*Key Words: valproate, divalproex sodium, pharmacotherapy, schizophrenia, aggression*

# Schizophrenia and Valproate

*By Leslie Citrome, MD, MPH*

***ABSTRACT*** *~ Valproate (the active moiety of both valproic acid and divalproex sodium) is commonly used as an adjunctive agent for the treatment of schizophrenia. Among the anticonvulsants, valproate is the most extensively studied in patients with schizophrenia. Theoretical underpinnings for valproate in schizophrenia include its effect on voltage-gated ion channels and on the γ-aminobutyric acid (GABA) system, thus modulating mesolimbic dopaminergic activity. Case reports, retrospective studies, and randomized clinical trials support the use of valproate combined with antipsychotics in managing schizophrenia. A recently completed 28-day, double-blind, randomized clinical trial of 249 patients with schizophrenia demonstrated faster improvement in psychopathology with a combination therapy of divalproex and risperidone or olanzapine, compared to monotherapy with risperidone or olanzapine. Additional research is needed to assess the utility of valproate in specialized populations such as those with treatment-refractory schizophrenia or agitation in schizophrenia. Regarding the latter, positive double-blind, randomized clinical trials have already been conducted in patients with borderline personality disorder, dementia, and with disruptive adolescents. It is anticipated that future research will focus on the new extended-release formulation of divalproex that can be administered on a once-daily basis.* Psychopharmacology Bulletin. *2003;37(Suppl 2): 74-88*



## INTRODUCTION

After a brief review of the history of valproate (the active moiety of both valproic acid and divalproex sodium), its use among patients with psychiatric disorders is enumerated. The adjunctive use of valproate in schizophrenia is described in terms of formulations available, utilization rates among the chronically mentally ill, theoretical underpinnings, and the scientific evidence that supports this indication. The strength of this evidence is compared to what is available regarding other mood stabilizers/anticonvulsants. The possible anti-aggressive activity of valproate is also discussed across diagnoses and in patients with schizophrenia. Future directions for clinical research are described.

Dr. Citrome is director of the Clinical Research and Evaluation Facility at the Nathan S. Kline Institute for Psychiatric Research in Orangeburg, NY, and professor of psychiatry at the New York University School of Medicine.

To whom correspondence should be addressed: Leslie Citrome, MD, MPH, Nathan S. Kline Institute for Psychiatric Research, 140 Old Orangeburg Road, Orangeburg, NY 10962; Phone: (845) 398-5595 Fax: (845) 398-5483 E-mail: citrome@nki.rfmh.org

## HISTORICAL CONTEXT

Valproic acid was first synthesized in 1882 by Burton[1] and used as a lipophilic solvent. It wasn't until Meunier's experiments with putative anticonvulsant agents that valproic acid was serendipitously recognized as having anticonvulsant properties in rats in 1963.[2] Valproic acid was subsequently tested in humans and introduced as a treatment for epilepsy in France in 1967. In 1978, it was approved in the USA by the Food and Drug Administration (FDA) for the monotherapy and adjunctive therapy of complex partial seizures, and simple or complex absence seizures. The divalproex sodium preparation received FDA approval in 1983, followed by an injectible formulation in 1996. An extended release preparation became available in 2000. For patients with mental disorders, the pivotal year was 1995, when divalproex sodium was approved by the FDA for the indication of manic episodes associated with bipolar disorder.

There are a number of off-label psychiatric indications that have been described for valproate. These include major depressive disorder, anxiety disorders, substance-induced withdrawal and dependence, tardive dyskinesia, schizophrenia and schizoaffective disorder, mood disorders and aggressive behavior resulting from a general medical condition, behavioral disturbances and agitation associated with dementia, mental retardation with mood disorders or behavioral disturbances, and aggression and agitation associated with personality disorders.[2] Scientific evidence for any of these indications varies in terms of quality and quantity.

Reasons for the use of valproate in patients with schizophrenia may be related to the observation that some patients do not have an adequate treatment response with antipsychotic monotherapy. Adding another type of medication to the treatment regimen may help optimize therapeutic response. In particular, the Expert Consensus Guidelines for the Treatment of Schizophrenia[3] recommends the use of adjunctive valproate, and ranks it first, for the problem of aggression/violence and for agitation/excitement (with history of substance abuse).[3] The research evidence supporting this will be discussed.



## FORMULATIONS

Up until recently, there have been only two commonly prescribed preparations of valproate: valproic acid and divalproex sodium. Equivalent oral doses of either preparation deliver equivalent quantities of the valproate molecule systemically.[4] Valproic acid is available as a gel capsule and as a syrup. Divalproex sodium is available as a tablet and also as sprinkle capsules (coated particles). The divalproex sodium tablets are a delayed release preparation; the enteric coating prevents the release of the divalproex sodium until it reaches the small intestine. In contrast, valproic acid gel capsules are absorbed in the stomach, possibly leading to gastric

irritation.[5] Biting the gel capsule can lead to local oral irritation. Half-lives of the two preparations of valproate also differ, with valproic acid having a half-life of 8 hours and divalproex sodium having a half-life of between 12 and 16 hours.[6] Thus, valproic acid is commonly administered in three or four divided doses while divalproex sodium can be administered two or three times daily.[4,7]

An extended release preparation of divalproex sodium was introduced in 2000.[4] The first FDA-approved indication was for prophylaxis of migraine headaches, and as of 2002 this new formulation has been approved by the FDA for seizure disorders. It is intended for once-a-day oral administration. It is available in 250 and 500 mg tablets. The extended-release divalproex sodium tablets are not bioequivalent to the delayed-release divalproex sodium tablets; the extended release tablet produced an average bioavailability of 81 to 89% relative to the delayed-release tablets given BID.

## UTILIZATION IN SCHIZOPHRENIA



Mood stabilizers such as lithium and anticonvulsants are extensively used, including among patients with a diagnosis of schizophrenia, with rates of utilization (adjunctive to antipsychotic therapy) approaching 50% for that group.[8] Valproate is the anticonvulsant/mood stabilizer most commonly used (Table), as demonstrated in a report of all patients with schizophrenia hospitalized in psychiatric centers operated by the New York State Office of Mental Health. In 1998, 2134 out of 4922 (43.4%) inpatients diagnosed with schizophrenia received a mood stabilizer, with

**TABLE**

ANTICONVULSANTS AND THEIR USE IN PATIENTS WITH SCHIZOPHRENIA HOSPITALIZED IN FACILITIES OPERATED BY THE NEW YORK STATE OFFICE OF MENTAL HEALTH[8]

| ANTICONVULSANT | YEAR INTRODUCED IN THE USA | UTILIZATION AMONG PATIENTS WITH SCHIZOPHRENIA IN HOSPITALS OPERATED BY NEW YORK STATE IN 2001 (N=4,139) |
|---|---|---|
| Carbamazepine | 1974 | 2.1% |
| Valproate | 1978 | 34.9 % |
| Gabapentin | 1993 | 8.8% |
| Lamotrigine | 1994 | 1.0% |
| Topiramate | 1997 | 2.9% |
| Oxcarbazepine | 2000 | 2.5% |
| ANY Mood Stabilizer (including Lithium) | N/A | 47.1% |

Citrome L. *Psychopharmacology Bulletin.* Vol. 37. Suppl. 2. 2003.

valproate the most commonly prescribed agent (1724 or 35.0%).[9] The utilization of valproate has increased during the period 1994 through 2001 (figure 1).[8] This adjunctive use of valproate in schizophrenia is not short-term, with patients receiving valproate for an average of 72% of their hospital stay in 1998.[9] The duration of treatment has increased in 2001 to 81% of the hospital stay, with 41% receiving valproate for their entire length of stay.[10]

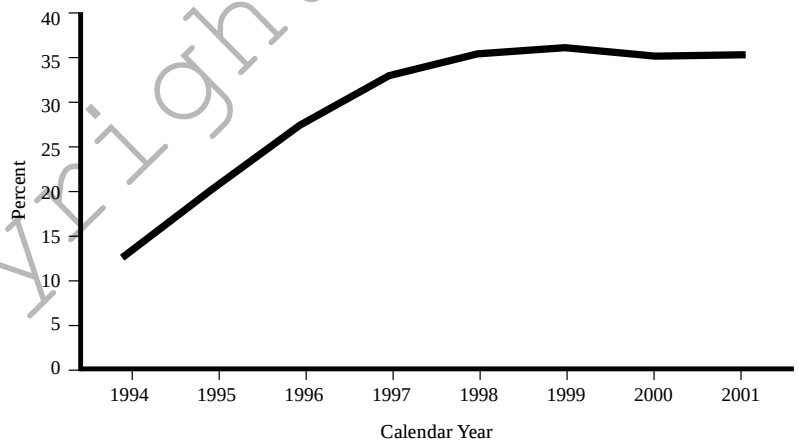
The increase in use of mood stabilizers in hospitalized patients with schizophrenia may be partly attributable to a changing state hospital population. One possibility is that as the census (capacity) decreases, the patients that remain in treatment and the patients that continue to be referred to these tertiary care psychiatric centers may be more treatment-resistant, prone to aggressive behavior, and therefore are more likely to be exposed to novel psychopharmacological approaches. However, this can only be a partial explanation because valproate utilization increased by 285% (from 12.3% to 35%) among this population.[3] It is also unlikely that the increase in utilization is attributable to the treatment of a concomitant seizure disorder. In a prior study of this state hospital population, about 10% of all patients receiving valproate in 1996 (regardless of psychiatric diagnosis) had a history of seizure disorder.[11]





**FIGURE 1**

PERCENT UTILIZATION OF VALPROATE FROM 1994 (N=8,405) THROUGH 2001 (N=4,139) IN PATIENTS WITH SCHIZOPHRENIA HOSPITALIZED IN FACILITIES OPERATED BY THE NEW YORK STATE OFFICE OF MENTAL HEALTH[8]




Citrome L. *Psychopharmacology Bulletin.* Vol. 37. Suppl. 2. 2003.

## THEORETICAL UNDERPINNINGS

Wassef et al[12] notes that schizophrenia may involve a disturbance in the g-amino butyric acid (GABA) system. GABA is an inhibitory neurotransmitter. Because GABA can regulate mesolimbic dopaminergic activity, valproate, by interacting with GABA, may reduce psychotic symptoms. GABA is actually the most common neurotransmitter in the brain after glutamate, thus controlling GABA levels may be an important strategy to improve brain function.[13] Prior to the introduction of valproate in the USA, the suggestion was made that there is a GABA deficiency in schizophrenia, and that valproate ought to be clinically tested to see if increasing brain GABA levels can lead to symptomatic improvement.[14] Others have pointed out that the therapeutic action of valproate may be more complex,[15] and this issue has been actively debated.[16,17] New imaging technologies may help elucidate the role of GABA in disease.[18,19]

A possible locus of action of valproate may be direct effects on voltage gated sodium ion channels.[20] Voltage gated actions may cause an increase in GABA levels, enhance inhibitory GABA actions, or inhibit excitatory glutamatergic neurotransmission. An understanding of the different types of voltage gated ion channels may help explain differences in efficacy among the anticonvulsant medications in treating both bipolar disorder and schizophrenia.[21]



Testing the efficacy of valproate in treating schizophrenia requires being mindful of possible diagnostic confusion such as with a mood disorder (eg, bipolar disorder, where valproate has an established indication). Another source of confusion may be disentangling effects on impulsivity versus effects on core psychotic symptoms such as hallucinations and delusions. Moreover, the effect of valproate on sedation needs to be distinguished from any intrinsic antipsychotic effect. Finally, plasma levels of valproate and of antipsychotics may need to be measured to rule out pharmacokinetic interactions that may possibly explain the effects of adjunctive valproate therapy.

## SUPPORTING CLINICAL EVIDENCE

The first signals indicating the utility of adjunctive valproate in the treatment of schizophrenia came from case reports and open-label studies. An open-label study of valproate and haloperidol in 30 patients suggested that augmentation with valproate resulted in improvements in suspiciousness, hallucinations, unusual thought content, and emotional withdrawal, as well as in fewer inpatient days.[22] Other uncontrolled studies reported improvement on emotional withdrawal in a group of seven inpatients with chronic schizophrenia,[23] improvement in positive symptoms among a group of ten hospitalized non-agitated paranoid schizophrenic patients,[24] reduced psychopathology in general as measured by the Brief Psychiatric

Rating Scale (BPRS) in 32 neuroleptic-resistant inpatients, 7 of whom were diagnosed with chronic schizophrenia,[25] shorter length of hospital stay in 59 inpatients with schizophrenia,[26] and reduction of positive symptoms and hostility in 4 patients with neuroleptic-resistant chronic schizophrenia.[27] Neuroleptic-resistant patients were the focus of a report of three subjects whose psychotic symptoms responded dramatically to the combination of valproic acid and neuroleptics and outpatient follow-up showed that the combination was effective in maintaining remissions.[28] A report of the combination of valproate with an atypical antipsychotic, risperidone, demonstrated clinical improvement in an otherwise treatment-resistant patient with schizophrenia.[29] In contrast, there is a chart review where 4 inpatients with chronic schizophrenia did not show improvement with valproate, although two were not receiving antipsychotic therapy.[30] There is one report that demonstrated marked clinical deterioration, but this was with valproate monotherapy in eight patients whose neuroleptics were discontinued shortly before study entry, a method of use not normally considered for patients with schizophrenia.[31] The above literature is somewhat faulty in that it includes patients with diagnoses other than schizophrenia,[25] or diagnostic and selection criteria that were not specified.[23-26] Generalizability is also made difficult because of heterogeneity in disease severity—some patients were neuroleptic-resistant,[25,27,28,29] and some reports, although showing a positive effect for valproate, did include patients who were not receiving neuroleptics.[23,24] Diagnostic uncertainty is a major issue in the evaluation of the efficacy of adjunctive valproate in patients with schizophrenia. If patients were actually bipolar or schizoaffective, benefit with a mood stabilizer such as valproate would be expected.



Findings from double-blind randomized controlled studies are needed to support initial efficacy signals generated from case reports. Initial studies of adjunctive valproate in patients with schizophrenia have been limited in terms of the number of subjects. Ko et al[32] found no additional benefit with adjunctive valproate in a 28-day crossover study with 6 neuroleptic-resistant patients with chronic schizophrenia (not experiencing an exacerbation). Dose et al[33] examined 42 patients with acute, non-manic schizophrenic or schizoaffective psychosis in a 28-day study comparing haloperidol and placebo versus haloperidol and valproate. No difference on the BPRS was observed, but a possible effect on "hostile belligerence" was noted. Wassef et al[34] studied 12 subjects with an acute exacerbation of chronic schizophrenia over a 21-day period. They were randomized to receive either haloperidol and placebo, or haloperidol and valproate. Significant Improvement in the Clinical Global Impression (CGI) scale was observed, as well as on the Schedule for Assessment of Negative Symptoms (SANS), but not on the BPRS. Although not double-blind, but using randomized

treatment assignment, another report[35] compared the effects of adjunctive carbamazepine versus adjunctive valproate on the plasma levels of haloperidol and on the psychopathologic outcome in 24 patients with schizophrenia and 3 patients with schizoaffective disorder. Subjects received 4 weeks of treatment with either haloperidol alone, haloperidol with carbamazepine, or haloperidol with valproate. Valproate had no significant effect on either plasma levels of haloperidol or on psychopathology, but carbamazepine was associated with significantly lower haloperidol plasma levels and with a worse clinical outcome compared with antipsychotic monotherapy.

These initial randomized studies enrolled relatively small number of subjects, hence differences between the groups might have been difficult to detect because of lack of sufficient statistical power. They also included different types of patients—neuroleptic-resistant patients in one[32] and acute patients in the other three reports.[33,34,35]

Casey et al[36] conducted and reported on a multi-center, randomized, double-blind, clinical trial of adjunctive divalproex in patients recently hospitalized with an acute exacerbation of schizophrenia. A total of 249 subjects from 29 centers from across the USA participated. The *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)* diagnosis of schizophrenia was established for each subject by administering the Structured Clinical Interview for Diagnosis (SCID). Schizoaffective and treatment-refractory patients were excluded and subjects were required to meet certain minimal requirements for severity of symptoms, assuring that there was a sufficient amount of measurable psychopathology. After a washout period of one to five days, patients were randomized to receive over a four-week period either: (1) olanzapine and divalproex, (2) olanzapine and placebo, (3) risperidone and divalproex, or (4) risperidone and placebo. Doses of risperidone 6 mg/day or olanzapine 15 mg/day were reached by day 6. Divalproex was started at 15 mg/kg/day and titrated to a maximum of 30 mg/kg/day by day 14. The mean dose of divalproex achieved was approximately 2300 mg/day with a mean plasma level of approximately 100 mg/mL. The Positive and Negative Syndrome Scale (PANSS) was the primary outcome measure. Ratings were done at baseline, day 3, day 5, day 7, day 10, day 14, day 21, and day 28. PANSS total score significantly improved in the combination therapy group compared to the monotherapy group at specific time points (days 3, 5, 7, 10, 14, and 21) and throughout the study period (repeated measures analysis of variance [ANOVA] $P$=.020). Significant treatment differences occurred as early as day 3. The major effect was on the positive symptoms of schizophrenia. There were no significant differences overall in the use of adjunctive medications (such as lorazepam or benztropine) for combination therapy versus monotherapy. Most adverse events were mild

to moderate in severity. No new safety concerns were observed—the combination therapy was as well tolerated as monotherapy. The early discontinuation rates were notable, demonstrating a more favorable outcome (fewer drop-outs) for combination therapy. Statistically significant was the difference between groups regarding the withdrawal of consent (a proxy measure of satisfaction with treatment): 25 (20%) of monotherapy group withdrew consent versus 12 (10%) of combination therapy group withdrew consent ($P \leq 0.05$). This study supports the conclusion that divalproex significantly enhances antipsychotic efficacy in patients with schizophrenia. Of particular interest was the observation that adjunctive divalproex resulted in faster improvement in psychopathology, including positive symptoms. A responder analysis demonstrated that 50% of the combination therapy group achieved a 20% reduction in total PANSS by day 7. It took the antipsychotic monotherapy group 14 days to reach this level of response (Figure 2).

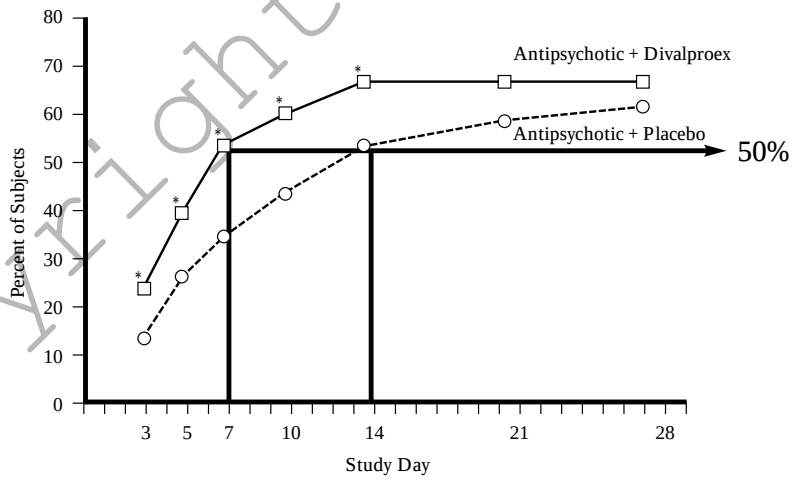
Although the large study described above is the strongest evidence so far on the utility of adjunctive valproate in the management of schizophrenia, the results are not easily generalizable to treatment-refractory patients because the selection criteria specifically excluded that population. In addition, the effect of valproate beyond 28 days remains untested. Further trials of longer duration and with more chronically ill patients will be needed.





**FIGURE 2**

A SHIFT TO THE LEFT: PERCENTAGE OF SUBJECTS WITH A 20% DECREASE IN TOTAL PANSS SCORE OVER TIME, LAST OBSERVATION CARRIED FORWARD[36]




*$p<0.05$

Citrome L. *Psychopharmacology Bulletin.* Vol. 37. Suppl. 2. 2003.

## ANTIAGGRESSIVE ACTION OF VALPROATE

There is an expectation that adjunctive mood stabilizers can reduce aggressive and impulsive behavior.[37] A recent review of the use of valproate in violent and aggressive behaviors in a variety of diagnoses[38] did reveal a 77.1 % response rate (defined by a 50% reduction in target behavior) based on 17 reports (164 patients), but included only 16 patients with schizophrenia. The remainder had diagnoses of dementia (78 patients), borderline personality disorder (37 patients), explosive temper and mood lability in children and adolescents (20 patients), bipolar disorder (16 patients), mental retardation (8 patients), organic brain syndromes, including brain injuries (7 patients), and schizoaffective disorder (2 patients). As expected, most of the studies were of the adjunctive use of valproate, but 4 out of 17 studies included patients on valproate monotherapy for the diagnoses of closed head injury, dementia, and borderline personality disorder. The predominant methodology was case reports (10 reports, 31 patients), followed by retrospective chart reviews (3 reports, 83 patients), and open-label studies (3 reports, 34 patients). Only one double-blind study was described in the review, and it consisted of 16 patients with borderline personality disorder.[39,40]



Regarding efficacy in controlling aggression among patients with schizophrenia, of the 16 patients with schizophrenia identified in this literature review,[38] 12 were from one retrospective case-control study that included 35 patients with a wide variety of diagnoses.[41] In that report, it was noted that the number of hours spent in seclusion per week was less for those patients receiving adjunctive valproate, but the best improvement was observed in the patients with bipolar disorder or borderline personality disorder. Another report, consisting of four patients with neuroleptic-resistant schizophrenia, found reduction in aggressive behavior with adjunctive valproate.[27] Another case report demonstrated a decrease in aggression as measured by the Overt Aggression Scale (OAS) in a patient with schizophrenia, but with a history of frontal lobotomy with resulting cognitive deficits.[42] Newly published is a retrospective uncontrolled study, where the effect of adjunctive divalproex on agitated and/or violent behavior in schizophrenia in 147 patients was reported.[43] Divalproex was preferentially prescribed for the more dangerous patients (n = 40). The authors' found that adjunctive divalproex facilitated a more routine hospital course for agitated psychotic patients, similar to that of less overtly disturbed individuals. New evidence includes a one-year open-label prospective trial of adjunctive valproate with olanzapine in 10 patients with paranoid schizophrenia, demonstrating statistically significant reductions in hostility.[44] The average daily dose of olanzapine was 19 mg/day, and that for valproate 1425 mg/day (with an average valproate plasma level of 76.8 µg/ml). In another report presented as a poster at a

US national meeting, 100 patient records were examined retrospectively, and the documentation of aggressive episodes was rated using the OAS.[45] Only patients with schizophrenia or schizoaffective disorder were included. After a baseline period of three months, comparisons were made on OAS scores at baseline versus scores at months 1-3 and months 4-6 after the prescribing of valproate. Statistically significant decreases in aggressive behavior were noted compared to baseline. The average daily valproate dose at the end of six months was 1220 mg. Antipsychotic dosage had not changed significantly.

Since Lindenmayer and Kotsaftis' review,[38] there have been additional double-blind reports on the antiaggressive action of valproate.[46-50] There is a six-week, double-blind, placebo-controlled trial of valproate in 20 children and adolescents with explosive temper and mood lability where valproate was superior to placebo.[46] In another placebo-controlled, double-blind study in 30 women with borderline personality disorder and comorbid bipolar II disorder, divalproex significantly decreased irritability, anger, and impulsive aggressiveness over a six-month treatment period.[47] Efficacy in reducing impulsive aggression and irritability in patients with Cluster B personality disorder (N=96), but not intermittent explosive disorder (N=116), nor post-traumatic stress disorder (N=34) was noted in a double-blind randomized study comparing divalproex with placebo over a 12-week period.[48] A negative report was also published where a three-week trial of valproate was compared to placebo in a double-blind cross-over study of 42 patients with dementia located on a psychogeriatric short-stay ward at a psychiatric teaching hospital.[49] Although secondary outcome measurements showed significant improvement on restless, melancholic, and anxious behavior, no effect of valproate over placebo on aggressive behavior was seen. This is in contrast to a six-week parallel-group randomized double-blind trial where 56 nursing home patients with agitation and dementia were treated with either placebo or individualized doses of divalproex, resulting in statistically significant reductions in agitation for those randomized to receiving divalproex.[50]

A post-hoc secondary analysis[51] of the study by Casey et al[36] found that combination therapy with divalproex had significantly greater antihostility effect at days 3 and 7 than antipsychotic monotherapy ($P<.05$), as measured by the PANSS hostility item. The effect on hostility appears statistically independent of antipsychotic effect on other PANSS items that reflect delusional thinking, a formal thought disorder, or hallucinations.

Thus the evidence for valproate as an antiaggressive agent in schizophrenia is limited. Double-blind, placebo-controlled studies of adjunctive valproate among persistently aggressive patients with schizophrenia

are necessary, similar to studies already done with patients who have borderline personality disorder,[40,47,48] disruptive adolescents,[46] and patients with dementia.[49,50] Such studies are difficult to do because of methodological concerns, such as the relative rarity of aggressive events, need for large sample size, need for lengthy baseline and trial periods, and problems with selection/consent bias.[52] Nevertheless, attempts should be made given the high utilization of adjunctive valproate in patients with schizophrenia[8] and the clinical impression that this treatment approach is effective in decreasing agitation and aggression.[3]

## EXTENT OF EVIDENCE AS COMPARED TO OTHER MOOD STABILIZERS

How does valproate compare with other mood stabilizers in terms of efficacy in treating patients with schizophrenia? Although lithium is a useful medication for patients with bipolar or schizoaffective disorder, the effectiveness of lithium therapy in schizophrenia is not established. In a double-blind, placebo- controlled, parallel-design clinical trial in 21 patients with nonaffective, antipsychotic, nonresponsive schizophrenia, the addition of lithium afforded no advantage over treatment with haloperidol alone.[53] When lithium was added to antipsychotics for the treatment of resistant schizophrenic patients classified as "dangerous, violent, or criminal", no benefits were seen after four weeks of adjunctive lithium.[54] However, there are case reports of patients with paranoid schizophrenia with aggressive or disorderly behaviors who have responded to the addition of lithium to their antipsychotic treatment, then deteriorated after the lithium was discontinued, but subsequently improved when it was reinstituted.[55]



The utilization rate of carbamazepine among patients with schizophrenia has been decreasing,[8] perhaps because alternatives such as valproate are easier to manage because carbamazepine induces its own metabolism. Nonetheless, carbamazepine has been utilized for the management of persistent aggressive behavior in patients with schizophrenia (and schizoaffective disorder). The evidence for efficacy comes mostly from small trials or case reports,[35,56-61] but the results of a larger trial (N=162) are also available.[62] In this latter report, a randomized clinical trial of carbamazepine in patients with *DSM-II* schizophrenia or schizoaffective disorder, there was a failure to detect significant improvement on the total BPRS. However, differences did emerge among the items of suspiciousness, uncooperativeness, and excitability.

Aside from valproate and carbamazepine, the only other anticonvulsant for which double-blind, randomized data are available in patients with schizophrenia is lamotrigine. Adjunctive lamotrigine may be effective in the management of treatment-resistant schizophrenia, as demonstrated

in a recent report of a small (N=34) double-blind, placebo-controlled, crossover trial.[63] Patients who had failed clozapine monotherapy received lamotrigine (200 mg/day) for up to 12 weeks. Adjunctive lamotrigine resulted in the improvement of positive, but not negative, symptoms.

There are no randomized clinical trials reported for gabapentin or topiramate in patients with schizophrenia, although retrospective reports exist,[64-68] and not all of them favorable.[66,68] These latter reports are cautionary in that the patients suffered general worsening of psychosis with gabapentin,[66] or deterioration in both positive and negative symptoms of schizophrenia with topiramate.[68] For gabapentin, there is no evidence to support its widespread use in patients with schizophrenia, which in 1998 exceeded that for carbamazepine within psychiatric centers operated by the State of New York.[8] No reports have been found, anecdotal or otherwise, favorable or unfavorable, regarding the adjunctive use of oxcarbazepine in patients with schizophrenia.

## FUTURE DIRECTIONS

Additional clinical research in the use of adjunctive valproate and other anticonvulsants in patients with schizophrenia is desirable. It is remarkable that adjunctive valproate at the onset of treatment of an acute episode of schizophrenia can result in a more rapid diminution of psychopathology, in particular positive symptoms. The effects beyond 28 days need to be assessed and such work is currently underway. Additional studies examining the utility of adjunctive valproate in more chronic populations would be helpful to support the current widespread use in this population. A tantalizing finding was that adjunctive lamotrigine lessened positive symptoms in patients with schizophrenia who have failed clozapine. This may be the case for valproate as well and needs to be tested with an appropriately designed study. Care must be taken to exclude patients with schizoaffective disorder or bipolar disorder because not doing so would make results difficult to interpret.

The extended release formulation of divalproex may be taken once a day, and thus may improve adherence to treatment. Studies investigating switching strategies from regular (delayed release) divalproex are underway, and will help answer the question whether or not the small difference in bioavailability has any clinical implications.

## CONCLUSIONS

Anticonvulsants, in particular valproate, are extensively used as adjunctive agents for the treatment of schizophrenia. Evidence supporting this use comes from case reports, open-label studies, and double-blind, randomized clinical trials. Evidence is strongest for the use of the combination of atypical antipsychotics and divalproex at the onset of treatment for an acute

episode of schizophrenia. Although not as compelling, randomized clinical trials have also been conducted for the adjunctive use of carbamazepine or lamotrigine in schizophrenia. There are no such trials for gabapentin or topiramate, and case reports for both of these agents are conflicting. There is an absence of information regarding oxcarbazepine and schizophrenia.

Adjunctive valproate appears to preferentially reduce the positive symptoms of schizophrenia, and this was also observed with other anticonvulsants such as lamotrigine. Further research into these effects, as well as on aggressivity, is anticipated. Given the extent of use of adjunctive anticonvulsants in the hospitalized mentally ill, this population also needs to be included in future clinical research. Treatment adherence may be enhanced with new formulations such as the once-daily extended-release preparation of divalproex. ⌘

## DISCLOSURE

Dr. L. Citrome receives grant and research support from, is a consultant for, or has received honoraria for advisory board meetings and lectures from: Abbott Laboratories, AstraZeneca, BMS, Eli Lilly Company, Janssen Pharmaceutica, Novartis, and Pfizer Pharmaceuticals.



## DISCLOSURE OF UNLABELED OR UNAPPROVED USES OF DRUGS

Please note that this review article contains discussions of unlabeled uses of FDA-approved pharmaceutical products. Please refer to the official prescribing information for approved indications, contraindications, and warnings.

## REFERENCES

1. Burton BS. On the propyl derivatives and decomposition products of ethyl acetoacetate. *Am Chem J.* 1982;3:385-395.
2. Davis LL, Ryan W, Adinoff B, Petty F. Comprehensive review of the psychiatric uses of valproate. *J Clin Psychopharmacol.* 2000;20(1, Suppl 1):1S-17S.
3. McEvoy JP, Scheifler PL, Frances A. The Expert Consensus Guideline Series, Treatment of Schizophrenia. *Journal of Clinical Psychiatry.* 1999;60(Supplement 11):43.
4. Abbott Laboratories. Depacon - valproate sodium injection, Depakene - valproic acid capsules and syrup, Depakote Sprinkle Capsules – divalproex sodium coated particles in capsules, Depakote Tablets – divalproex sodium delayed-release tablets, Depakote ER – divalproex sodium extended-release tablets product information In *Physicians' Desk Reference,* 57th Edition. Thomson PDR, Montvale, NJ, 2003:416-441.
5. Wilder BJ, Karas BJ, Penry JK, Asconape J. Gastrointestinal tolerance of divalproex sodium. *Neurology.* 1983;33(6):808-811.
6. Keck PE. The use of divalproex. *J Clin Psychiatry.* 1997;15:18-19.
7. Wilder BJ, Karas BJ, Hammond EJ, Perchalski RJ. Twice-daily dosing of valproate with divalproex. *Clin Pharmacol Ther.* 1893;34;501-504.
8. Citrome L, Jaffe A, Levine J, Allingham B. Use of mood stabilixers among patients with schizophrenia, 1994-2001. *Psychiatric Serv.* 2002;53:1212.
9. Citrome L, Levine J, Allingham B. Changes in use of valproate and other mood stabilizers for patients with schizophrenia from 1994 to 1998. *Psychiatric Serv.* 2000;51:634-638.
10. Citrome L. Adjunctive Mood Stabilizers/Anticonvulsants in Schizophrenia Presented at the 42nd Annual NCDEU Meeting. Boca Raton, FL, June 12, 2002.

11. Citrome L, Levine J, Allingham B. Utilization of valproate: Extent of inpatient use in the New York State Office of Mental Health. *Psychiatr Q.* 1998;69:283-300.
12. Wassef AA, Dott SG, Harris A, et al. Critical review of GABA-ergic drugs in the treatment of schizophrenia. *Clin Psychopharmacol.* 1999;19:222-232.
13. Daniel DG. The role of GABA in schizophrenia. *Clin. Psychiatry Visuals.* 2003;5:1-2.
14. Koran LM. Gamma-Aminobutyric-acid deficiency in schizophrenia. *Lancet* 1976;2:1025.
15. van den Berg CJ. Gabergic compounds and schizophrenia. *Lancet* 1976;2:1301-1302.
16. Garbutt JC, van Kammen DP. The interaction between GABA and dopamine: implications for schizophrenia. *Schizophr Bull.* 1983;9:336-353.
17. Lara DR. Inhibitory deficit in schizophrenia is not necessarily a GABAergic deficit. *Cell Mol Neurobiol.* 2002;22:239-247.
18. Ball S, Busatto GF, David AS, et al. Cognitive functioning and GABAA/benzodiazepine receptor binding in schizophrenia: a 123I-iomazenil SPET study. *Biol Psychiatry.* 1998;43:107-117.
19. Yatham LN, Liddle PF, Shiah IS, et al. PET study of [(18)F]6-fluoro-L-dopa uptake in neuroleptic- and mood-stabilizer-naive first-episode nonpsychotic mania: effects of treatment with divalproex sodium. *Am J Psychiatry.* 2002;159:768-774.
20. Soderpalm B. Anticonvulsants: aspects of their mechanisms of action. *Eur J Pain.* 2002;6(Suppl A):3-9.
21. Stahl SM, Muntner N. Essential Psychopharmacology: Neuroscientific Basis and Practical Applications, 2nd edition. Cambridge University Press, 2000.
22. Wassef AA, Hafiz NG, Hampton D, Molloy M. Divalproex sodium augmentation of haloperidol in hospitalized patients with schizophrenia: clinical and economic implications. *J Clin Psychopharmacol.* 2001;21:21-26.
23. Nagao T, Ohshimo T, Mitsunobu K, Sato M, Otsuki S. Cerebrospinal fluid monoamine metabolites and cyclic nucleotides in chronic schizophrenic patients with tardive dyskinesia or drug-induced tremor. *Biol Psychiatry.* 1979;14:509-523.
24. Gundurewa V, Beckmann H, Zimmer R, Ruther E. Effect of valproic acid on schizophrenic syndromes. *Arzneimittelforschung Drug Res* 1980;30:1212-1213.
25. Linnoila M, Viukari M, Hietala O. Effect of sodium valproate on tardive dyskinesia. *Br J Psychiatry.* 1976;129:114-119.
26. Altamura AC, Basile R, Mauri M, Cazzullo CL. Le valpromide dans le traitment d'etats psychotiques aigus: Une etude clinique ouverte. *Acta Psychiatr Belg.* 1986;86:297-304.
27. Morinigo A, Martin J, Gonzalez S, Mateo I. Treatment of resistant schizophrenia with valproate and neuroleptic drugs. *Hillside J Clin Psychiatry.* 1989;11:199-207.
28. Wassef A, Watson DJ, Morrison P, Bryant S, Flack J. Neuroleptic-valproic acid combination in treatment of psychotic symptoms: a three-case report. *J Clin Psychopharmacol.* 1989;9:45-48.
29. Chong SA, Tan CH, Lee EL, Liow PH. Augmentation of risperidone with valproic acid. *J Clin Psychiatry.* 1998;59:430.
30. McElroy SL, Keck PE, Pope HG. Sodium valproate: Its use in primary psychiatric disorders. *J Clin Psychopharmacol.* 1987;7:16-24.
31. Lautin A, Angrist B, Stanley M, Gershon S, Heckl K, Karobath M. Sodium valproate in schizophrenia: Some biochemical correlates. *Br J Psychiatry.* 1980;137:240-244.
32. Ko GN, Korpi ER, Freed WJ, Zalcman SJ, Bigelow LB. Effect of valproic acid on behavior and plasma amino acid concentrations in chronic schizophrenia patients. *Biol Psychiatry.* 1985;20:209-215.
33. Dose M, Hellweg R, Yassouridis A, Theison M, Emrich HM. Combined treatment of schizophrenic psychoses with haloperidol and valproate. *Pharmacopsychiatry.* 1998;31:122-125.
34. Wassef AA, Dott SG, Harris A, et al. Randomized, placebo-controlled pilot study of divalproex sodium in the treatment of acute exacerbations of chronic schizophrenia. *J Clin Psychopharmacol.* 2000;20:357-361.
35. Hesslinger B, Normann C, Langosch JM, Klose P, Berger M, Malden J. Effects of carbamazepine and valproate on haloperidol plasma levels and on psychopathological outcome in schizophrenic patients. *J Clin Psychopharmacol* 1999;19:310-315.
36. Casey DE, Daniel DG, Wassef AA, Tracy KA, Wozniak P, Sommerville KW. Effect of divalproex combined with olanzapine or risperidone in patients with an acute exacerbation of schizophrenia. *Neuropsychopharmacology.* 2003;28:182-192.
37. Citrome L. Use of lithium, carbamazepine, and valproic acid in a state-operated psychiatric hospital. *J Pharmacy Technology.* 1995;11:55-59.
38. Lindenmayer JP, Kotsaftis A. Use of sodium valproate in violent and aggressive behaviors: a critical review. *J Clin Psychiatry* 2000;61:123-128.
39. Hollander E, Margolin L, Wong C, et al. Double-blind placebo trial of divalproex sodium in the treatment of borderline personality disorder. Poster presented at the 38th annual meeting of the New Clinical Drug Evaluation Unit; June 10-11, 1998; Boca Raton, Florida.

40. Hollander E, Allen A, Lopez RP, Bienstock CA, Grossman R, Siever LJ, Merkatz L, Stein DJ. A preliminary double-blind, placebo-controlled trial of divalproex sodium in borderline personality disorder. *J Clin Psychiatry.* 2001;62:199-203.
41. Wilcox J. Divalproex sodium in the treatment of aggressive behavior. Ann Clin Psychiatry. 1994;6:17-20.
42. Mazure CM, Druss BG and Cellar JS. Valproate treatment of older psychotic patients with organic mental syndromes and behavioral dyscontrol. *J Am Geriatr Soc.* 1992;40:914-916.
43. Afaq I, Riaz J, Sedky K, et al. Divalproex as a calmative adjunct for aggressive schizophrenic patients. *J Ky Med Assoc.* 2002;100:17-22.
44. Littrell KH, Petty RG, Hilligoss NM, Kirshner CD, Johnson CG. Valproate for hostility in schizophrenia patients. *J Clin Psychiatry.* 2003.
45. Lindenmayer JP, Kotsaftis A, Ying P, Reddy J, Chowdhury Q, Kashyap. The use of valproate in the treatment of aggressive behaviors in patients with schizophrenia. Poster presented at the US Psychiatric Congress; November 16, 2000; San Diego, CA
46. Donovan SJ, Stewart JW, Nunes EV, et al. Divalproex treatment for youth with explosive temper and mood lability: a double-blind, placebo-controlled crossover design. *Am J Psychiatry.* 2000;157:818-820.
47. Frankenburg FR, Zanarini MC. Divalproex sodium treatment of women with borderline personality disorder and bipolar II disorder: a double-blind placebo-controlled pilot study. *J Clin Psychiatry.* 2002;63:442-446.
48. Hollander E, Tracy KA, Swann AC, et al. Divalproex in the treatment of impulsive aggression: efficacy in Cluster B personality disorders. *Neuropsychopharmacology.* 2003;28:1186-1197.
49. Sival RC, Haffmans PM, Jansen PA, Duursma SA, Eikelenboom P. Sodium valproate in the treatment of aggressive behavior in patients with dementia--a randomized placebo controlled clinical trial. *Int J Geriatr Psychiatry.* 2002;17:579-585.
50. Porsteinsson AP, Tariot PN, Erb R, et al. Placebo-controlled study of divalproex sodium for agitation in dementia. *Am J Geriatr Psychiatry.* 2001;9(1):58-66.
51. Citrome L, Casey DE, Daniel DG, Wozniak P, Kochan LD, Tracy KA. Effects of Adjunctive Valproate on Hostility in Patients with Schizophrenia Receiving Olanzapine or Risperidone: A Double-Blind Multi-Center Study. *Psychiatric Serv*. (in press).
52. Volavka J, Citrome L. Atypical Antipsychotics in the Treatment of the Persistently Aggressive Psychotic Patient: Methodological Concerns. *Schizophr Res.* 1999;35:S23-S33.
53. Wilson WH. Addition of lithium to haloperidol in non-affective, antipsychotic non-responsive schizophrenia: a double blind, placebo controlled, parallel design clinical trial. *Psychopharmacology.* 1993;111:359-366.
54. Collins PJ, Larkin EP, Shubsachs AP. Lithium carbonate in chronic schizophrenia: a brief trial of lithium carbonate added to neuroleptics for treatment of resistant schizophrenic patients. *Acta Psychiatr Scand.* 1991;84:150-154.
55. Prakash R. Lithium-responsive schizophrenia: Case reports. *J Clin Psychiatry.* 1985;46:141-142.
56. Simhandl C, Meszaros K. The use of carbamazepine in the treatment of schizophrenic and schizoaffective psychoses: a review. *J Psychiatr Neurosci.* 1992;17:1-14.
57. Luchins DL. Carbamazepine in violent non-epileptic schizophrenics. *Psychopharmacol Bull.* 1984;20:569-571.
58. Yassa R, Dupont D. Carbamazepine in the treatment of aggressive behavior in schizophrenic patients: a case report. *Can J Psychiatry.* 1983;28:566-568.
59. Hakola HPA, Laulumaa VA. Carbamazepine in treatment of violent schizophrenics [letter]. *Lancet.* 1982;1:1358.
60. Neppe VM. Carbamazepine as adjunctive treatment in nonepileptic chronic inpatients with EEG temporal lobe abnormalities. *J Clin Psychiatry.* 1983;44:326-331.
61. Dose M, Apelt S, Emrich HM. Carbamazepine as an adjunct of antipsychotic therapy. *Psychiatry Res.* 1987;22:303-310.
62. Okuma T, Yamashita I, Takahashi R, et al. A double-blind study of adjunctive carbamazepine versus placebo on excited states of schizophrenic and schizoaffective disorders. *Acta Psychiatr Scand.* 1989;80:250-259.
63. Tiihonen J, Hallikainen T, Ryynanen OP, et al. Lamotrigine in treatment-resistant schizophrenia: a randomized placebo-controlled trial. *Biological Psychiatry.* 2003;54:1241-1248.
64. Chouinard G, Beauclair L, Belanger MC. Gabapentin: long-term antianxiety and hypnotic effects in psychiatric patients with comorbid anxiety-related disorders. *Can J Psychiatry.* 1998;43:305.
65. Megna JL, Devitt PJ, Sauro MD, Dewan MJ. Gabapentin's effect on agitation in severely and persistently mentally ill patients. *Ann Pharmacotherapy.* 2002;35:12-16.
66. Jablonowski K, Margolese HC, Chouinard G. Gabapentin-induced paradoxical exacerbation of psychosis in a patient with schizophrenia. *Can J Psychiatry.* 2002;47:975-976.
67. Drapalski AL, Rosse RB, Peebles RR, Schwartz BL, Marvel CL, Deutsch SI. Topiramate improves deficit symptoms in a patient with schizophrenia when added to a stable regimen of antipsychotic medication. *Clin Neuropharmacol.* 2001;24:290-294.
68. Millson RC, Owen JA, Lorberg GW, Tackaberry L. Topiramate for refractory schizophrenia. *Am J Psychiatry.* 2002;159:675.