Anticonvulsants for Severe Behavioral Disturbances in Alzheimer Dementia

Daniel Vasile¹, Octavian Vasiliu²

Abstract: Patients diagnosed with Alzheimer dementia could have, during their illness evolution, associated features like aggression, self-harming behaviors, psychomotor agitation, impulsivity, disinhibition and other types of behavioral dyscontrol. The management of these manifestations is of obvious clinical importance, since they interfere with patients' and caregivers' quality of life, patients' prognosis and safety, compliance to treatment and risk for institutionalization. Anticonvulsants are frequently used for the purpose of behavioral dyscontrol management, not only in dementias, but also in bipolar disorder, depression, personality disorders, impulse control disorders etc. We selected a group of 32 patients, diagnosed with Alzheimer dementia, according to DSM IV TR criteria, who also presented severe behavioral symptoms of sufficient importance to necessitate treatment. Patients received either sodium valproate (Orfiril long) 450 mg mean daily dose, pregabalin 100 mg mean daily dose or carbamazepine 350 mg mean daily dose for 4 weeks. All participants in this trial were assessed using Functional Assessment Staging (FAST) scale, BEHAVE-AD, Global Assessment of Functioning (GAF) and Mini Mental State Examination (MMSE). Patients receiving Orfiril long had a better efficacy/tolerability rapport, reflected in the lowest rate of discontinuation due to side events (n=2, 16.6%, p=0.035) while the improvements in behavioral symptoms (BEHAVE-AD) were only slightly superior in the valproate group (-10.5±1.2, p=0.122). There were no significant inter-group differences regarding the cognitive symptoms after 4 weeks (overall -0.3±0.1 points on MMSE, no change in FAST scale). The global functioning improved as the BEHAVE-AD score decreased and the differences between completers in all the three groups weren’t significant (p=0.342). Sodium valproate is an efficient therapeutic and a well tolerated strategy in patients diagnosed with Alzheimer dementia that associate severe behavioral disturbances.

Key-words: aggression, Alzheimer dementia, anticonvulsants, behavioral disturbances

I. Introduction

Alzheimer dementia (AD) is a frequent pathology in the elderly population and its prevalence increases exponentially with age. Epidemiological data suggest the existence of 1% prevalence at age 60 and over 30% at age 85, almost doubling every 5 years [1]. Also, an important aspect of the AD epidemiology is that disease onset could be precocious, in the context of a genetic susceptibility. It is estimated that 5 to 10% of all the people developing AD have an onset of symptoms before age 65 [2]. The evolution of AD is frequently associated with behavioral symptoms and these manifestations are common reason for such patients to receive psychopharmacological treatment. Symptoms of behavioral dyscontrol are observed in all types of dementias and occur in as much as 50 percent of community dwelling patients and 70 to 90 percent of nursing home patients with dementia [3].

In the category of behavioral disturbance are included purposeless activities like wandering, pacing, packing and unpacking, arranging various items in the wardrobe, continuous searching for inexistent items, making repeated requests or complaints etc. Also, aggression is likely to appear in the advanced stages of the disease and it could manifest through hitting, biting, yelling, verbal outbursts, self-injurious behaviors. Aggressive manifestations are observed in approximately 25% of patients with moderate and severe-stage AD [3].

Psychotic symptoms (paranoid ideation, hallucination-driven behavior, psychomotor bizarre manifestations), sleep-wake cycle disturbances (insomnia, inversion of sleep-wake rhythm, sleepwalking), nighttime confusion (“sundown syndrome”) and resisting care (resisting to bathing or dressing) are also observed in patients with dementia.

Agitation and related behaviors are sources of great discomfort for patients and their caregivers. Therefore, it is important for a clinician to manage these symptoms as quickly as possible. Whenever these symptoms are evaluated it is important to find out if there is a somatic source of distress, like infection, inflammation, other pain causing conditions, constipation, hydro-electrolytic imbalance, transient strokes, cardiologic conditions, renal failure etc. Pain and behavioral disturbances are more common in severe-stage dementia. Since older patients with AD have poorer communicative skills, they have a diminished capacity to express their

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somatic symptoms and therefore they express themselves through agitation and aggressive behaviors.

There are cases when medication itself could explain the genesis of behavior disturbances, for example when an antihistaminergic or anticholinergic drug is used in a patient diagnosed with AD.

Mood stabilizers are one of the main therapeutic choices used for the control of aggression in patients diagnosed with AD. Most literature consists of open-label trials, retrospective charts reviews, case series and case reports. There are also several randomized, controlled trials, but they are still small-scale research. Carbamazepine, oxcarbazepine, valproic acid/sodium valproate, lamotrigine, topiramate and gabapentin have all been evaluated for this specific purpose [4]. To date, most positive results are for carbamazepine but the pharmacokinetic interactions with cytochrome P450 enzymes limit its use.

There is a number of negative studies involving divalproex in AD [5,6], including a 2009 Cochrane meta-analysis [7]. There are also a number of studies reporting good efficacy of low-dose valproate in agitated patients with AD [8,9]. In this context, it is rather difficult to make a solid recommendation for an anticonvulsant agent in AD with agitated behavior. We must take into account that patients with somatic comorbidities tolerate agents like carbamazepine poorly and they usually take more than one concommitant medication, thus increasing the risk of pharmacokinetic interactions. Valproate seems a safer option in these elderly, multiple-drug treated patients. Valproate is metabolized primarily in the liver by glucuronidation and, in addition, oxidative pathways yield a large number of metabolites, some of which having an antiepileptic effect [10].

There is lack of head-to-head comparison studies, involving the main anticonvulsants and there is no study we know of that involved pregabalin for the purpose of agitation management in AD. Therefore, we focused upon the evaluation of efficacy and tolerability of three mood stabilizers- carbamazepine, sodium valproate and pregabalin.

II. PROBLEM FORMULATION

The main objective of this research is to delineate an efficacy/tolerability profile for the above mentioned drugs in patients with moderate to severe stages of AD, who also present severe behavioral problems that have a considerable impact over both patients’ and caregivers’ quality of life.

2.1 Methodology

This is a prospective, open-label, comparison trial in which we have included for this research a number of 32 patients diagnosed with AD, according to DSM IV TR criteria, both with early-onset type (n=4, 12.5%) and late onset-type (n=28, 87.5%). All patients were evaluated at the admission in our department by a psychiatrist and a clinical psychologist, who assessed the symptoms, their impact over patient’s daily activities, the global status of functioning and the level of behavioral dyscontrol. Patients with AD that were admitted in the liver by glucuronidation and, in addition, oxidative pathways yield a large number of metabolites, some of which having an antiepileptic effect [10].

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A Mini Mental Status Examination (MMSE) score under 20 was an inclusion criterion, in order to select the moderate and severe forms of AD. A Functional Assessment Staging (FAST) of at least 5 was also recommended as inclusion criterion.

Patients recruited for this trial were monitored for 4 weeks, using weekly BEHAVE-AD, MMSE, Global Assessment of Functioning (GAF) evaluations and matching in a FAST stage.

The patients were randomized in 3 groups: 12 patients received sodium valproate (Orfiril long) dose range 200-700 mg/day, mean daily dose 450 mg; 10 patients were treated with pregabalin 75-150 mg/day, mean daily dose 100 mg; 10 patients were treated with sodium valproate dose range 100-500 mg, mean daily dose 350 mg. The dose regimen was flexible, being adjusted to the patient’s clinical response. All adverse events were registered throughout the length of the study.

2.2 Results

Patients treated with sodium valproate had a good tolerability, as the rate of drop-outs and the overall rate of side events were lower than in other two groups (fig.1, 2).

![Fig.1 Incidence of drop-outs and adverse events (total reports)](image-url)
Orfiril long comparatively good tolerability is reflected in 2 case of drop-outs due to side events (16.6%) and 8 patients (66%) reporting mild to moderate side events, while pregabalin was associated with 4 drop-outs (40%) and 9 reports of mild to moderate side events (90%), and carbamazepine was associated with 5 (50%) and 9 (90%), respectively.

Inter-group differences were statistically significant between Orfiril long and the other two anticonvulsants regarding the rate of drop-outs (p=0.022) and adverse events reports (p=0.032).

<table>
<thead>
<tr>
<th>Anticonvulsants</th>
<th>Mild SE</th>
<th>Moderate SE</th>
<th>Severe SE (drop-out reasons)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium valproate</td>
<td>Nausea, sedation</td>
<td>Difficulty urinating, loss of coordination</td>
<td>Confusion, allergic reactions</td>
</tr>
<tr>
<td>(Orfiril long)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Pregabalin</td>
<td>Dizziness, drowsiness</td>
<td>Dysarthria, depression</td>
<td>Urinary incontinence, suicidal thoughts</td>
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<td></td>
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<tr>
<td>Carbamazepine</td>
<td>Drowsiness, headaches</td>
<td>Motor coordination difficulties, epigastralgia</td>
<td>Cardiac arrhythmia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Severe sedation</td>
</tr>
</tbody>
</table>

SE=side events

The efficacy of anticonvulsants over the behavioral symptoms was assessed through BEHAVE-AD scale. This is a 25-item scale with items largely independent of primary, cognitive symptoms of AD. We have chosen this instrument because it allows us to quantify various symptomatic dimensions like activity disturbances (wandering, cognitive abulia etc), aggressiveness, diurnal rhythm variations, but also paranoid ideation, hallucination, affective and anxious symptoms. The last symptomatic dimensions could be reasons for secondary behavioral disturbances and therefore should be accurately assessed. BEHAVE-AD also has a global rating scored from 0 (not at all troubling the caregiver or dangerous to the patients) to 3 (severely troubling the caregiver or dangerous to the patients).

Patients treated with sodium valproate (Orfiril long) had only slightly superior improvement in BEHAVE-AD symptomatology score reported to baseline values (-10.5+/−1.2 to baseline, p=0.122). Patients registered no significant differences in the BEHAVE-AD global rating score (-0.1+/−0.3 to baseline, p=0.651).
A cluster analysis showed more effect of valproate over “Activity Disturbances” and “Aggressiveness” (-35% and -37.8% to baseline) than for “Diurnal Rhythm Disturbances”, “Anxieties and Phobias” (-15% and -17.2% to baseline). Only a marginal effect was registered in BEHAVE-AD dimensions “Hallucinations”, “Paranoid or Delusional Ideation” and “Affective Disturbance” (+2.2%, +3.4% and -5.5% to baseline).

Therefore, it is important to note that sodium valproate efficacy is seen especially in primary behavioral disturbances like agitation, wandering, purposeless activity, verbal outbursts, violence and less in the domains of secondary behavioral dysfunctions, like hallucinations or delirious behavior, affective symptoms or anxiety manifestations.

When compared to other two anticonvulsants, Orfiril long was almost equally effective to carbamazepine on the BEHAVE-AD Symptomatology and Global Rating (-11.2+/-.0.4 to baseline, p=0.119 and -0.2+/-.0.3 to baseline, p=0.661) as well as on the subscales of BEHAVE-AD symptoms (-36% and -36.2 on “Activity Disturbances” and “Aggression”, -16.2 on “Anxiety and Phobias”, -12.2 on “Diurnal Rhythm Disturbances” and practically unchanged values for the other 3 dimensions, compared to baseline).

Pregabalin was slightly less efficient in the management of AD associated behavioral disturbances, as BEHAVE-AD Symptomatology and Global Rating (-8.3+/-.2.2 to baseline, p=0.322 and -0.1+/-.0.2 to baseline, p=0.714). The subscales analysis of BEHAVE-AD also showed less efficacy of pregabalin on the “Activity Disturbances” and “Aggression” (-22% and -24% to baseline). The expected positive influence over the “Anxiety and Phobias” items was not observed (-10.2%). Pregabalin did not have any effects on the other BEHAVE-AD dimensions (under 5% variation to baseline).

There were no significant differences either reported to baseline or comparative end-point inter-group values regarding the cognitive symptoms after 4 weeks (overall -0.3+/-.0.1 points on MMSE, no change in FAST scale).

The global functioning improved as the BEHAVE-AD score decreased and the differences between completers in all the three groups weren’t significant (p=0.342). The GAF score increased by 8.2 points in sodium valproate treated patients, 7.9 points in the carbamazepine group and only 5.2 points in the pregabalin treated subjects.

There are some limitations of this research, because we included only a small number of patients in each group, therefore the statistical analysis results could have been negatively influenced. The short duration of this trial is also an issue to be considered, but the long-term administration of any anticonvulsant drug for behavioral disturbances has not been yet supported by the literature and is not recommended by international guidelines.

Valproate, carbamazepine and pregabalin were not previously compared in any clinical trial and therefore this work should be continued in further, large scale studies, possibly with placebo control or other active comparators.
Although the data from literature does not convincingly support recommendations for when to administer anticonvulsants rather than trazodone, antipsychotics or other agents for behavioral disturbances in AD patients, timostabilizers could have a better tolerability profile than other anti-aggressive agents. Antipsychotics are associated with risk of inducing stroke in AD patients, trazodone causes hypotension and secondary risk for traumas, benzodiazepines determine paradoxical reactions or confusion in elderly and so on. Since there are few head-to-head comparisons of different drugs in AD patients with behavioral disturbances, this clinical trial shows the necessity of considering the best agents from an efficacy/tolerability profile point of view, when a recommendation for treatment is to be made.

IV. CONCLUSION

Sodium valproate (Orfiril long) proved to have the best efficacy/tolerability profile in a non-placebo controlled, 4 weeks comparison with carbamazepine and pregabalin. The efficacy of sodium valproate and carbamazepine were similar in controlling the key behavioral symptoms, like aggression, wandering, purposeless behavior, and superior to pregabalin. Although the differences between groups weren’t statistically different, small differences were registered between agents and endpoint.

Tolerability of sodium valproate was superior to that of carbamazepine and pregabalin, as both rate of drop-outs and total reports of adverse events showed. Also, an important aspect not evaluated in this study, the pharmacokinetic interactions of anticonvulsants, could further support a differentiation in overall tolerability profiles between valproate and carbamazepine, favoring the first agent.

REFERENCES: