Levetiracetam in Patients With Impulsive Aggression: A Double-Blind, Placebo-Controlled Trial

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Objective: There are few controlled studies evaluating drug treatment for impulsive aggression. The objective of this study was to evaluate levetiracetam in patients with impulsive aggression, and whether diagnosis or other baseline characteristics predict response.

Method: Outpatients with clinically significant impulsive aggression (meeting Coccaro et al. revised criteria for intermittent explosive disorder), without other psychiatric symptomatology clearly requiring treatment, were randomly assigned to levetiracetam or placebo, double-blind, for 10 weeks, at a variable dose with a maximum dose of 3000 mg/day. The primary efficacy measure was change in the total aggression score from the revised Overt Aggression Scale-Modified. The study was conducted from September 2005 to July 2006.

Results: Of 40 patients (20 in each treatment group), 34 completed at least 4 weeks of treatment with double-blind medication. There was no overall statistical evidence of levetiracetam benefit, and no subgroup more responsive to levetiracetam could be identified.

Conclusions: Levetiracetam was not as efficacious as oxcarbazepine was in a prior similar study. Additional studies of medications for impulsive aggression seem warranted.

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Treatment studies for impulsive aggression are relatively rare[1] (and inconclusive[2]), despite the fact that aggression is a common psychiatric symptom,[3] and many patients who have clinically significant impulsive aggression do not have another psychiatric diagnosis that clearly accounts for their aggression.[4] The reasons for the relative dearth of treatment studies for impulsive aggression are multiple.

First, impulsive aggression is a common symptom of other psychiatric disorders, such as mania, schizophrenia, attention-deficit/hyperactivity disorder (ADHD), and antisocial personality disorder, and this overlap of symptomatology has complicated attempts to focus on the treatment of impulsive aggression as a symptom. However, many areas of psychopathology are not well circumscribed; for example, attentional difficulties are found in a multitude of diagnoses, but the diagnosis of ADHD is still useful for patients in whom the attentional difficulties are primary. Also, generalized anxiety disorder (GAD) is generally associated with concomitant psychiatric disorders,[5] but this does not necessarily preclude a diagnosis of GAD, or the use of specific treatments. It seems fairly self-evident that people with "bad tempers," whose temper has significantly interfered with their lives, are not rare.

DSM-III, -III-R, and -IV have, in a sense, impeded treatment studies for impulsive aggression, since the criteria for intermittent explosive disorder (IED) are very restrictive and exclude most patients with a chief complaint of impulsive aggression.[4] DSM-III excluded patients with generalized impulsivity; this exclusion criterion was eliminated in DSM-IV, but DSM-IV still requires "serious assaultive acts or destruction of property"; many patients with clinically significant impulsive aggression have met this criterion at some time in the past,[6] but relatively few seeking clinical treatment have met this criterion within the past 6 to 12 months, making it difficult to justify a current diagnosis of IED. Coccaro et al.[4] have devised research criteria for IED that allow the diagnosis if patients have clinically significant aggression, even if the aggression is only verbal or if it involves assault or destruction of property that is less severe than "serious." Using these research criteria, it has not been difficult to recruit patients for treatment studies.[7,8]

Another impediment to studies of impulsive aggression has been the lack of a valid and reliable efficacy measure. Coccaro et al.[9] modified the Overt Aggression Scale (developed by Yudofsky et al.[10] for rating inpatients) to create a scale for rating outpatients (the OAS-M). However, in the first large multicenter study[8] using the OAS-M, scores were highly skewed, which prevented the use of parametric statistics (nonparametric tests are less powerful). The skewness was due to the scoring method; the score was a multiple of the actual number of aggressive episodes per week, which could be a very large number, especially for relatively mild episodes. This study did not show consistent superiority for divalproex compared with placebo,

and may have discouraged other pharmaceutical companies from conducting large treatment studies for impulsive aggression. However, Mattes[7] revised the OAS-M, condensing the frequency scores into a 0-to-4 range of scores (e.g., 4 = more than 10 episodes per week), which resulted in a less skewed distribution. This also increased face validity, in that previously a patient with many episodes of mild irritability could have a total aggression score much higher than a patient who had less frequent but more severe aggression. A study using this revised OAS-M demonstrated statistically significant superiority for oxcarbazepine compared with placebo in patients with impulsive aggression.[7] With the research criteria for IED and the revised OAS-M, it appears that treatment studies for impulsive aggression are now quite feasible and promising. A final impediment to such research is the belief that impulsive aggression is more of a social problem than an illness. However, this obstacle has been overcome for other conditions, for example, alcohol and drug abuse, pathologic gambling, and kleptomania, so it is not unlikely that impulsive aggression will increasingly be recognized as a symptom appropriate for treatment.

Levetiracetam is an anticonvulsant approved for complex partial seizures. It has a unique pharmacologic profile,[11] in that it is inactive in conventional animal seizure models (e.g., maximal electroshock-induced seizures), but is active in some nonconventional models (e.g., epileptiform activity induced by bicuculline[12]) and inhibits both completed amygdala-kindled seizures and the initial phase of amygdala kindling.[13,14] Recently, a binding site for levetiracetam was found and identified as the synaptic vesicle protein 2A (SV2A),[15] although the clinical and pharmacologic significance of this site is unknown. Levetiracetam may also be distinct from other anticonvulsants due to its ability to antagonize synchronization of neuronal activity.[16] Like other treatments for complex partial seizures, levetiracetam is thought to affect the temporal lobe and other parts of the limbic system, areas of the brain thought to be involved in aggression. Of the relatively new anticonvulsants useful for complex partial seizures, levetiracetam is one of the easiest to use, with few side effects and no requirement for laboratory or electrocardiogram monitoring; there are also relatively few interactions with other medications. An open, naturalistic pilot study[17] suggested efficacy for levetiracetam in aggressive patients (primarily adolescents). Therefore, it seemed reasonable to more systematically evaluate levetiracetam for the treatment of impulsive aggression. The current study was a placebo-controlled trial of levetiracetam, with a variable dose, in patients with impulsive aggression.

METHOD

This was a 10-week, single-center, randomized, parallel-group, double-blind, placebo-controlled, variable-dose study of outpatients with impulsive aggression. After institutional review board approval was obtained, the study was conducted from September 2005 to July 2006. The intended N was 40 (20/group), which provided sufficient power based on the oxcarbazepine study[7] (in which the total N was 48), if levetiracetam was as efficacious as oxcarbazepine.

Inclusion Criteria

Patients met the Coccaro et al.[4,18] revised criteria for IED; specifically:

1. Recurrent incidents of aggression manifest as verbal or physical aggression toward other people, animals, or property occurring twice weekly on average for 1 month.
2. The degree of aggressiveness expressed is grossly out of proportion to the provocation or any precipitating psychosocial stressors.
3. The aggressive behavior is generally not premeditated (i.e., is impulsive) and is not committed to achieve some tangible objective (such as money, power, intimidation, etc.).
4. The aggressive behavior causes either marked distress in the individual or impairment in occupational or interpersonal functioning.
5. The aggressive behavior is not better accounted for by another mental disorder (e.g., major depression, mania, schizophrenia or another psychotic disorder, ADHD), a general medical condition (e.g., head trauma or Alzheimer's disease), or the direct physiologic effects of a substance.

In addition, patients had to be 18 to 65 years of age and in generally good health, and women of childbearing potential had to be practicing effective contraception. Written informed consent was obtained.

Exclusion Criteria

The exclusion criteria were as follows:

1. Lifetime history of schizophrenia, bipolar disorder, epilepsy, dementia, mental retardation or autism, or substance abuse in prior 6 months.
2. Need for treatment with antipsychotics, anticonvulsants, or mood stabilizers, or any recent change (within 3 months) in psychotropic medication. Patients on treatment with antidepressants, anxiolytics, stimulants, or hypnotics were eligible.
3. Significant risk of severely injuring others or self.
4. Any current psychiatric or neurologic conditions that required specific treatment (e.g., major depression, obsessive-compulsive disorder, panic disorder, ADHD). However, if the other condition had been adequately treated and was clinically stable,

and if impulsive aggression was the most clinically important current symptom, the patient was eligible.

Thus, this was a heterogeneous group of patients with a chief complaint of impulsive aggression.

Treatments

At baseline, patients were randomly assigned to either levetiracetam or placebo in a 1:1 ratio. The 10-week study included 4 weekly, then 3 biweekly visits. The initial dose of levetiracetam was 250 mg b.i.d.; dosage was increased by 250 mg b.i.d. after 1 week of treatment with each dose to at least 1000 mg/day (500 mg b.i.d.) (if tolerated), with a maximum of 3000 mg/day (1500 mg b.i.d.) by week 6, if needed. Due to tolerability, the dose could be escalated more slowly, and more could be given at bedtime.

Efficacy Assessments

The primary efficacy measure was change in the total aggression score from the revised (described in Mattes[7]) version of the OAS-M.[9]

Secondary efficacy assessments included the Global Overt Aggression rating from the revised OAS-M, a patient-rated global improvement score (PGI; 0 = no change, 1 = slight, 2 = moderate, and 3 = much improvement), a Relative Rating of Aggressive Behavior (derived from the Rating Scale for Aggressive Behavior in the Elderly[19]), the Hostility score on the Brief Psychiatric Rating Scale (BPRS),[20] and the scores for (1) verbal aggression, (2) aggression against objects, and (3) assault against others and the Subjective Irritability rating from the revised OAS-M.

The revised OAS-M and PGI ratings were completed at weeks 4, 6, 8, and 10 (the revised OAS-M was also completed at baseline). The BPRS and the Relative Rating were completed only at baseline and at weeks 4 and 10.

Statistical Methods

All efficacy parameters were analyzed on an intent-to-treat basis. Covariance analyses, covarying out baseline or "initial" scores, were the primary analyses for all variables that had initial or baseline scores. The "initial" score used in these analyses was the mean of the screening and baseline scores (if both scores were available), to provide a more stable measure of initial symptoms (as was done by Hollander et al.[8] and Mattes[7]).

RESULTS

Forty patients were randomly assigned to double-blind medication, 20 to levetiracetam and 20 to placebo. Thirty-four of the patients had an adequate trial (at least 4 weeks) of double-blind medication. Only 19 patients completed the full 10-week trial, but this high dropout rate was expected; the relatively long duration (10 weeks) was chosen to allow initial "placebo" effects to wane (a dropout due to lack of efficacy with placebo does not reduce statistical power).

Table 1. Initial[a] and Baseline[b] Measures of Aggressiveness in Patients With Impulsive Aggression

	Levetiracetam (N = 20)		Placebo (N = 20)			
Measure	Mean	SD	Mean	SD	t	p
OAS-M score						
Total aggression	11.9	3.7	11.3	4.1	0.51	.62
Global overt aggression[c]	3.50	0.54	3.43	0.49	0.59	.65
Global subjective irritability	3.28	0.43	3.28	0.44	0	1.00
Verbal aggression	8.58	2.07	8.05	2.07	0.80	.43
Aggression against objects	2.88	1.52	2.38	1.11	1.19	.24
Assault against others	0.23	0.50	0.42	1.05	0.77	.45
BPRS hostility	3.55	0.51	3.45	0.51	0.62	.54

[a]OAS-M scores are "initial scores," or the mean of ratings at screening and baseline, the 2 ratings (1 week apart) performed prior to double-blind medication.
[b]BPRS was not completed at screening; the hostility score is a baseline score.
[c]The OAS-M was revised (according to Mattes[7]). The ratings of global overt aggression were as follows: 0 = not at all (or only subjectively felt anger); 1 = slight: occasional snappiness of doubtful clinical significance; 2 = mild: argumentative, quick to express annoyance; 3 = moderate: e.g., often shouts/loses temper/slams doors; 4 = moderately severe: worse than moderate, e.g., some breakage, pushing others; 5 = severe: e.g., more breakage, more seriously assaultive; 6 = extreme: repeatedly seriously violent against things or persons.
Abbreviations: BPRS = Brief Psychiatric Rating Scale, OAS-M = Overt Aggression Scale-Modified.

Demographic and Baseline Characteristics

The levetiracetam and placebo groups did not differ significantly (statistically) on demographic variables including age, sex, marital status, and years of education. The mean age was 45.38 years (SD = 11.2; range, 21–64 years), 87.5% (N = 35) of the patients were male, 57.5% (N = 23) were currently married (20% [N = 8] had never been married), and the mean number of years of education was 12.9 (SD = 2.2).

As shown in Table 1, the groups were also compared on initial aggression ratings. These included the revised OAS-M scores and the BPRS ratings. There was no significant difference between the groups (levetiracetam vs. placebo).

The 2 groups were also compared regarding diagnoses. Only 4 diagnoses occurred frequently enough (in at least 8 patients) to warrant analysis. These were ADHD (either residual or in remission) (N = 13), prior alcohol or drug abuse or dependence (N = 12), prior major depression (N = 11), and IED by DSM-IV criteria (N = 8). The percentage with these diagnoses did not differ significantly between the groups.

Table 2. Efficacy Measures in Patients With Impulsive Aggression Treated With Levetiracetam or Placebo

	Levetiracetam			Placebo				
Measure	Mean Change	SD	N[a]	Mean Change	SD	N	t	p
OAS-M[b]								
Total aggression[c]	–4.68	5.54	19	–4.88	4.70	20	0.67	.51
Global overt aggression	–0.84	0.94	19	–0.93	0.98	20	0.74	.47
Subjective irritability	–0.66	0.80	19	–0.68	0.95	20	0.11	.92
Verbal aggression[c]	–3.00	3.30	19	–2.75	2.69	20	–0.08	.94
Aggression against objects[c]	–1.42	2.22	19	–1.28	1.23	20	0.95	.35
Assault against others[c]	–0.13	0.64	19	–0.43	1.05	20	1.04	.30
BPRS hostility rating[d]	–1.00	0.94	19	–0.85	0.95	20	–0.14	.89
Relative rating of aggression[d]	–7.63	11.75	11	–7.14	7.95	14	–0.39	.70
	Mean Score			Mean Score				
Patient-rated global improvement[e]	1.74	1.45	19	1.60	1.39	20	0.39	.71

[a]N = 19 for all measures except relative rating of aggression because 1 patient dropped out before any postbaseline ratings were obtained. All results are last observation carried forward.
[b]Analyses were covariance analyses (using the General Linear Model) comparing levetiracetam versus placebo on change scores (final – initial), covarying out the relationship between initial scores and change scores. The initial score is the mean of the screening and baseline scores.
[c]A calculated score, multiplying severity × frequency.
[d]Analysis as for OAS-M scores, except that change = final – baseline (this rating was not completed at screening).
[e]Scored as follows: 0 = no change, 1 = slight, 2 = moderate, and 3 = much improvement.
Abbreviations: BPRS = Brief Psychiatric Rating Scale, OAS-M = Overt Aggression Scale-Modified.

Other relevant baseline characteristics (also not different between the groups) included the following: 9 patients had a history of perinatal trauma, and 13 had been physically abused as children. Thirty-four patients had a history of "road rage" (16 had gotten out of a car to fight or argue). Ten patients had been arrested previously and 9 had been in jail due to aggressiveness (9 had been arrested for other reasons), and 10 had had restraining orders instituted against them. Thirty patients had received prior psychiatric treatment (13 specifically for aggressiveness), and 2 had attempted suicide. In their family history, 30 patients had a first-degree relative with a bad temper (an ad hoc definition), 10 had depression, and 9 had alcoholism.

Treatment

Patients treated with placebo received a mean of 7.55 weeks of double-blind medication; patients treated with levetiracetam received a mean of 7.30 weeks (t = 0.25, NS). Only 6 patients dropped out before receiving at least 4 weeks of double-blind medication. As expected, the optimal daily dose was higher for placebo; patients treated with placebo received the equivalent of a mean of 2313 (SD = 854) mg/day (as placebo), while patients treated with active medication received a mean of 1738 (SD = 1028) mg/day (p = .06).

Medication Effects on Aggressiveness

Results on the efficacy measures are shown in Table 2. None of the measures showed a significant difference between levetiracetam and placebo. As suggested by Table 2, effect sizes were small (most < 0.1), and differences were as likely to favor placebo as levetiracetam.

Analyses by Diagnosis

To determine if any diagnostic group had a better (or worse) response to levetiracetam, compared with placebo, a series of 2-way analyses of variance (ANOVAs) were performed with drug (levetiracetam vs. placebo) on one axis and diagnosis (present or absent) on the other axis. This was done for the 4 diagnoses with more than 8 patients, i.e., ADHD, intermittent explosive disorder by DSM-IV criteria, prior substance abuse or dependence, and prior major depression. The primary analyses of interest in these ANOVAs were the interactions between drug and diagnosis; a significant interaction would indicate that the diagnostic group responded differently than other patients to levetiracetam and placebo. Results showed no significant interactions between drug and diagnosis.

Other Analyses

Following the above planned analyses, since more patients taking levetiracetam dropped out early, due to adverse events, before receiving a therapeutic trial, the question of whether this confounding factor influenced the results was explored. The major efficacy analyses were therefore repeated, excluding the 6 early dropouts (5 on treatment with levetiracetam). Results moved slightly in the expected direction, but in no case was statistical significance approached.

Also, since there is evidence that increased severity of baseline aggression may predict better drug-placebo discrimination,[21] another 2-way ANOVA was performed, with levetiracetam versus placebo on one axis and above versus below the mean initial total aggression score on the other axis. While, as expected, more aggressive patients

Table 3. Adverse Events Occurring in More Than 1 Levetiracetam-Treated Patient and Occurring More Frequently With Levetiracetam Than Placebo

Adverse Event	Levetiracetam (N = 20), N (%)	Placebo (N = 20), N (%)
Sedation	13 (65)	11 (55)
Dizziness	4 (20)	1 (5)
Headaches	5 (25)	2 (10)
Indigestion	4 (20)	0 (0)
Diarrhea	2 (10)	1 (5)
Nausea	2 (10)	0
Impaired coordination	2 (10)	0
Suicidal ideation with depression	2 (10)	0

(at baseline) improved more than less aggressive patients (i.e., a significant main effect for initial aggressiveness), there was no significant interaction between initial aggression and levetiracetam-placebo discrimination (i.e., patients with more severe aggressiveness at baseline did not improve more with levetiracetam, compared with placebo [interaction $F = 0.112$, $p = .74$]).

Adverse Events

Patients receiving levetiracetam lost an average of 0.22 lb over the 10 weeks; patients receiving placebo lost an average of 0.35 lb ($t = 0.05$, NS). Table 3 is a list of adverse events experienced more frequently with levetiracetam than with placebo. Since this was a variable-dose study, most of the adverse events had either ended or been minimized to tolerable levels (by reducing the dose) by the end of the double-blind trial. While rates of adverse events were high, most were mild. The rates of adverse events were not unexpected, since dose was increased as high as tolerated to maximize the opportunity for benefit. Suicidal ideation (though no attempts) occurred in 2 patients, both taking levetiracetam (for both patients, this led to study termination within the first week); in these 2 cases, environmental and interpersonal stressors were involved, but levetiracetam has been reported to be associated with behavioral abnormalities including (in 0.5% of patients) suicide attempts.[22] The other early (first week) dropouts had depressed mood (patient treated with placebo) and sedation and impaired coordination (patient treated with levetiracetam). The 2 patients, both receiving levetiracetam, who dropped out between 1 and 3 weeks did so because of increased irritability (1 patient) and sedation and dizziness (1 patient).

DISCUSSION

In this study, there was no evidence of levetiracetam efficacy in patients with impulsive aggression. This lack of efficacy did not appear to be due to confounding factors such as the higher dropout rate seen with levetiracetam or the relatively small sample. Nonsignificant differences between levetiracetam and placebo were as likely to favor placebo as levetiracetam, so there is no evidence that a larger sample or fewer dropouts would have led to different conclusions.

These results compare with the consistent evidence of benefit from oxcarbazepine[7] in a similar population with a similar study design. Comparison of baseline features (e.g., ratings of aggression, history of arrests) of this sample with the samples in the oxcarbazepine[7] and divalproex[8] studies indicates that the populations are similar. If the studies to date are confirmed by additional studies, this would suggest that one of the pharmacologic properties of oxcarbazepine not shared by levetiracetam, e.g., blockade of voltage sensitive sodium channels, modulation of high-voltage activated calcium channels, or anticonvulsant activity in conventional animal seizure models (e.g., maximal electroshock-induced seizures), is responsible for the benefit in patients with impulsive aggression. Carbamazepine, similar to oxcarbazepine, is another of the anticonvulsants that may reduce impulsive aggression.[2,23]

Of note, this study excluded many aggressive patients, for example, schizophrenic patients with paranoid delusions, irritable manic patients, and angry depressed patients, all of whom require other treatment for their underlying illness. Similarly, patients whose aggression occurred only under the influence of alcohol or drugs were excluded; these patients would primarily require substance abuse treatment. Aggressive patients with dementia, mental retardation, or autism were also excluded to increase homogeneity, but the resulting population was still heterogeneous, e.g., patients could have residual or remitted ADHD, personality disorders (including cluster B), prior substance abuse, or prior depression. Some met DSM-IV criteria for IED (all, by definition, met the Coccaro research criteria for IED). Prior studies[2] have not clarified if specific diagnostic or other patient characteristics predict response to specific medications, although Hollander et al.,[8] in a secondary analysis, suggest that divalproex may be specifically helpful in aggressive patients with cluster B personality disorders. β-Blockers (which have been evaluated primarily in aggressive schizophrenics and aggressive patients with organic brain disease), anticonvulsants (including sodium valproate, carbamazepine, and topiramate), antipsychotics (especially the atypicals), lithium, and antidepressants have all been studied in aggressive patients to some extent.[1,2] One might expect that diagnosis or other patient characteristics would predict medication response; for example, patients with bipolar features (though not sufficient to warrant a diagnosis) might do better with mood stabilizers, but this and similar hypotheses require further study. A history of ADHD might suggest a trial with a stimulant or atomoxetine, but giving a stimulant to an adult aggressive patient, who might have a history of substance abuse, is problematic.

The diagnostic distinction between IED (either by DSM-IV or the research criteria) and borderline personality disorder or cluster B personality disorder not otherwise specified (NOS) is not always clear. Hollander et al.[8] define cluster B personality disorder NOS (this is not in DSM-IV) as requiring a total of at least 5 criteria from more than 1 of the cluster B personality disorders. However, any patient who is aggressive and impulsive will meet this definition (3 criteria for borderline personality and 2 for antisocial personality); thus, the same patient can be categorized differently (IED or cluster B personality disorder NOS), depending on one's perspective. Similarly, it is unclear how best to diagnose aggressive patients who had ADHD as children, but who, as adults, have neither clinically significant attentional difficulties nor the types of impulsivity described in the DSM-IV criteria for ADHD. These diagnostic uncertainties make it difficult to integrate studies; for example, in the Hollander et al.[8] study, if patients met criteria for both IED and a cluster B personality disorder, it was up to the investigator to decide which was primary, and this determined which group the patient was in.

Of note, the present study, like the oxcarbazepine[7] and divalproex[8] studies, shows that patients with impulsive aggression can respond to placebo; this suggests that psychological factors can influence the expression of aggression (cognitive-behavioral therapy may also reduce aggression[24]). However, the oxcarbazepine study[7] suggests that the placebo effect may wane with time (it decreased after week 4), so medication remains a potentially useful treatment (analogously, a relatively high placebo response in depression does not mitigate against the use of antidepressants).

Overall, this study showed no evidence that levetiracetam was helpful in patients with impulsive aggression. Oxcarbazepine, to date, has more evidence of efficacy, but further studies are needed to confirm efficacy and to clarify whether specific subgroups respond differently to different medications.

Drug names: atomoxetine (Strattera), carbamazepine (Equetro, Carbatrol, and others), divalproex (Depakote), levetiracetam (Keppra), oxcarbazepine (Trileptal and others), topiramate (Topamax), valproate sodium (Depacon and others).

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