was started at 300 mg one to two times a day and titrated as tolerated. The mean dosages and ranges are shown in Table 2.

Of the 28 patients treated with adjunctive gabapentin, an overall positive response (CGI-BP much or very much improved) was seen in 20 (72%) of the 28 patients. Time to response was most rapid for hypomania (100%; 12.7 ± 7.2 days). The response rate was lowest and the time to response was longest for patients with mixed mania (56%, and 31.8 ± 20.9 days, respectively). Five of the five patients treated for depression had a positive response within 21 ± 13.9 days. Only one of five patients with rapid cycling (20%) were judged to respond favorably to gabapentin. Mean follow-up time on gabapentin for this patient was 274 days.

The average length of the gabapentin trial in those who did not have a positive response is shown in Table 2 and was longer than the time required for a positive response in those who displayed such a response.

Side-effects were reported in 12 (46%) patients. The most common side-effect was sedation (n = 5; 18%), followed by gastrointestinal upset (n = 4; 14%), ataxia (n = 2; 7%), dizziness (n = 1; 3.5%), and headache (n = 1; 3.5%). In all cases, side-effects were rated as mild, and no patient discontinued the treatment trial due to side-effects.

Discussion

Gabapentin adjunctive therapy appeared effective in 72% of bipolar patients treated in an open-label add-on fashion. As most of these patients were either treatment resistant, only partially responsive to ongoing pharmacologic regimen, or intolerant to the side-effects of their mood stabilizer, gabapentin represented an alternative and effective acute adjunctive agent for these patients. Gabapentin appeared to be therapeutic in both the manic and depressed phases of the illness as adjunctive treatment for many of these patients. The time course for the anti-depressant response appeared similar to standard anti-depressant pharmacotherapy. Response for hypomania tended to occur more quickly than for mania when similar doses were used (average dose ~ 1800 mg/day). Whether higher doses titrated more rapidly would produce a more robust or rapid rate of response in mania remains to assessed.

To date, a small number of case reports and case series have provided preliminary clinical data regarding the efficacy of gabapentin in bipolar disorder. Stanton et al. (13) described marked reductions in manic and psychotic symptoms after 10 days of gabapentin monotherapy (3600 mg/day) in a 40-year-old male with bipolar I disorder and alcohol dependence (12).

In the first case series, Schaffer and Schaffer (12) reported that 18 (64%) of 28 patients with various forms of bipolar disorder, who were refractory to standard mood stabilizers, responded to gabapentin (mean dose, 539 mg/day; range, 33–2700 mg/day) (11). In the second case series, Bennett et al. (18) reported moderate or marked improvement in four (80%) of five patients with treatment-refractory bipolar I (n = 3) or schizoaffective disorder, bipolar type (n = 2), who received adjunctive treatment with gabapentin (range, 600–2400 mg/day) (17). In the third case series, Young et al. (14) specifically studied the anti-depressant properties of gabapentin monotherapy (n = 7) or adjunctive treatment (n = 8) in 15 patients with bipolar I (n = 10) or bipolar II (n = 5) depression in a 6-week trial (15). Ten patients were rapid cyclers. There was a significant reduction in Hamilton Depression Rating Scale (HDRS) scores from baseline to endpoint; eight (53%) of 15 patients were rated as responders (> 50% reduction in HDRS scores). A wide range of doses of gabapentin (300–2400 mg/day) were used, with a mean dose of 1050 ± 640 mg/day.

In another series, Ryback et al. (17) presented the results of a retrospective survey of 73 adolescent and adult patients with treatment-refractory bipolar I and II disorder or schizoaffective disorder (16). Response to gabapentin (900–2400 mg/day for adolescents; 200–3500 mg/day for adults) was globally rated as 'positive' in 67 (92%) of 73 patients. In a prospectively evaluated case series, McElroy et al. (14) reported moderate or marked improvement in manic symptoms in seven (78%) of nine patients with bipolar I (n = 7) or bipolar II (n = 2) disorder after 1 month of adjunctive treatment with gabapentin (1600–4800 mg/day) (13). An additional patient displayed moderate improvement after 3 months of treatment. In the most recent report, 12 consecutive out-patients with refractory bipolar spectrum disorders were treated adjunctively in an open fashion with gabapentin (23). Eight patients had a moderate to marked response, two had a mild response, and two had no response to treatment. Patients were followed from 3 to 60 weeks, and the average length of time on drug when improvement was noted was not reported.

Our response rates are similar to those previously reported and provide optimism about the potential usefulness of a new, well-tolerated anti-convulsant in the treatment of bipolar illness. Patients with mixed mania and rapid cycling did not have as positive a response to gabapentin as those with classic mania or depression. This finding, if borne out with larger studies, distinguishes it from the other anti-convulsants and aligns it more closely with lithium in being relatively less effective in treating the mixed and rapid cycling presentations of bipolar illness.

Gabapentin may thus emerge as an important addition to the anti-convulsants used for treating bipolar disorder. The exact dosage range needed for maximum likelihood of a positive response and the ideal rate of titration to achieve the most rapid response could not be assessed in this small sample. The current study is limited by its open design and small number of patients in heterogeneous mood states. Future double-blind randomized studies are needed to determine the therapeutic range for treating bipolar disorder. Gabapentin was well tolerated by all patients. As gabapentin is excreted by the kidney, not hepatically metabolized, and no drug–drug interactions between gabapentin and either carbamazepine or divalproex sodium have been reported to date, it can be added to other mood stabilizers without the heightened risk of hepatoxicity and pharmacokinetic interactions associated with many other agents used in combination therapy. Additionally, a recent study suggests that gabapentin and lithium may be administered in combination without significant renal pharmacokinetic interaction (24).

As this was an adjunctive study, the role of gabapentin as an effective monotherapy agent remains to be further studied.

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