

How many patients, particularly elderly patients, have this syndrome but their signs and symptoms have been attributed to worsening of their underlying, degenerative neurological disease OR to a new, degenerative neurological disease not "recognized" earlier?

VALPROIC ACID TREATMENT

"OTHER CONSIDERATIONS"

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Until recently, the most common side effects I had attributed to VPA treatment were these:

Sedation
Ataxia
Thrombocytopenia

I had noted that a number of elderly patients, for whom VPA had been prescribed, "took to their chairs" and never walked again. Now and then a patient developed delirium while taking VPA. For the most part, other symptoms and signs—such as the ones seen in the Case Example above—were attributed to one or more of the patients' progressive neurological diseases, e.g. Alzheimer's disease, Parkinson's disease, vascular dementia, etc.

Tremors associated with VPA treatment were first noted in 1982
Karas, et.al, *Neurology* 1982 Apr;32(4):428-32

Case reports began in 1989:

Van der Zwan, *Ned Tijdschr Geneeskde* 1989 June 17;133(24):1230-2
Netherlands

Over a two-year period, six (out of 88) patients started on VPA for treatment of epilepsy, developed tremor or full parkinsonian syndrome—which disappeared when dose reduced or VPA stopped

Alvarez-Gomez, et.al., *Clin Neuropharmacol* 1994 Oct;16(5):451-5
Spain

Reduction of VPA dosage and subsequent discontinuation 4 months later resulted in disappearance of clinical symptoms with a 20-point improvement at IQ testing and recovery of previous PM score. Repeat MRI showed disappearance of pseudoatrophic changes.

To date, only one study has been performed:

Armon, et.al., Reversible parkinsonism and cognitive impairment with chronic valproate use. *Neurology* 1996 47(3):626-35

“Following our initial report of the insidious development of reversible, valproate-induced hearing, motor, and cognitive dysfunction in two patients, we evaluated 36 patients in an epilepsy clinic who had been taking therapeutic levels of valproate for at least 12 months.”

Armon C, Brown E, Carwile S, Miller P, Shin C. Sensorineural hearing loss: a reversible effect of valproic acid. *Neurology* 1990;40:1896-1898

Methods

Patient selection criteria

All patients followed in the Epilepsy Clinic who had been taking therapeutic doses of valproate for 12 or more consecutive months at the time of initial evaluation (March 1, 1990 to February 28, 1991) were included in the study. Serum levels of 40 to 100 micro gram/ml were considered therapeutic. No patient who met these criteria was excluded.

Clinical evaluation (36 patients)

From March 1 to September 30, 1990 (7 patients)—Retrospective cases

These were patients who presented or were hospitalized because of neurologic disease, and in whom a causal role for valproate in producing the neurologic symptoms was suspected. As a result, valproate was discontinued in these patients. [All were thoroughly investigated, neurologically.] All patients were judged severely affected and their condition improved after valproate was stopped.

From October 1, 1990 to February 28, 1991 (29 patients)—Prospective cases

These patients underwent a **prospective** detailed neurologic examination with systematic documentation of motor and cognitive functions before and after discontinuation of valproate. The Unified Parkinson's Disease Rating Scale (UPDRS) [10] was used to score symptoms and signs of parkinsonism, and the Short Test of Mental.

12 year-old girl with epilepsy developed parkinsonism 7 days after the initiation of VPA therapy—disappeared completely when VPA was replaced with CBZ.

Delsoldato, et.al., *Epilepsia* 1994 Mar-Apr;35(2):391-3

Italy

Two young patients with epilepsy—transient parkinsonism resolved when VPA withdrawn

Del Real Francia, et.al., *Neurologia* 1995 Nov;10(9):381-3

Spain

Two elderly women, parkinsonism developed several years after starting VPA therapy—problems disappeared when VPA stopped

Wils, et.al., *Int J Geriatr Psychiatry* 1997 Feb;12(2)272

Netherlands

70 year-old woman with bipolar illness, started on VPA, 10 days later she developed sedation, cogwheel rigidity, shuffling gait, dysarthria, drooling and dysphagia. VPA withdrawn; mania relapsed

Park-Matsumoto, et.al., *No To Shinkei* 1998 Jan;50(1):81-4

Japan

Three cases of elderly patients who developed rigidity, akinesia and postural instability months after VPA started—with resolution after VPA stopped

Onofrj, et.al., *J Neurol* 1998 Dec;245(12):794-6

Italy

Reversible parkinsonism induced by prolonged treatment with valproate

Guerrini, et.al., *Epilepsia* 1998 Jan;39(1):27-32

Italy

Described an 11-year-old girl with symptomatic localization-related epilepsy and normal intelligence that developed reversible mental deterioration and pseudoatrophic brain changes while receiving valproate (VPA). After 2 years and 6 months on VPA the girl insidiously developed mental deterioration (loss of 18 IQ points and drop in age-adjusted PM score from the 95th to the 50th percentile) associated with MRI-documented pseudoatrophy of the brain. There were no other manifestations of drug toxicity or hyperammonemia. Background EEG activity was normal.

Additional testing.

Additional studies were obtained to exclude alternate etiologies for motor and cognitive impairment, and to document the extent of impairment: (a) Hematologic, metabolic, and endocrine studies (CBC, chemistry panel, ammonia, thyroid, vitamin B12, and VDRL); (b) CT of the head; (c) EEG, awake; (d) **Neuropsychometric testing:** (1) Wechsler Adult Intelligence Scale, Revised (WAIS-R) Subtests: Information, Arithmetic, Vocabulary, Digit Symbol; (2) The Neurobehavioral Cognitive Status Examination (NCSE); (3) Trail Making Test, parts A and B; (4) Aphasia Screening Exam; (5) Wechsler Memory Scale-Russell Revision; (6) **Grip dynamometry of dominant and nondominant hands;** (7) **Finger Oscillation Test;** (e) **Audiometric studies,** for each ear separately, including air and bone conduction pure-tone threshold measurement, speech discrimination assessment, and acoustic stapedial reflex threshold assessment, with principal focus on puretone thresholds at 250 to 8,000 Hz (the audiogram).

Therapeutic intervention.

Discontinuation of valproate was considered and discussed with all patients who had developed personality changes, social or cognitive impairment, motor dysfunction, sexual dysfunction, or progressive hearing difficulties, or who were found on neurologic examination to have evidence of cognitive impairment or parkinsonism. **As a result, valproate was discontinued in 32 patients.** Patients receiving valproate monotherapy were switched to monotherapy with another antiepileptic medication. Patients receiving polytherapy continued to take their other antiepileptic medications.

Follow-up studies.

The **clinical evaluation and additional studies, as outlined above, were repeated 3 to 6 months after valproate was discontinued.** Follow-up CT of the head was obtained only in two patients, after they had been 12 and 11 months without valproate, respectively, to see if a previously reported observation of reversible cerebral atrophy with valproate [14] was reproduced in some of our patients. Additional clinical assessment, as part of ongoing care, was performed as needed.

Results.

Demographics, clinical diagnoses, and treatment with valproate.

All adult age groups were well represented, ranging from 22 to 74 years.

Median and mean ages were identical: 51.5 years; the SD was 14.1 years.

Thirty-five were men, one was a woman.

Duration of treatment with valproate ranged from 12 months to 131 months, and was skewed toward a shorter duration:

Median was 36 months, mean +/- SD: 44.8 +/- 31.5 months.

Most patients had been maintained on mid-therapeutic or high-therapeutic valproate levels.

Clinical features: symptoms, signs, UPDRS and STMS scores (36 patients)

Patient symptoms:

92% reported some symptoms or had some abnormalities on neurologic examination.

Only three patients were free of symptoms or of findings.

69% had memory dysfunction

63% had progression of hearing difficulties

53% had gait instability or unsteadiness

44% had tremor

Findings on examination:

86% had cognitive impairment
50% of the patients would be
considered to have met the screening criterion for dementia.

83% had rigidity

75% had rigidity plus two or more of these findings
Tremor
Bradykinesia
Postural instability

Severity of parkinsonism on valproate was associated with that of the cognitive impairment.

Cerebral atrophy on CT.

New cerebral atrophy or progression of cerebral atrophy on CT of the head was seen in 11 of 16 patients (69%).

Audiometric findings.

Six patients had serial audiograms while taking valproate, or an audiogram receding the use of valproate followed by one or more audiograms while taking valproate. Hearing worsened in both ears in three patients, in the right ear only in two patients, and did not change in one patient.

Therapeutic intervention--safety.

Of the 36 patients, 33 had one or more abnormal symptoms or signs of motor or cognitive dysfunction. Discontinuation of valproate was thus considered in these 33 patients and discussed with them. One patient, who was affected only mildly, elected to continue valproate therapy because it was the first antiepileptic medication to have controlled his seizures, enabling him to rejoin the work force. Valproate was therefore discontinued in 32 patients, who constitute the "intention-to-treat" group. Discontinuation of valproate was

accomplished in the first few outpatients using a rapid taper. After we saw that it was safe to stop it abruptly in the inpatient setting, we applied that approach to the remaining outpatients, with no complications.

Duration of follow-up off valproate therapy ranged from 3 to 12 months. It was 3 to 6 months in 24 of 32 patients (75%), and 6 months or more in eight others (25%).

A few patients reported transient cold-or flu-like symptoms, headaches, or increased irritability, which resolved spontaneously within weeks.

Seizure control was not changed by discontinuing valproate during the course of follow-up. Patients who had been seizure-free remained seizure-free; patients who had not been seizure-free did not become seizure-free or experience increased seizure frequency.

Therapeutic intervention--efficacy: improvement of abnormalities after stopping valproate.

Clinical features (symptoms and signs):

81% reported some improvement on follow-up
Instability, unsteadiness and tremor improved most frequently
No patient reported worsening of symptoms

On examination:

91% had some improvement on follow-up examination

96% had improvement in parkinsonism—their Unified Parkinson's Disease Rating Scale scores improved—remember: not every patient had this finding.

72% had significant cognitive improvement

Reversible cerebral atrophy on CT: pseudoatrophy.

Head CT was performed 1 year after valproate had been discontinued in only two patients. Both patients had received valproate monotherapy. One was a 75-year-old man with a moderate degree of cognitive impairment and cerebral atrophy even before starting valproate, whose condition had worsened significantly with the medication, and whose cerebral atrophy had increased. The other was a 35-year-old man with no atrophy or cognitive impairment before starting valproate, who became moderately impaired and developed mild cerebral atrophy with the medication. Scans were obtained after 17 and 14 months on valproate, and after 12 and 11 months off valproate, respectively. Evolution of atrophy on valproate and its partial reversal off the medication was confirmed in both patients by a neuroradiologist blinded to the clinical history.

A semantic note: since atrophy is by definition an irreversible process, "pseudoatrophy" is a more precise term to describe the reversible component of the findings that we report, recognizing that not all the

apparent progression of atrophy was reversible in the 75-year-old man who had cognitive impairment and cerebral atrophy before treatment with valproate.

Audiometric findings.

23 patients had audiometry performed both before discontinuation of valproate and at follow-up.

10 patients improved
1 worsened
10 had no change
2 were unclassifiable.

Discussion

The principal findings of this study are that a constellation of abnormal symptoms and signs related to motor and cognitive function was present in patients receiving long-term valproate therapy.

These signs and symptoms improved after discontinuation of valproate.

The manifestations may not be apparent unless looked for specifically in the minimally or mildly affected patients and may be mistaken for idiopathic Parkinson's disease or dementia in those who are affected severely.

We found a spectrum of severity for a reversible syndrome of parkinsonism and cognitive impairment that may develop in long-term users of valproic acid, which we propose to call a syndrome of reversible valproate-induced parkinsonism and cognitive impairment.

A major limitation possibly affecting our findings is if a placebo effect involving patients, observers, or all accounted for the improvement in our patients after stopping valproate. In each patient, multiple observers and observations confirmed the improvement.

The improvement was noted by the patients themselves, their families, and the authors.

Laboratory measures corroborated the clinical observations. Most of the improvement occurred in moderately to severely affected patients, because they had more room for improvement.

There is no precedent for this extent of motor, cognitive, EEG, audiometric, psychometric, and CT improvement to have been caused by or attributed to a placebo effect.

The multiple independent testing modalities, all of which showed changes in the same direction in many patients, reinforce the patients' reports and the clinical observations.

However, we recognize that lack of blinding may be a stumbling block for the full acceptance of our findings.

We did not consider a double-blinded, placebo-controlled discontinuation study at the time because we knew of no precedent for such a study, we did not doubt our own observations, reinforced by each improving patient, and we did not believe it ethical to continue to treat patients with a medication that might be harming them.

If we had planned a double-blinded discontinuation study, it would have been necessary for us to treat patients with valproate not just for the 3 onths required by the study design, but for an undefinable additional period, until the study was approved by an institutional review board (IRB) and funded.

It would be deemed unethical to continue to treat patients with a medication for research purposes, for which there was clinical evidence that the drug was causing harm to the patients, if alternative therapies are available.

Notwithstanding, we did use all of the methods that have traditionally been required to prove that a particular agent has caused an adverse drug reaction, except rechallenging and watching for a relapse (which we could not ethically do).

This study attempted to avoid selection bias, which would have led to the identification of only the worse-affected patients, by reporting on all Epilepsy Clinic patients who had been taking valproate for at least 12 months.

The increased severity with age parallels the increased frequency of iatrogenic disease and adverse drug reactions in older patients.

In addition, while most of the patients were receiving valproate monotherapy, and some developed reversible valproate-induced parkinsonism and cognitive impairment while taking no other medications, others were taking additional medications for general medical conditions.

We showed that the presence of an additional antiepileptic medication did not affect the severity of parkinsonism or of cognitive impairment at presentation.

Previously, findings of reversible valproate-induced parkinsonism and cognitive impairment were reported in isolated cases, is likely due to under-recognition and under-reporting.

The insidious onset of symptoms—months to years after uneventful valproate treatment—decreases the likelihood that physicians will suspect valproate as the cause of apparent neurodegenerative diseases in their patients.

Author's Hypotheses concerning cause:

Comparison of reversible valproate-induced parkinsonism and cognitive impairment to other forms of parkinsonism leads us to conclude that its insidious onset and evolution make it more similar to idiopathic Parkinson's disease or the Western Pacific parkinsonism/dementia complex than to neuroleptic-induced or MPTP-induced parkinsonism. We propose that *production of mitochondrial respiratory chain dysfunction by valproate* may be the mechanism for the production of reversible valproate-induced parkinsonism and cognitive impairment. There is defective function of the mitochondrial enzyme NADH CoQ reductase (Complex I) of the respiratory chain in idiopathic Parkinson's disease, and possibly in MPTP-induced parkinsonism. Progressive hearing impairment is common in patients with mitochondrial encephalomyopathies, which are also due to respiratory chain dysfunction. Valproate affects Complex I activity in vitro.

An additional mechanism by which valproate may produce parkinsonism is its GABAergic activity: there is excess activity of GABA neurons in the globus pallidus externa in patients with Parkinson's disease and MPTP-induced parkinsonism. However, we would expect the latter effect to

manifest itself more rapidly and resolve sooner after discontinuation of valproate; thus, it may have only a secondary role in the patients we described. The dependence of the severity of both cognitive impairment and parkinsonism in reversible valproate-induced parkinsonism and cognitive impairment on the patient's age suggests a strong relationship, or interaction, with age-related mechanisms, such as mitochondrial dysfunction, which may also account for the increase, with age, of age-specific incidence of the classic neurodegenerative diseases.

Conclusions:

We suggest that a causal role for valproate should be considered in patients who develop parkinsonism and cognitive impairment after treatment with valproate for more than 12 months.

Development or progression of hearing impairment may precede some of the cognitive or motor changes, and should prompt evaluation for their presence.

Although the parkinsonism and cognitive impairment appear to be largely reversible when valproate is stopped, the question of residual dysfunction is a lingering concern, which could not be resolved by our study design.

If discontinuation of valproate is considered in symptomatic patients, the side effects of the medication should be balanced against its effectiveness in seizure control, taking into account the availability of other antiepileptic drugs.

I spoke with the principle author and:

He strongly supports development of criteria for the use of VPA:

1. VPA should be used only when there is no other alternative reasonable and untried remedy
2. In addition to gaining fully informed consent from the patient, he feels the following pre-VPA tests should be done to establish a pre-treatment baseline:
 - a. CT or MRI
 - b. Hearing evaluation
 - c. Cognitive testing
 - d. Neurological examination with particular attention paid to tremor, rigidity, gait disturbance

OUR EXPERIENCE IN BUILDING 324 (VA EXTENDED CARE/NHCU)

In the elderly patients we see in Building 324, VPA is prescribed for two primary reasons: for mood stabilization in patients with bipolar illness; for control of aggressive behavior in patients with brain injuries or diseases such as the various dementias. As a result of our recent experience with VPA, the only patients on valproic acid are those admitted to us on this drug. We are vigilant and watch carefully for the development of the syndrome described by Armon and, to date, have identified several patients who probably had it, were taken off VPA (only medication change made) and who recovered their previous level of functioning:

Our most striking case was a 74 year-old veteran very similar to the case example given in the beginning. In July 1998 his MMSE score was 28/30. Shortly after stopping VPA, his MMSE score (January 1999) had plunged to 0/30. The score was steadily improved to its current level of 24/30. For months he was stiff, non-ambulatory and incontinent. Recently he began to ambulate on his own and is now, again, continent. This 74 year-old veteran developed significant cerebral atrophy from 12/97 to 12/98 and was described as having a "Pick's disease-type CT scan." Of course, since VPA was discontinued, his cognition has dramatically improved over the past 8 months, almost to the point where it was in 7/98.

A follow-up CT scan has been scheduled for 8/30 and we are very interested in the results of this scan, particularly with respect to the patient's previously noted cerebral atrophy.

CT Scan report of 12/14/98:

FINDINGS: enlargement of the sulci and ventricle throughout the cerebral hemispheres consistent with atrophy. This has increased compared to prior examination and appears to be more global. In addition, there has been interval increase in patchy low attenuation throughout the periventricular white matter. There is no abnormal attenuation to suggest intra or extra axial hemorrhage. No midline shift or mass effect. Gray white differentiation intact. Regional bones and soft tissues grossly unremarkable.

Impression:

1. INTERVAL INCREASE IN CEREBRAL ATROPHY WHICH APPEARS GLOBAL. INTERVAL INCREASE IN PERIVENTRICULAR WHITE MATTER CHANGES. THIS COMBINATION OF FINDINGS SUGGESTS A PROGRESSIVE DEMENTIA SUCH AS PICK'S OR LESS LIKELY, ALZHEIMERS DISEASE.

I have identified 4 other patients over the past six months (Dr. Peyser may have identified one other patient during her brief time working in 324) of patients either taking VPA by my prescription or admitted to us on VPA who had developed varying degrees of the syndrome described by Armon:

All patients were elderly
Three were receiving VPA for behavior problems; one for mood stabilization
Tremor, rigidity, gait problems were the most common problems
No patient had CT scans for logistical reasons
Audiologic testing was not done for similar reasons
Three patients became “weepy, clinging, and disorientation” with marked worsening of cognition—at times it appeared like delirium but without the other hallmark signs of that disorder.
Some patients developed the syndrome after many months of VPA treatment, others developed it rather quickly (after a few weeks of VPA treatment).

All patients returned to their pre-VPA neurological including cognitive levels after VPA was discontinued.

Eight cases of this syndrome from Santa Clara County Conservator’s Office

Questions to consider:

How many 2-4 years studies have there been of the neurological, audiologic and cognitive status of bipolar patients taking VPA treatment?

How many patients, particularly elderly patients, have this syndrome but their signs and symptoms have been attributed to worsening of their underlying, degenerative neurological disease OR to a new, degenerative neurological disease not “recognized” earlier?

How many patients with migraine, after taking VPA for prophylaxis over the next two years will develop this syndrome?

Why are psychiatrists so unaware, seemingly, of this syndrome?

Why has Abbott Labs not further researched this problem and responded to the issues raised by Armon and his associates as well as the case reports?

I’ve made an effort to get a response from Abbott—verbally and in writing—to the findings of Armon’s study but I’ve only been

asked complete a cumbersome 22 page document on all the details of any patient I think has the syndrome.

I've heard nothing from Abbott Labs in response to my request for their response to the study by Armon.

Who in the psychiatric community is ready to take on the task of alerting psychiatrists to this probable syndrome by doing a follow-up study on bipolar and other patients who've taken VPA for 2 or more years?

FINALLY:

We need to be aware of this syndrome, which is probably not as rare as some may have thought, particularly with the increasing use of valproic acid for mania as well as behavior disorders in our elderly patients.

IF YOU DON'T LOOK FOR IT, YOU MAY NOT FIND IT!

Ask yourself:

You have a patient with a chronic illness.

This patient will need treatment for many years.

Do you wish to give this patient a drug treatment, which after 1-2 years has up to a 90% chance of causing cognitive impairment, a movement disorder, hearing loss and/or cerebral atrophy?

Is it medically wise to do this when there are other equally effective drugs available for treatment of the chronic illness?