Use of Sodium Valproate in Violent and Aggressive Behaviors: A Critical Review

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Background: Valproate was initially introduced as an antiepileptic agent in 1967, but has been used over the years to treat a variety of psychiatric disorders. Its use in the treatment of patients exhibiting aggressive and violent behaviors has been reported in the literature as far back as 1988. However, these reports are uncontrolled, which is in marked contrast to the actual wide and established use of valproate for the treatment of aggressive behaviors. The aim of this report is to critically review the available data on valproate's use in nonbipolar patients with aggressive and violent behaviors.

Data Sources: The MEDLINE and PsycLIT databases were searched for all reports published from 1987–1998 containing the keywords *valproate*, the names of all commercial preparations, *aggression,* and *violence.*

Study Findings: Seventeen reports with a total of 164 patients were located. Ten of these were case reports with a total of 31 patients. Three were retrospective chart reviews with 83 patients, and 3 were open-label prospective studies with a total of 34 patients. No double-blind, placebo-controlled study could be found. An overall response rate of 77.1% was calculated when response was defined as a 50% reduction of target behavior. Most frequent diagnoses recorded were dementia, organic brain syndromes, and mental retardation. The antiaggressive response usually occurred in conjunction with other psychotropic medication. The dose and plasma valproate level required for response appeared to be the same as in the treatment of seizure disorders.

Discussion: While valproate's general antiaggressive effect is promising, in the absence of controlled data, conclusions are limited at this time. Specific recommendations for study design are given to obtain interpretable data for this indication.

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Valproate was initially introduced as an antiepileptic agent in 1967, but over the years it has been used to treat a variety of psychiatric disorders. On the basis of double-blind studies, valproate has been found to be effective in the treatment of patients with bipolar disorder who have not responded adequately to lithium (for a review see Guay[1]). It has recently been approved for this indication by the U.S. Food and Drug Administration.

Another indication for valproate that has been reported in the literature as far back as 1988[2] is its utility in the treatment of nonbipolar patients exhibiting aggressive and violent behaviors. However, reports on this indication are uncontrolled. This is in marked contrast to its actual wide use for the treatment of aggressive behaviors in a number of psychiatric diagnoses. For example, a recent report by Citrome et al.,[3] using the New York State computerized medication utilization system, found a high utilization rate of valproate in New York State psychiatric patients who show a comparatively low incidence of bipolar illness. These authors report that in 1994, 15.5% of all inpatients received valproate, while in 1996, the number increased to 34.1%, representing a 124% increase. Of particular importance is the increase in prescriptions of valproate for schizophrenic patients. The authors report that 12.1% of patients with a diagnosis of schizophrenia had valproic acid preparations prescribed in 1994, while 20.8% of these patients received it in 1996. Our informal inquiries with clinicians from different state psychiatric centers as to the indications of valproate in nonbipolar illness revealed its use in patients with aggressive and violent behaviors. Given this important nonlabeled use of valproate preparations in chronic, nonbipolar patients, it is useful to examine the actual database for this indication.

The aim of this report is to review the available data on valproate's use in nonbipolar patients with aggressive and violent behaviors with the focus on (1) critically assessing its efficacy in this domain, (2) examining whether possible antiaggressive effects of valproate are related to specific diagnostic or clinical features, and (3) formulating recommendations for future studies to obtain controlled evidence of its efficacy in this indication.

DATA SOURCES

The literature was reviewed using MEDLINE and PsycLIT, and all citations covering the last 11 years (the

period between 1987 and 1998) were retrieved. Keywords used were *valproate*, the names of all commercial preparations of valproate available in the United States (*valproic acid, Depakene; divalproex sodium, Depakote; sodium valproate*), *aggression,* and *violence*. Only case reports with a clear diagnostic description, specific reference to the presence of aggressive or violent behavior at baseline, and specific details on treatment course and outcome were included in our review. Reports on patients with aggression and bipolar diagnosis were excluded since the efficacy of valproate for that indication has been well documented. Likewise, studies in patients with aggression in the context of an acute organic delirium were excluded, because of the multitude of medical factors and concomitant medications usually involved that would make it difficult to draw valid conclusions.

STUDY FINDINGS

We were able to locate 17 reports with a total of 164 patients describing the use of valproate in patients with aggressive or violent behaviors (Table 1). Ten of these were case reports including a total of 31 patients,[4,5,7,9–12,15,17,20] 3 were retrospective chart reviews including 83 patients,[13,16,19] and 3 were open-label studies with a total of 34 patients.[8,14,18] Only 1 pilot double-blind study examined the effectiveness of valproate in 16 patients with borderline personality disorder.[6]

Patients included in case reports had a wide range of diagnoses briefly summarized in 4 groups: (1) dementia, (2) organic brain syndromes including brain injuries, (3) mental retardation, and (4) other diagnoses associated with aggressive behaviors, such as schizophrenia and schizoaffective and bipolar disorders.[19] There were 2 chart review studies on patients with dementia[13,16] and 1 on patients with various diagnoses such as schizophrenia, schizoaffective disorder, bipolar disorder, and borderline personality disorder.[19] In addition to case reports and chart review studies, we found 3 open-label studies and 1 double-blind study on antiaggressive effects of valproate. Two studies included patients with dementia[8,14] and the other 2, patients with borderline personality disorder.[6,18] Below we will first summarize the study results and then review diagnosis-specific issues.

The mean age of all patients reported in the reviewed studies was 53.81 years, with a range from 8–97 years. The predominance of the older age group was related to the frequency of reports of dementia. Duration of treatment with valproic acid ranged from 2 to 34 weeks. The mean maximum dose of valproate used was 1393.5 mg/day, with a very wide range from 250 mg/day to 4000 mg/day. Similarly, the mean reported plasma valproate level was 62.44 μg/mL, with a range from 13 to 111 μg/mL. While some of the plasma levels were rather low, most were within the range considered therapeutic for the treatment of seizure disorders. No clear conclusion could be drawn regarding the relationship between plasma level and clinical response. Only 5 studies included patients on valproate monotherapy. All other patients were treated in combination with other psychotropics including benzodiazepines, neuroleptics, antidepressants, and other mood stabilizers. Often these concomitant treatments were not specified and plasma levels of concomitant medication were not indicated, making the interpretation of possible drug interactions difficult.

Response to treatment was most often measured by global clinical impressions. The reviewed case reports list 50% of all patients as having fewer aggressive outbursts while taking valproic acid. Only 1 study reports a significant decrease in the number of hours per week spent in the seclusion room for patients taking valproate.[19] Of the 6[6,8,10,11,13,18] studies using a rating scale to measure aggression, 4 report a numerical decrease in aggression as measured by the Overt Aggression Scale (OAS).[21] Overall, marked reduction in target symptoms of verbal and physical aggression are reported in about 50% of patients observed. Side effects in the reviewed reports were rare. The most frequently reported side effects were sedation, drowsiness, and confusion. Apraxia, tremor, and gait disturbance were reported less frequently.[18,20] Only one study[18] reported nausea, headaches, dyspepsia, and hair loss.

In terms of diagnosis-specific results, we found that patients diagnosed with dementia and treated with valproate showed improvement on global measures of aggression and behavioral agitation in the majority of cases.[10,12–15] The results are comparable when these patients are treated with valproate alone or with concomitant medication. The improvement seems to be unrelated to the dose of concomitant psychotropic medications.

Patients with borderline personality disorder characterized by aggression and impulsivity have also received treatment with valproate. The 2 preliminary studies included in this report yielded encouraging results. Stein et al.[18] describe the effects of 8 weeks of monotherapy with valproate in 11 patients with borderline personality disorder. Patients were well characterized, and an operationalized outcome measure (OAS) was used. There was a nonsignificant decrease in the OAS measure. In another study, Hollander et al.[6] treated 16 patients diagnosed with borderline personality disorder for 10 weeks in variable doses, but with an effort to maintain plasma levels at 80 μg/mL. They reported a significant decrease in global measures of symptoms and depression and a lower score on an aggression questionnaire. However, the results from the OAS were nonsignificant.

Regarding other psychotic disorders treated with valproate, Wilcox[19] reported on schizophrenic, schizoaffective, and bipolar patients based on a chart review using a retrospective case control design. Thirty-five patients

Table 1. Studies of Valproate in Psychiatric Disorders[a]

Study	N	Age Range (mean), y	Diagnosis	Design	Duration, wk	Dose, mg/d	Plasma Valproate Level, µg/mL	Concurrent Medication	Outcome
Geracioti, 1994[4]	1	18	Closed head injury	Case report	6	750–1000	45.6	No	Decrease in number of aggressive outbursts
Giakas et al, 1990[5]	1	51	Organic mood syndrome	Case report	12.86	900–1500	50–75	Yes	No further outbursts
Hollander et al, 1998[6]	16	(36.11)	Borderline personality disorder	Double blind	10	250–?	80	No	Improvement in CGI, GAS, BDI, and an aggression questionnaire
Kastner et al, 1990[7]	3	8–16 (12.3)	Mental retardation; 1 with bipolar disorder, manic	Case report	12.86	1500–3000	75–111	Yes	Decrease in number of outbursts
Lott et al, 1995[8]	10	71–94 (NA)	Dementia	Open label	4–34	375–750	13–52	Yes	50% improvement in global scale for behavioral agitation in 80% of the patients
Mattes, 1992[9]	2	34–55 (44.5)	Mental retardation	Case report	25.7	750–1000	22–64	Yes	Decrease in number of outbursts in both patients
Mazure et al, 1992[10]	2	63–68 (65)	Mental retardation/ schizoaffective disorder, schizophrenia, history of lobotomy	Case report	4–6	500–1500	60, 46	Yes	Reduction in aggression measured by OAS (by 47%–92%)
Morinigo et al, 1989[11]	4	21–40 (28)	Schizophrenia	Case report	21.4–34.3	1500–3000	55–81	Yes	Reduction in aggressive behavior assessed by clinical impression and total score on BPRS
Mellow et al, 1993[12]	4	65–83 (70)	Dementia	Case report	4–12.86	750–2500	45–93	No	2/4 of the patients showed improvement in agitation and aggression
Narayan and Nelson, 1997[13]	25	62–86 (77)	Dementia	Chart review	NA	250–4000	14–102 (mean = 64)	Yes	56% of patients reached CGI score of very much and much improved
Porsteinsson et al, 1997[14]	13	65–97 (81.6)	Dementia (12), mental retardation (1)	Open label	5–21	250–1500	33–107	Yes	Improvement in target symptoms (verbal and physical aggression) 6/13 patients
Sandborn et al, 1995[15]	4	65–79 (71)	Dementia	Case report	NA	1000–1500	24–54.7	Yes	Improvement in aggressive behavior in patients
Sival et al, 1994[16]	23	NA (80.2)	Dementia	Chart review	NA	240–1200	NA	Yes	Complete improvement in physical aggression for 56% of patients and in verbal aggression in 33%
Sovner, 1989[17]	5	24–44 (37)	Bipolar with autistic disorder	Case report	NA	NA	61–88	Yes	Marked reduction in assaultive behavior and irritability
Stein et al, 1995[18]	11	NA (34.8)	Borderline personality disorder	Open label	8	NA	50–100	No	Nonsignificant decrease in OAS
Wilcox, 1994[19]	35	19–62 (31.2)	Schizophrenia; bipolar disorder, manic; bipolar disorder, depressed; schizoaffective disorder, borderline personality disorder	Chart review (retrospective case-control design)	2 after plasma valproate level reached 50–100 µg/mL	750–1500	50–100	Yes	Significant reduction in number of hours in seclusion per week; borderline personality disorder and atypical or mixed bipolar patients responded best
Wroblewski et al, 1997[20]	5	30–63 (38.2)	Brain injury	Case report	4–25.7	750–2250	60–110	No	Reduction in aggression and "behavioral" outbursts in all patients

[a]Abbreviations: BDI = Beck Depression Inventory, BPRS = Brief Psychiatric Rating Scale, CGI = Clinical Global Impressions, GAS = Global Assessment Scale, NA = not available, OAS = Overt Aggression Scale.

with aggressive behaviors and treated with valproate were randomly chosen from consecutive admissions for inclusion. Specified target behaviors were recorded during a 2-week baseline period. As an objective indirect measure of aggressive behavior, the number of hours per week spent in seclusion was recorded prior to the start of valproate treatment and after a 2-week period of treatment. The mean number of hours spent in seclusion significantly fell from 18 hours per week at baseline to 2 hours per week after 2 weeks of treatment. Patients most likely to respond were patients with atypical or mixed bipolar disorder or borderline personality disorder and patients

with abnormal electroencephalogram (EEG) results. Concurrent other psychotropic medications did not have a significant effect on treatment response. However, there was no control for the effect of time nor the effect of acute hospitalization. Only 1 case report of 4 patients with neuroleptic-resistant schizophrenia found a reduction of positive symptoms and hostility as assessed with Clinical Global Impressions and an overall reduction on the total score on the Brief Psychiatric Rating Scale.[11]

DISCUSSION

Considering the widespread use of valproate for patients who have aggressive and violent behaviors, it is surprising that, with the exception of a preliminary study by Hollander et al.,[6] no data from controlled prospective double-blind studies exist for this indication. Given the absence of double-blind designs and the variability of length of open-label treatments, dosages, and concurrent medications, conclusions are difficult to draw. In addition, case reports tend to overemphasize positive responses and underreport negative responses. Another difficulty is that only a minority of studies report the effects of valproic acid monotherapy,[8,18,20] while all others report the adjunctive effect of valproate in other psychotropic regimens without controlling for pharmacokinetic or time factors affecting the response. Our conclusions need to be seen within these limitations.

We calculated an overall approximate response rate of 77.1%, when response was defined by a 50% reduction of target behavior. However, this number has a limited value given the shortcomings we pointed out and the lack of uniform outcome measures.

At the diagnostic level, patients who respond best to valproate are, in hierarchical order, those with (1) organic brain syndromes, (2) a diagnosis of dementia or mental retardation, and (3) a diagnosis of bipolar disorder, manic type. The first 2 groups and possibly the third group share underlying central nervous system impairments that are sometimes reflected in EEG abnormalities. This may explain why the antiaggressive response to valproate transcends diagnostic categories and may be related to an effect on an underlying subclinical seizure disorder or on dysrhythmic EEG patterns in these patients.[22] In support of this is the fact that many of the reported patients had abnormal EEG results at baseline.

An important hypothesized mechanism for this action is valproate's enhancing effect on central levels of γ-aminobutyric acid (GABA), a major inhibitory neurotransmitter within the central nervous system. Valproate exerts its effect by inhibiting GABA transaminase, allowing increased GABA to counteract increased dopaminergic activity in the mesolimbic and mesoprefrontal cortical areas.[23] Patients with the diagnoses described above may have reduced levels of GABA, as has been reported in brains of patients with dementia.[24] Animal studies have reported that GABA agonists, including valproate, have anticonvulsant effects as well as anxiolytic and antiaggression effects.[25–27]

Another possible mechanism for valproate's antiaggressive effect is its enhancing effect on serotonergic neurotransmission.[28] Various animal and human studies have demonstrated a link between aggressive and impulsive behaviors and reduced serotonergic neurotransmission.[29,30] In addition, it is not surprising that patients with bipolar disorder show a good antiaggressive response. In these patients, aggression may be part of the manic syndrome that responds well to valproate treatment and that also may be associated with abnormal underlying brain functions. Pope et al.[31] have reported significant improvement in manic symptoms in 9 of 10 cases of bipolar patients with a history of head injury when valproate was added after inadequate response to standard treatment. This hypothesis is further supported by a report by Stoll et al.,[22] who reviewed 115 bipolar and schizoaffective lithium-refractory patients. Those with a seizure or head injury history and abnormal EEG findings were much more likely to have a robust response to valproate (70%). An extension of the previous hypothesis may be that the positive response to valproate in dementia may be related in some cases to the presence of a secondary or organic mania.[8]

Finally, the ameliorating effects of valproate may also be mediated by antikindling effects, i.e., the effective control of persistent subthreshold electrical impulses in the limbic system, which could contribute to behavioral dysregulation and aggressive behavior in these patients.[32]

The effective dose level of valproate in these patients appears to be extremely variable. Each patient needs to be individually titrated for best response. While the relationship of response to plasma level appears to be in a similar range as for treatment of seizures, lower levels have also been reported to be effective. However, no definitive conclusion can be drawn in the absence of studies using predetermined different fixed plasma levels and examining clinical response.

The effect of concurrent psychotropic medications is difficult to assess given the uncontrolled nature of the present data. In most reviewed reports, treatment with neuroleptic medications combined with mood stabilizers (except valproate) before the administration of valproate had been ineffective. When valproate was added to the existing regimen, improvements in target symptoms were noted. This suggests a possible pharmacodynamic effect of the combinations. Pharmacokinetic factors mediating valproate's effects also cannot be ruled out since none of the reports examined plasma levels of the preexisting medications before and after valproate treatment was started.

Side effects were overall very low. Only a minority of patients are reported to have experienced sedation,

tremor, or gait disturbances. No patients experienced hepatic transaminase elevation, thrombocytopenia, or pancreatitis.

RECOMMENDATIONS

There are many methodological shortcomings of the reviewed reports on valproate's effects in patients with aggressive and violent behaviors that limit the evaluation of efficacy for this indication. Outcome measures are rarely operationalized or assessed in a blind and systematic fashion. We therefore recommend that trials with controlled designs be instituted to allow valid conclusions. The following parameters should be included in future studies.

Studies must be prospective, double-blind, and sufficiently long, given the relatively infrequent occurrence of violent behaviors. The baseline period measuring aggressive behaviors should be at least 1 month. Patients at acute hospital admission are probably poor candidates for study given the concomitant acute psychotic symptom presentation. Therefore, it would be preferable to include patients who are not in an acute and florid psychotic state and to exclude patients with bipolar illness. Improvements in aggressive and violent behaviors in these patients might be highly correlated with improvement in their acute or manic psychotic state. If valproate is used as an adjunctive treatment, there must be a placebo add-on in the comparison group. This will allow control for the effect of passage of time. In addition, the possible effects of pharmacokinetic interactions need to be clarified. Aggressive and violent behaviors need to be operationalized and assessed in a reliable fashion with standardized rating scales. Aggressive behaviors can be assessed using single-incident scales or incident-pattern scales.[32] An example of a frequently used and useful single-incident scale is the OAS.[21] For patients in whom aggressive incidents occur frequently, incident-pattern scales, which measure aggressive behavior over a certain time span, are more appropriate. A retrospective adaptation of the OAS is useful for this purpose.[33] Studies using these methodological procedures have indeed been successful in demonstrating antiaggressive effects with other compounds such as carbamazepine[34] or fluoxetine.[35] Such studies need to be conducted with valproate.

In the meantime, conclusions about valproate's antiaggressive efficacy have to remain cautious. Such an effect appears to be diagnostically nonspecific, although the best responses appear to occur in patients with bipolar disorder and organic disorders such as dementia and brain injuries. The response usually occurs in conjunction with other psychotropic medications, such as antipsychotic medications. The dose and plasma level of valproate required for response appear to be the same as in the treatment for bipolar and seizure disorders. Side effects tend to be few. While valproate's general antiaggressive effect is promising, there is a clear need for controlled, double-blind studies before confirming a specific antiaggressive effect for this medication.

Drug names: carbamazepine (Tegretol and others), divalproex sodium (Depakote), fluoxetine (Prozac), valproic acid (Depakene).

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