

ORIGINAL STUDIES

Management of neuropsychiatric symptoms in people with neurocognitive disorder - using add-on antidepressants or NMDA antagonists in relieving agitation

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Abstract

Background. Alzheimer’s disease (AD) is by far the most common type of dementia and it is commonly considered as a memory disorder although behavioral and psychological (including psychiatric) symptoms (BPSD) are largely represented in these patients. Psychosis could explain the worsening of the functional prognosis in these patients, therefore antipsychotic drugs are commonly prescribed. The risks associated with antipsychotics use limit their recommendation and antidepressants or NMDA (N-methyl-d-aspartate) antagonists could represent an alternative.

Aims. The aim of this study was to evaluate changes in the clinical status of the psychomotor agitated patients with neurocognitive disorder on stable antidementia therapy after the addition of antidepressants or NMDA antagonists.

Methods. The primary variables of this study are related to the severity of agitation under the action of pharmacological factors. Agitation as part of the BPSD was evaluated by CMAI (Cohen-Mansfield Agitation Inventory)-short version. A total of 37 subjects (24 female, 14 male) participated in this observational study. They received as add-on antidepressants between weeks 1-8 or NMDA antagonists between weeks 8-16. Inclusion criteria were DSM IV-TR criteria for diagnosing dementia, AD and vascular dementia (VD) and also NINDS-ADRDA clinical criteria. Data analysis was achieved through SPSS software, version 20, using ANOVA- paired t-tests and independent t tests.

Results. The efficacy of memantine over general agitation was significantly superior to antidepressants. Regarding the modulation of the CMAI scores evolution by the type of neurocognitive disorder, treatment and duration, it was observed that the statistical difference between groups became significant after 8-16 weeks of memantine treatment. At the endpoint visit the decrease in agitation was superior in the AD versus VD group ($p = 0.012$).

Conclusions. The overall trend was toward a decrease of the agitation severity after each treatment trial for both types of dementia, including cumulative drugs effects. In the literature, the data are controversial in terms of prescribing antidepressants in the neurocognitive disorders even when BPSD is important, the keystone being the general consensus of limiting the use of antipsychotics and polypharmacy.

Keywords: aging, psychosis, Alzheimer dementia, vascular dementia, beta amyloid, agitation

Introduction

Alzheimer’s disease (AD) is a neurodegenerative disease of the brain, of unknown etiology, usually characterized by obvious memory deficits (***, 2004), which has a specific anatomopathological substrate, consisting of senile plaques and neurofibrillary tangles. Over time, AD causes neurochemical dysfunction and prominent brain atrophy. AD is by far the most common form of dementia, being the cause of about 75% of cases of dementia either *per se* or in combination with other conditions.

More than 45 million people worldwide are currently living with dementia (Livingston et al., 2017). While AD is commonly considered a memory disorder, behavioral and psychological symptoms of dementia (BPSD) are nearly universal and include psychotic symptoms (Livingston et al., 2017; Ballard & Corbett, 2009). Also, more than 50% of patients with AD will present with psychosis during their illness (Murray & Kumar, 2014; Ropacki & Jeste, 2003). These phenomena could explain these patients’ overall worse prognosis, including accelerated cognitive

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decline, earlier admission to institutional care (El Haj et al., 2017), more hospital admissions (Beydoun et al., 2015), and increased mortality (Peters et al., 2015). Currently, no treatments have been approved for AD psychosis (Cummings et al., 2019).

Pathology and neurochemistry

Microscopically, Alzheimer's pathology consists of two main features: senile plaques and neurofibrillary tangles. Currently, the exact relationship between beta amyloid, plaque, clots, cognitive impairment and disease progression is an active area of research. The senile plaques contain a specific amyloid, called beta amyloid - " β A". This β -amyloid is a peptide of either 40 or 42 amino acids, and it is a fragment of the parent molecule known as APP, amyloid precursor protein, a transmembrane glycoprotein. The function of β -amyloid is currently unclear, the senile plaques are located extracellularly and they contain dystrophic neural processes in addition to β -amyloid. Therefore, the axonal disconnection from the dendrites results in poor inter-neuronal communication. And because the microglial cells support the removal of β -amyloid and axonal-dendritic debris, the inflammatory reaction will increase and trigger even more cellular toxicity.

The main neurotransmitter involved in the pathogenesis of AD is acetylcholine. From the early onset of the disease, there is a loss of acetylcholinesterase with a decrease in the reuptake of choline in the synaptic cleft, as well as a decrease in acetylcholine synthesis. Subsequent studies have shown a directly proportional correlation of acetyltransferase loss with cognitive impairment (López et al., 2013). Therefore, the cholinergic hypothesis of AD and the initiation of anti-dementia treatment with acetylcholinesterase inhibitors emerged. In the last decade, research has shown that, in addition to acetylcholine, a plethora of neurotransmitters are involved such as norepinephrine, glutamate, or dopamine, but also, in the foreground, serotonin.

Also, it seems that maintenance of the proteome and organelle population is an important key to the augmentation of lifespan and/or attenuation of many pathologies associated with the aging process. Knowing that regular exercise promotes healthy aging and mitigates age-related pathologies, it is possible that a common pathway in health and longevity may exist (Petrescu et al., 2021).

Neuropsychiatric symptoms in people with dementia

It is known that age is the greatest risk factor for major or minor neurocognitive disorder (***, 2013). Dementia affects 5% of adults over the age of 65 and up to 30% of people over the age of 85. Between 80 and 90% of people with dementia have psychosis, agitation or discomfort, collectively referred to as neuropsychiatric symptoms (BPSD) (Ballard et al., 2009). In addition, 20% of people diagnosed with Alzheimer's disease living in the community and 40-60% living in long-term care (LTC) units have varying degrees of psychomotor agitation.

Moreover, up to 15% of people living in the Alzheimer's community experience delusional ideas, visual hallucinations or auditory hallucinations and 20% of them have moderate to severe clinical depression (Ballard & Corbett, 2010). Neuropsychiatric symptoms often lead to decreased quality of life or increased risk behaviors that

can be life-threatening for patients, leading to difficulties in managing healthcare. People with these symptoms may need long-term institutional care and can be a considerable treatment challenge for all medical and support staff (Seitz et al., 2011; Kalapatapu & Neugroschl, 2009).

Patients with psychosis or agitation are frequently treated with antipsychotic drugs (Ballard et al., 2009; Wang et al., 2005). In 18 randomized controlled trials with short-term monitoring, atypical antipsychotic drugs used to treat neuropsychiatric symptoms have been associated with three times the risk of stroke and almost twice the risk of death compared with placebo (Ballard & Corbett, 2010). Haloperidol treatment was associated with a higher risk of mortality than treatment with atypical antipsychotics (Wang et al., 2005), and typical and atypical antipsychotics have been associated with an increased rate of cognitive decline compared with placebo (Ballard et al., 2009). Antipsychotics are used off-label for BPSD, especially when agitation, aggression and psychotic symptoms are present. However, these agents may pose an increased risk of mortality when used for dementia-associated psychosis (Schneider et al., 2005; Gill et al., 2005; Wang et al., 2005; Sahlberg et al., 2015). Other side effects of antipsychotics include extrapyramidal symptoms, metabolic changes, or even cognitive decline due to anticholinergic effects. Due to the risks associated with antipsychotics, many clinicians are looking for other pharmacological options for polymorphic BPSD when non-pharmacological therapies fail. Several studies show that selective serotonin reuptake inhibitors (SSRIs) are effective in treating BPSD. In clinical trials, citalopram, escitalopram and sertraline are the most studied drugs in this class (Gaber et al., 2001; Finkel et al., 2004).

Due to the risks associated with antipsychotic use and the literature supporting SSRI treatment for BPSD, clinicians may want to use SSRIs instead of antipsychotics. In general, clinical trials have shown little benefit after the use of antipsychotics commonly prescribed today with the increasing incidence of symptoms of agitation and psychosis in elderly patients. In addition, adverse effects (e.g., cognitive impairment, morbidity) often outweigh the perceived benefits of using antipsychotics. Given these factors, the guidelines recommend "assessing the psychological and behavioral symptoms of dementia, developing a comprehensive treatment plan, evaluating the benefits and antipsychotic risks and the prudent use of antipsychotics, including the specifics of dosage, duration and monitoring" (Martin, 2016).

Objectives

It is estimated that up to 8 out of 10 people with major neurocognitive disorders suffer from polymorphic BPSD. These symptoms are divided into 4 clusters that include:

- hyperactivity: agitation, aggression, euphoria, disinhibition, irritability, behavioral disorders;
- psychosis: hallucinations and delusional ideas;
- mood disorders: depression and anxiety, and
- instinctual disorders: appetite disorders, hypnotic disorders or apathy.

The working hypothesis is that general serotonin deficiency in patients with neurocognitive disorder may

contribute to many of these symptoms.

Antipsychotics are used off-label for this syndrome, especially when agitation, aggression and psychotic symptoms are present, but their use in clinical practice may lead to an increase in mortality, extrapyramidal symptoms, metabolic disorders or even cognitive decline due to anticholinergic effects.

Due to the risks associated with antipsychotics and the literature that does not support antipsychotic treatment for BPSD, clinicians could use SSRIs instead of antipsychotics. The aim of this study was to evaluate changes in the clinical status of psychomotor agitation in patients with neurocognitive disorder on stable anti-dementia therapy after the addition of SSRI/NaSSA (noradrenergic and specific serotonergic antidepressant) to treatment.

a. General-theoretical objectives:

Determination of the pharmacological factors (SSRI/NaSSA or NMDA antagonists) and clinical variables that impact BPSD as well as cognitive and functional decline in patients diagnosed with AD, vascular dementia (VD) or mixed dementia (vascular aggravated Alzheimer's) with or without depressive symptoms. Establishing the ways in which pharmacological factors modulate agitation in the study population.

- Clinical practice-oriented objectives:

- Establishing a model of pharmacological intervention in cognitive disorders, based on the efficacy and tolerability of anti-dementia agents in combination with antidepressants (SSRIs/NaSSA) or NMDA glutamatergic agonists in combination with drugs with different but synergistic pharmacological properties, weighing the remaining options or switch, depending on the particularity of the case (e.g., severity of agitation or depression). If patients present depressive symptoms objectified by the Geriatric Depression Scale, $GDS > 5$ at V1, and at V4 - at 8 weeks will have remission of depressive symptoms objectified by $GDS \leq 5$, antidepressants will be continued. If patients have $GDS > 5$ at V1, and at V4 at V8 they do not have remission of depressive symptoms objectified by $GDS \geq 5$, they can be considered responders but not remitters, and they will receive memantine (switch). If patients do not have depressive symptoms with $GDS < 5$ at V1, they will also receive memantine at V4 (switch).

- Correlation of changes in all parameters with the type of pharmacological intervention and the severity of symptoms. From the perspective of ranking the objectives, we established two categories, according to the research hypotheses stated below.

The main objective of the study: the observational study compared the benefits of SSRIs - sertraline, NaSSA - mirtazapine, and memantine - an NMDA receptor antagonist with a pro-cognitive role in neurocognitive disorders, as an add-on therapy to pre-existing anti-dementia medication (mainly cholinesterase inhibitors). Participants are eligible if they meet the criteria for dementia in AD, VD, or mixed dementia, without depressive symptoms, mild or moderate, determined by GDS-15 score ≤ 10 .

Secondary objectives: to evaluate the effectiveness of antidepressants / memantine on:

- Functionality
- Global clinical impression

- Safety objective - assessment of the safety and tolerability of antidepressants/memantine during treatment.

Also, establishing how certain clinical or social factors (e.g., social or family support, level of schooling, change in mild depressive symptoms) reduce patients' responsiveness to anti-dementia pharmacological agents.

Other results considered for the inclusion/exclusion criteria were laboratory results and brain CT/MRI, also to rule out stroke, trauma or concussion (Constantin et al., 2018). Lab results were considered for the monitoring of the treatment safety profile.

Data analysis was done through SPSS software, version 20 (***, 2011) using ANOVA-paired t-tests and independent t tests.

The criteria for inclusion in the study were the existence of the diagnosis of AD or VD at the time of admission, as well as the recording of possible comorbidities according to the DSM IV-TR and ICD-10 criteria. For all patients who met the criteria for inclusion in the study and for whom the consent to participate was obtained, somatic, psychiatric and psychological evaluation was performed for diagnosis confirmation. The patients included did not present severe comorbidities and had no contraindications to the drugs used.

Hypotheses

For this study we stated the following hypotheses:

1. The evolution of the parameters in patients diagnosed with neurocognitive disorders differs depending on the type of pharmacological agents used and the duration of the treatment.

2. The therapeutic response is influenced differently by pharmacological agents modulated by the variable 'agitation'.

3. Depending on the type of neurocognitive disorder (Alzheimer's or vascular), patients will respond differently to treatment.

Materials and methods

All patients participated based on the free consent expressed prior to the first investigations. They completed and submitted their written consent to the proper authorities, more specifically to the Psychiatry Department of 'Carol Davila' University Emergency Central Military Hospital (Bucharest, Romania).

Data confidentiality was ensured throughout the study. Drug therapy was administered according to national and international treatment guidelines for BPSD (1); (***, 2019) and in accordance with the indications in the summary of product characteristics for the respective antidepressants and glutamatergic agonists. No invasive methods were used and no special blood samples were taken for the study. There was no conflict of interest.

Research protocol

a) Period and place of the research

Patients were consulted in the Psychiatry Department of the University Emergency Central Military Hospital in Bucharest, or in its integrated outpatient clinic during March 2018 - November 2019.

b) Subjects and groups

The inclusion and exclusion criteria in this research

described below were assessed at the initial visit and underlay the formation of the study group.

The inclusion criteria were DSM IV-TR criteria for diagnosing dementia, AD and VD, and also the clinical criteria according to NINDS and ADRDA (National Institute of Neurological Disorders and Stroke/Alzheimer's Disease and Related Disorders Association) (McKhann et al., 2011) were met. The initial MMSE examination at screening was 12-26. CT / MRI imaging corroborated with the Haciniski score (Moroney et al., 1995) is considered to highlight:

- for AD: medial temporal atrophy plus Haciniski score of ischemia ≤ 4
- for RV: Haciniski score ≥ 7
- for mixed dementias Haciniski score = 5 or 6.

Patients with vascular dementia had a history of stroke.

The minimum age limit for inclusion was 55 years, with no maximum age limit. GDS score (Greenberg, 2006) at inclusion had a maximal value of 10, corresponding to a depression of mild or moderate intensity. The CGI-S score (Guy, 1976) was at least 3 (mild severity of global symptoms). Patients did not take more than one acetylcholinesterase inhibitor, treatment was used continuously for at least 2 months prior to the screening visit, and they did not receive prior treatment with memantine.

A total of 37 subjects participated in the research, which presented the following demographic characteristics: 13 subjects (35.1%) were male and 24 (representing 64.9%) were female. The gender distribution was in favor of females, with a female / male ratio of about 2: 1. A slightly supra-unitary ratio of the "sex" variable (women / men) is allowed in the general population in the case of the prevalence of neurocognitive disorders, with women having a longer life expectancy.

According to the "age" variable, the following structure of the study group is registered: out of the total number of patients included in the study, most were included in the age range 71-75 years (n = 12), followed by those aged between 76 and 80 years (n = 6), those over 80 years (n = 5) and patients aged 60 years (n = 4). Also, the distribution according to the type of neurocognitive disorder was very balanced - Fig. 1.

The age distribution was normal, with an average of 72.22 years, a median of 71.00, Std. Deviation (SD) 7.269, with a minimum age of 58 and a maximum age of 90 years. The percentiles show the following stratification: 25-67.00, 50-71.00, 75-77.00.

According to the environment in which the patient's current domicile was located: the urban / rural average ratio was almost unitary, the patients in the urban environment being slightly more numerous (51.4% -19 patients).

- According to the type of neurocognitive disorder, the AD/VD ratio is almost unitary, the patients being in almost equal numbers (51.4% -19 patients with AD).

- Interestingly, patients presented the same basic characteristics, so the distribution was uniform at visit 1 (week 0).

- Secondly, the distribution of the average ages can be observed in Fig. 2.

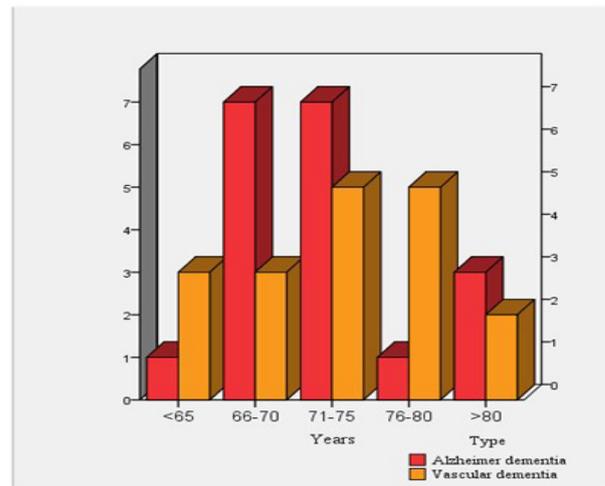


Fig. 1 – Age categories by dementia type.

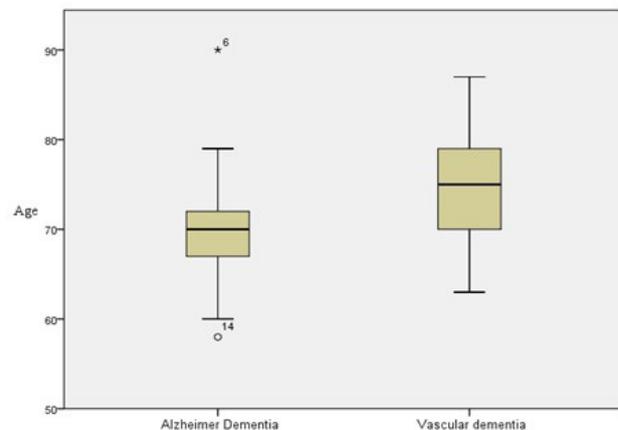


Fig. 2 – Distribution of mean age.

According to the level of education, the following structure of the group stands out: the average number of classes is 10.43, the average 8.00 and SD 4.688. The minimum value is 4 and the maximum value is 17. The percentiles are: 25-8.00, 50-8.00, 75-16.00. Regarding the level of education, it was found that most patients belonged to the category of those with a lower level (primary school or middle school), followed by those with an intermediate level (high school or vocational school), and 29.7% (11 patients) representing almost a third of the participants had college / college or postgraduate studies.

From the point of view of the clinical variables detected at the first visit, the following can be observed:

- patients were on treatment for at least 4 weeks on stable doses of donepezil, rivastigmine and galantamine, in doses according to their summary of product characteristics;

- patients had up to 2 previous treatments and only a minority of subjects (7 patients - 18.9%) were diagnosed with neurocognitive disorder for the first time;

- the average scores of MMSE/CDR correspond to moderate-mild severity (Folstein et al., 1975; Morris et al., 1995; Morris et al., 1997), but the extreme values show the inclusion in the study of patients with all forms of dementia, except the severe one;

- with the coexistence of depressive disorders in 29/37 of the evaluated patients, 8 patients representing 21.6% did not show depressive symptoms;

- CGI-S scores at V1 correspond to neurocognitive disorder severity scores, with an average value of 4.30, minimum 3, maximum 6, SD 1.077;

- safety indicators, respectively physiological parameters, have average values within normal limits, even if extreme values are recorded, congruent with comorbid diagnoses.

The distribution of the study group according to demographic parameters and initial clinical variables is found in Table I.

Table I
Distribution of the study group according to demographic parameters and variables at the initial clinical visit.

Indicator	Min	Max	Mean	Std. Dev
Age	58	90	72.22	7.269
Education level (yrs)	4	17	10.43	4.688
MMSE score week 0	12	25	20.68	3.859
CDR score week 0	3.0	11.0	5.716	2.6603
CGI-S week 0	3	6	4.30	1.077
GDR week 0	1	10	6.59	2.608
CMAI week 0	19	42	31.11	5.130

The pharmacological classes used in this clinical study were: antidepressant between weeks 1-8: SSRI - sertraline or NaSSA - mirtazapine, and weeks 8-16: NMDA glutamatergic antagonist - memantine. Absolute values indicate the following stratification: 26 of the 37 patients received sertraline, and 11 received mirtazapine treatment. Regarding the maximum doses received by patients, these were: sertraline 100 mg/day, mirtazapine 30 mg/day and memantine 20 mg/day. At the end of week 7, antidepressants will be discontinued in a maximum of 3 days. Then, after complete discontinuation, memantine 5 mg will be initiated at the beginning of week 8, which will be gradually increased according to protocol in the following weeks until the end of the study.

c) Applied tests

Definition of dependent and independent variables.

The primary variables analyzed in this study are related to the severity of agitation symptoms under the action of pharmacological factors. A part of BPSD defined by side A - "AGITATION" was evaluated by the CMAI (Cohen-Mansfield Agitation Inventory) scale-short version, which has 3 subscales (score between 14 and 70) (Cohen-Mansfield, 1986). The elements related to monitoring the tolerability of pharmacological therapy were body weight and BMI - body mass index, waist circumference, QTc interval, systolic and diastolic blood pressure values. The dependent variables are therefore the scores for assessing the severity of agitation and depression, cognitive performance and overall functionality, executive performance, fluency and language, duration of treatment.

The independent variables consist mainly of the classes of pharmacological agents administered, and also the type of neurocognitive disorder, the presence or absence of the diagnosis of severe depressive disorder as well as comorbidity in secondary analyzes.

d) Statistical processing

The primary efficacy analysis is based on the change in CMAI scores at visit 4 from the initial visit, and then the change in CMAI scores at visit 6 compared to visit 4 and the initial visit. A secondary analysis of efficacy is based on CGI-S scores.

The method of data processing regarding the analysis of changes in dependent variables according to the action of pharmacological agents was the t test for dependent samples, $df = 30$ (36), the result being related to a threshold of significance $\alpha = 0.05$ bilateral.

The impact of add-on pharmacological agents (sertraline or mirtazapine, then memantine) during treatment on the variable was evaluated using unifactorial ANOVA, $df = 30$, $p < 0.05$ bilateral.

The Pearson association test was applied to verify the links between agitation (on a continuous scale) and: cognition and functionality, depression severity, age/dementia type, etc.

Results

Evolution of CMAI agitation scores under treatment. The t test was used for dependent samples, at an alpha value = 0.05 bilaterally, $df = 30$. The data obtained show a decrease in general agitation less under the action of antidepressants at visit 4-week 8 compared to the initial visit V1-week 0 than under the action of memantine, the averages Δ CMAI1 and Δ CMAI 2 being -2.2581 and -4.5161, respectively (SD = 3.56808, se = 0.64085 and SD = 5.12426, se = 0.92034, respectively). The reduction was statistically significant, with an average difference of 2.25806, SD = 5.17022, se = 0.92860, $p = 0.021$, and $t = 2.432$. The effect size (d Cohen) calculated $d = t / \sqrt{n}$, $n = 31$ was 0.43, which is a modest value; therefore the effect size is small. What is interesting is the linear decrease in time of the general agitation score and the better response in the second part of the treatment according to Fig. 3.

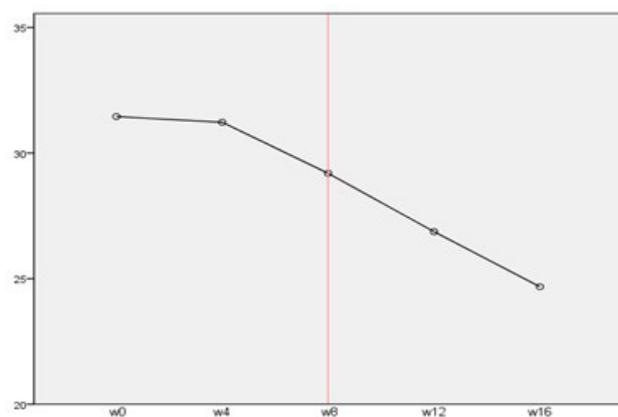


Fig. 3 – Means of CMAI scores in weeks 0, 4, 8, 12 and 16.

The analysis of differences between agitation modification groups (CMAI) depending on the type of neurocognitive disorder, treatment and duration (including the total effect between V0-V16 after the 2 treatments) included 3 defined groups: 1 - antidepressants lasting 8 weeks - 'ADT' group, 2 - memantine with a duration of 8 weeks - 'MEM' group, and 3 - treatment 1 then 2 with a duration of 16 weeks - 'ADT + MEM' group.

Table II
Description of parameters - Decreased agitation score (CMAI) of Alzheimer's and vascular dementia treatment function and duration ANOVA.

	Indicator	Sum of squares	df	Mean square	F	Sig.
dCMAI1	between groups	4.852	1	4.852	.373	.546
	in groups	377.083	29	13.003		
	Total	381.935	30			
dCMAI2	between groups	155.904	1	155.904	7.156	.012
	in groups	631.838	29	21.788		
	Total	787.742	30			
dCMAIf	between groups	105.749	1	105.749	2.142	.154
	in groups	1431.671	29	49.368		
	Total	1537.419	30			

	Indicator	N	Mean	SD	SE	95%CI for mean		Min	Max
					min	max			
dCMAI1	Alzheimer dementia	16	-1.8750	3.66742	.91686	-3.8292	.0792	-12.00	3.00
	Vascular dementia	15	-2.6667	3.53890	.91374	-4.6264	-.7069	-11.00	3.00
	Total	31	-2.2581	3.56808	.64085	-3.5668	-.9493	-12.00	3.00
dCMAI2	Alzheimer dementia	16	-6.6875	5.53436	1.38359	-9.6366	-3.7384	-13.00	2.00
	Vascular dementia	15	-2.2000	3.50917	.90606	-4.1433	-.2567	-9.00	2.00
	Total	31	-4.5161	5.12426	.92034	-6.3957	-2.6365	-13.00	2.00
dCMAIf	Alzheimer dementia	16	-8.56	8.214	2.053	-12.94	-4.19	-25	3
	Vascular dementia	15	-4.87	5.475	1.414	-7.90	-1.83	-14	2
	Total	31	-6.77	7.159	1.286	-9.40	-4.15	-25	1

The one way ANOVA test was used for the 3 groups, with the threshold of statistical significance $\alpha = 0.05$ bilateral. It can be observed that there are differences between the actions of pharmacological agents on certain symptomatic dimensions (factors) which, even if they do not reach the level of significance, indicate a favorable trend for one treatment in relation to another. All analyzes aimed to detect significant differences between pharmacological agents regardless of the dependent variable pursued. The aim was to define the F value, as well as the η^2 value in order to identify the proportion of the influence of the independent variable in the fluctuation of the dependent variable.

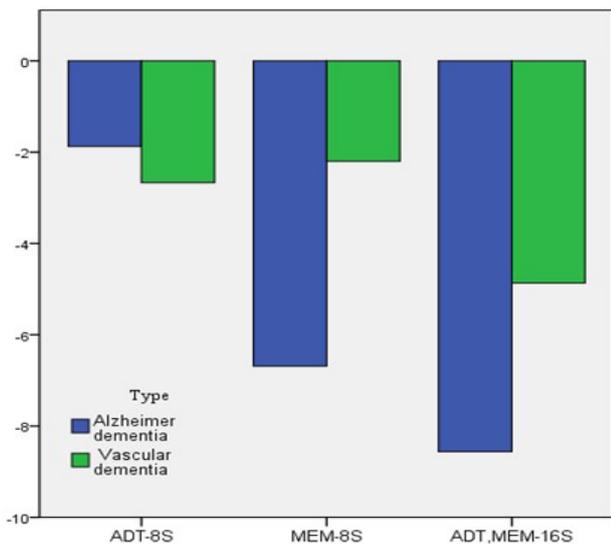


Fig. 4 – (Decreased) CMAI score of Alzheimer's and vascular dementia depending on treatment and duration.

According to the graph, the decrease of the CMAI score in Alzheimer's and vascular dementia can be observed depending on the treatment and duration in the 3 compared groups 1, 2 and 3, respectively (Fig. 4).

The statistical difference was obvious in weeks 8-16 after memantine treatment, at the end of which the decrease in agitation in Alzheimer's dementia was superior to vascular dementia, statistically significant according to Table II, $F = 7.15$, $p = 0.012$.

Discussion

A limitation of this study is the small number of patients, statistical power increasing with large groups. In the literature, data are controversial in terms of prescribing antidepressants in the neurocognitive disorder even when BPSD is important, the keystone being the unilateral consensus in limiting the use of antipsychotics and polypharmacy, in general. This paper shows a partial and stratified improvement of a limited number of patients, and that the creation of a clinical profile of the typical patient could lead us to practice a personalized medicine, adapted to the geriatric population.

Currently, only short-term symptomatic treatment is available. Although there is ongoing research in the field in this area, there is a need for exponential research dynamics. At the same time, there needs to be more collaboration and a multidisciplinary approach in the field of research for neurocognitive disorders. The review of grants should be supported by governmental and non-governmental institutions through the facilitation of cooperation between neurobiologists, clinicians and psycho-pharmacologists. Innovation and continuous work are needed to encourage the diversity of therapeutic options for the ongoing fight against dementia.

Conclusions

1. The efficacy of memantine in decreasing the severity of the general agitation is significantly superior to that of antidepressants, and this is probably due to the multiple therapeutic factors involved.

2. Regarding the differences between the agitation modification groups (CMAI) depending on the type of neurocognitive disorder, treatment and duration, it was observed that the statistical difference was obvious in weeks 8-16 after memantine treatment, at the end of this treatment the decrease in agitation in Alzheimer's dementia being superior to vascular dementia ($p = 0.012$); the general trend was to decrease agitation after each treatment, including cumulative, for each type of dementia.

3. The primary endpoint, i.e. the benefits of treatment with SSRI/NaSSA/NMDA glutamatergic antagonists as adjunctive therapy to cholinesterase inhibitors are correlated with reduced severity of agitation symptoms and increased overall functionality in patients aged ≥ 55 years diagnosed with neurocognitive disorders (Alzheimer and vascular dementia).

4. This paper proposes a pharmacological strategy in the treatment of neurocognitive disorder, not only for decreasing agitation, but for a better global functionality for patients, and also helping carriers with better care.

Conflicts of interests

None declared.

Acknowledgments

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