COGNITIVE FUNCTIONING IN PATIENTS WITH COMPLEX ABSENCE FOLLOWING TREATMENT WITH SODIUM VALPROATE

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SUMMARY
The association of sodium valproate with cognitive functions was studied in 29 patients with complex absence seizures. Seventeen patients were on monotherapy and twelve on polypharmacy with sodium valproate. Cognitive functions assessed were attention, speech, visuo-special perception, memory and intelligence. Behavioral disturbances were also assessed. Two assessments were made six months apart; in the first assessment, attention and speech were adequate, while memory, visuo-spatial perception, and behavioral functioning were impaired. Intelligence was lower in the polypharmacy group, while other functions were similar. In the second assessment, intelligence and visual memory improved in the monotherapy group, while no changes were present in the polypharmacy group.

INTRODUCTION
Antiepileptic drug therapy is found to affect cognitive functioning (Vining, 1987). In normal volunteers, cognitive deficits in memory and information processing tasks were recorded in association with phenytoin, carbamazepine, sodium valproate, clobazam and clonazepam, fewer deficits being associated with sodium valproate, carbamazepine and clobazam (Trimble, 1987). Sodium valproate has been found to improve intellect, as patients become more alert and co-operative (Volzke & Doose, 1973). Better attention and school performance has been reported in children on sodium valproate (Jeavons & Clark, 1974), while reaction time has been reported as decreased in children and adolescents on sodium valproate (Harding et al., 1978). Valproate is associated with better behavioral and neuropsychological functioning compared with phenobarbital (Vining et al., 1987); in addition, in normal volunteers, it is associated with improved alertness (Bettis et al., 1982). Contrary to these observations, there are a few reports that sodium valproate has a few adverse effects on cognitive functions. In normal volunteers, sodium valproate was associated with slowing down of mental processing speed which reached significance only when the demands of the task increased (Trimble, 1987). Addition of sodium valproate to drug resistant epileptics resulted in increased reaction time as well as increased time on tasks which required attention and had competing responses (Sommerbeck et al., 1977). As a monotherapy in high doses, it led to impairment of memory and auditory detection (Trimble & Thompson, 1983).

In view of the contradictory findings reported above, the present study was undertaken to evaluate the effect of sodium valproate on cognitive functioning in epileptic patients. It is increasingly felt that, in managing any patient with epilepsy, reduction in cognitive dysfunction and seizure frequency should be viewed together, without sacrificing one for another (Vining, 1987). In the present study, the association of sodium valproate with cognitive functioning was investigated by comparing two groups of patients. In the first group sodium valproate was used singly (monotherapy), whereas in the second group, it was used in conjunction with other antiepileptic drugs [AED] such as phenobarbitone, phenytoin, carbamazepine or benzodiazepines. By comparing its effect in isolation (monotherapy group) with its effect in interaction with other AEDs (polypharmacy group), the effect of sodium valproate on cognitive functioning in epileptics could be studied.

MATERIALS AND METHODS
Subjects
Twenty-nine patients, with complex absence as the predominant seizure type who were on monotherapy with sodium valproate (n=17) or on polypharmacy (i.e., phenobarbitone, phenytoin, carbamazepine & benzodiazepines) inclusive of sodium valproate (N=12) were included in the study. This sample was drawn from the Neurology out-patient service of the National Institute of Mental Health and Neurosciences (NIMHANS) between 1984-86 and formed the sample for a clinical drug trial on sodium valproate. Six patients in the monotherapy group and five patients in the polypharmacy group were males. Sample characteristics are shown in Table I.

Assessment Of Cognitive Functions
Two assessments were conducted, the initial after the commencement of sodium valproate and the second, six months later. The period of sodium valproate use before the first assessment varied from 1 to 23 months with a mean of 16 months in the monotherapy group. In the polypharmacy group, it ranged from 3-22 months, the mean being 17 months (Table I). The second assessment enabled evaluation of cognitive and behavioral functions associated with continued use of sodium valproate either as monotherapy or as a component of polypharmacy.

Attention was assessed using the components of spontaneous arousal, distractibility, fatiguability and perseveration. Speech was assessed in terms of the adequacy of expressive and receptive speech. Attention and speech were rated on a 5 point scale with 5 indicating adequate functioning. Visuo-spatial perception was assessed using the complex figure test, an adaptation of Rey-Osterich figure (Mukundan et al., 1979). Copying of this figure was
TABLE I: SAMPLE CHARACTERISTICS

| Clinical Variable          | MONOTHERAPY n=17 | POLYPHARMACY n=12 | N | Significance level |
|---------------------------|------------------|--------------------|---|-------------------|
| Age (Yrs)                 | Mean             | Range             | Category | N | Mean | Range | Category | N |          |
|                           | 11.6             | 5-22              | ≤ 12      | 11| 18.0 | 12-22  | ≤ 12      | 2 | p<0.001  |
|                           | (4.6)            | >12               |           |   | (3.1) | >12    |           |   |          |
| Education (yrs of)        | 6.0              | 1-12              | ≤ 10      | 14| 7.3   | 0-10   | ≤ 10      | 8 | NS       |
| schooling                 | (3.4)            | ≥ 10              |           |   | (3.0) | ≥ 10    |           |   |          |
| Age of onset (Yrs)        | 13               | >10               |           |   | 4     | >10    |           |   |          |
| Duration of seizures (yrs)| ≤ 3              | 9                 |           |   | ≥ 3   | 9      |           |   |          |
| Seizure Frequency         | ≥ 3              | 8                 |           |   | >3    | 9      |           |   |          |
| Before Valproate use      | 50-100/day       | ≤ 10/day          |           |   | 6-15/day | ≤ 10/day |           |   | NS       |
|                           | >10/day          |                  |           |   | numerous | >10/day |           |   |          |
| Duration (mths)           | 16               | 1-23              | ≤ 18      | 7 | 17.0  | 3-22   | ≤ 18      | 10| NS       |
| of Valproate treatment    | (6.4)            | >18               |           |   | (5.8) | >18    |           |   |          |
| Duration of seizure control| 12.6             | 5-20              | ≤ 12      | 7 | 8.8   | 1-18   | ≤ 12      | 9 | NS       |
| with Valproate (mths)     | (5.0)            | >12               |           |   | (5.3) | >12    |           |   |          |
| Co-existent seizure type  | Normal           | 7                 |           |   | Normal | 5      |           |   |          |
| Tonic-clonic              | Abnormal         | 9                 |           |   | Abnormal | 7      |           |   |          |
| EEG                       | Normal           | 7                 |           |   | Normal | 5      |           |   |          |
| Serum Level               | <50ug/ml         | 4                 |           |   | Abnormal | 6      |           |   |          |
| of Valproate              | 50-100ug/ml      | 9                 |           |   | Normal | 5      |           |   |          |
|                           | >100ug/ml        | 2                 |           |   | Abnormal | 1      |           |   |          |

NB: In the monotherapy group, serum level was ascertained in 15 patients only. Significance levels refer to the X² test between the categories of patients in the two groups for each variable.

RESULTS

The two groups were comparable with respect to most of the clinical variables known to affect cognitive functioning in epileptics (Table I). These include age of onset, seizure duration, seizure frequency, presence of EEG abnormalities, seizure free period prior to psychological assessment and serum level of the AED (Dodrill & Wilkus, 1978; Thompson & Trimble, 1982). Patients in the polypharmacy group were significantly older, the difference being four years. Tonic-clonic seizures as a co-existent seizure type was also present in a significantly larger number of patients in the polypharmacy group.

The performance of the monotherapy and polypharmacy groups in the first assessment are depicted in Table II. T test for uncorrelated means revealed that the two groups differed significantly in intelligence; the polypharmacy group being 17 I.Q. points below the monotherapy group. The two groups performed similarly on all other functions. A clinical profile of the mean scores reveal that in both groups attention and speech were adequate. Visuospatial perception was minimally impaired, i.e., 14-15/21 (maximum score). Immediate memory was moderately impaired. Visual and verbal memory were moderately impaired i.e., 8-9/20 (maximum score) and 10-12/21 (maximum score), respectively. Intelligence was in the normal range in the monotherapy group, but in the polypharmacy group, the mean I.Q. was below the normal range. Behavior functioning was minimally impaired in both groups, i.e. a mean rating near 4. Performance on the second assessment was compared with that on the first
using the *t* test for dependent means. Table III shows that performance did not differ between the first and second assessments on any of the functions in the polypharmacy group. In the monotherapy group, visual memory and intelligence had improved significantly in the second assessment. The gain in intelligence is nearly 9 points and is substantial and significant. Performance on the other functions had not changed in the second assessment.

**DISCUSSION**

Sodium valproate administered as monotherapy in complex absence is associated with normal intellectual functioning. Administration in conjunction with other AEDs is associated with a below normal level of intellectual functioning. This poor intellectual functioning may not entirely be due to polypharmacy alone. The other significant clinical variables on which the two groups differed were age of the patient and co-existent type of seizures. The polypharmacy group was older, i.e. mean age of 16 years as compared to 11.6 years in the monotherapy group. However, as the I.Q. was scored on age appropriate norms, the age of the patient is unlikely to have influenced the I.Q. scores. The other significant difference was the presence of tonic-clonic seizures and the use of multiple anticonvulsant drugs in these patients.

Intellectual performance and other cognitive functions in epilepsies are known to be affected by age of onset (O'Leary et al, 1981), duration of seizures (Lennox & Lennox, 1960), frequency of attacks (Dikmen & Mat-
The second assessment after six months indicated that continued use of sodium valproate was not associated with any improvement or worsening of cognitive or behavioral functions in the polypharmacy group. However, in the monotherapy group, it was associated with improvement of visual memory and intelligence; it is difficult to attribute this improvement to practice effects, as these effects are not group or function specific. Further studies with larger samples are required to clarify these preliminary observations regarding the effect of sodium valproate on cognitive functions in patients with complex absence seizures.

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