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SM Journal of Neurology and Neuroscience

Research Article

Depression in Alzheimer's disease: Citalopram and Rivastigmine can better?

Magda Tsolaki*, Krishna Prasad Pathak, Eleni Verikouki, Chaido Zchou Messini, Tara Gaire and Paschalis Devranis

Department of Neurology, Aristotle University of Thessaloniki, Greece

Article Information

Received date: May 30, 2017
Accepted date: Jun 08, 2017
Published date: Jun 12, 2017

***Corresponding author**

Dr. Magda Tsolaki, Professor of Neurology, Neuropsychiatrist, 3rd Department of Neurology of Aristotle University of Thessaloniki, Greece, Telephone: +306942918933; Email: tsolakim1@gmail.com

Keywords AChEIs: Acetylcholinesterase inhibitors; (AD) Alzheimer Disease; Rivastigmine and Citalopram; Dementia

Abstract

Background: Pharmacological treatment for AD and depression are unfortunately few and of limited efficacy to cure the disease.

Objectives: To assess the combined effects of rivastigmine and citalopram on Alzheimer's Disease.

Methods: Longitudinal clinical prospective study with 1278 AD patients on rivastigmine 9,5mg/patch and citalopram 20-40 mg/day over 48 months was assessed on the basis of NINCDS-ADRDA, MMSE, DSM-IV, FRSSD, GDS, HRS-D and follow up of the patients.

Results: Four years after the baseline assessment, there were no significant differences in MMSE, Geriatric depression scale and Hamilton rating scale for depression between patients treated with rivastigmine alone or combined rivastigmine with citalopram with or without depression ($p>0.05$). Functional Rating Scale for symptoms of dementia, Activities of Daily Living of patients with AD and depression treated with rivastigmine was significantly worse than patients treated with rivastigmine and no depression ($p=0.027$).

Conclusions: The combination of rivastigmine and citalopram had no better results than rivastigmine alone in patients with AD.

Introduction

Alzheimer's Disease (AD) is a degenerative disorder of the central nervous system with progressive cognitive, psychological, functional and behavioral decline. Agitation, depression [1] and language deficit [2] are common [3,4] among elderly with AD and depression is considered as comorbidity [5]. Depressive symptoms in elderly or patients with AD appear at 7%-42% [6]. Dementia in combination with depression is strongly associated with an increase of cognitive dysfunction [7]. A case study in 2002 [8] found that 20% of the persons who suffered from dysphoria also suffered from irritability and many kinds of depression. Depression is one of the most common psychiatric illnesses with high rates in the general population. Furthermore, due to its long-term nature, the illness requires psychopharmacological treatment over long periods of time. However, patients with depression can be prescribed with higher doses of citalopram. As a result, treatments need to be reliable and efficacious, since such illness requires long term medication and acceptability of patients should also be addressed [9].

Today, in Europe 9.25 million people are living with AD and this is expected to increase to 14 million by 2030 and to 20.25 million by 2050 [10,11]. Despite the enormous efforts in research, no treatment has been found to date. Nevertheless, medication like rivastigmine and citalopram are used in everyday clinical praxis. Rivastigmine is an Acetylcholinesterase Inhibitor (AChEI) with the activity of a Butyrylcholinesterase Inhibitor (BuChEI) which showed a better cognitive progression in patients with AD [12]. Both are hydrolytic enzymes that act on acetylcholine (ACh) to terminate its actions in the synaptic cleft by cleaving the neurotransmitter to choline and acetate. Moreover, both are present in the brain and they have been detected in neuritic plaques and neurofibrillary tangles. Citalopram is a Selective Serotonin Reuptake Inhibitor (SSRI) which inhibits the un-activated and substrate-activated forms of BuChE [13,14]. Citalopram is used to treat depressive symptoms that are very common in patients with AD. One review study summarizes and evaluates clinical experience with citalopram for approval for the treatment of depression in the United States. A review study summarized that citalopram was an attractive agent for the treatment of depression and panic disorder, especially among the elderly and patients with comorbid illness and showed that citalopram was effective as an antidepressants theraphy [15].

A study of Leblhuber F (1994) showed that there was an improvement in 20 patients with dementia regarding confusion, restlessness, behavioral disturbance symptoms and Geriatric Scale (Gottfries-Brane-Steen) after they were treated with citalopram for three weeks. It also emphasized the effect of citalopram as an emotional "stabilizer" for those patients [16]. In other study investigators of a Nordic multicenter, found that Alzheimer's patients who had been treated with citalopram showed greater improvements for considering irritability and restlessness [17]. To date,

citalopram is used as an antidepressant medicine because it is less expensive and clinically safe; tolerability and efficacy are guaranteed, and it does not cause adverse cardiovascular or anticholinergic effects [18]. In comparison to citalopram, other anti-depressant drugs like; mirtazapine, venlafaxine and reboxetine, or non-conventional ones like hypericum, citalopram have shown to be significantly less effective than escitalopram but more effective than paroxetine and reboxetine. Therefore, citalopram is more reliable as an antidepressant therapy for the AD patients and thus more acceptable, than paroxetine and reboxetine or than tricyclics, reboxetine and venlafaxine [19].

Citalopram is implicated in cell survival and it does not interfere with the molecular controls of the cell [20]. Now a day, many of the therapeutic options including three new anti-dementia drugs (galantamine, rivastigmine and memantine) are available. As of 2011, donepezil was the one available cholinesterase inhibitor. Recent studies suggest a synergic activity of rivastigmine and citalopram in a complete inhibition of AChE and BuChE. A study of 150 AD patients on combined rivastigmine and citalopram treatment has shown significantly better results than monotherapy, which indicates a protective effect against cognitive decreases due to depression [21]. However, these results need to be proved in everyday clinical praxis.

Rivastigmine is taken on a daily basis by those who suffer from AD in both capsule and patch forms and is prescribed for the treatment of mild, moderate and severe memory problems of AD [22]. It is suggested that the rivastigmine transdermal patch is an effective treatment option for patients with AD with the potential for improved compliance while providing sustained clinical benefits because of its ease of use and generally favorable tolerability profile. As a result, rivastigmine is commonly prescribed for the treatment of AD. However, like all cholinesterase inhibitors it has side effects, which include cardiac risk.

A double-blind phase of another study showed that patients on any patch treatment for 24 weeks reported no adverse experiences with signs and symptoms for their most severe application-site reaction [23]. Furthermore in AD patients, rivastigmine formulation was not associated with increasing arrhythmogenic or hypotensive effects, and neither of these effects was, superior to the other. In addition, the results of 85 AD patients who were treated with 12 mg oral/10 cm^2 transdermal rivastigmine, and were retrospectively evaluated, showed no change in any of the ECG results, but were found to have increasing heart rates (P ¼ .035) [24]. Additionally, another study showed that 2 years on rivastigmine treatment on 2010 probable AD patients resulted to less cognitive deterioration than in the historical-control subjects. Cognitive improvements were considered clinically meaningful relative to expected global decline as the effect of rivastigmine and commonly-seen side effects as with ChEIs [25].

In medical experiments the proof of rivistigimne and citalopram on AD patients has been studied and new innovative results are coming. To our knowledge, various clinically based studies are being investigated. This study aims to investigate treatment effects of Citalopram and rivastigmine on different domains, with special attention to depression, and those suffering from Alzheimer's disease. In the hospitals of Greece, rivastigmine may only be prescribed if evaluation is regularly performed. But citalopram is currently being used with the AD diagnosed patients who also have depression. In our hospital, both therapies have been prescribed since 2010 via the G Papanikolau Outpatient service, and every 6 months follow-up appointments are made. In this longitudinal study of patients, we performed analysis with respect to the effectiveness of rivastigmine and citalopram over a 48 month period. It is our belief for the last 10 years, that newly adapted drugs were able to relieve the symptoms, but poorly affect the progression of the disease.

Methods

Participants and procedure

In this longitudinal clinical prospective study we assessed 1278 AD patients who were collected from the archives of the 3rd Department of Neurology, "G. Papanikolaou" Hospital, Aristotle University of Thessaloniki and the archives of the Greek Association of Alzheimer's Disease and Related Disorders, Day Care Units "Saint Helen" and "Saint John", Thessaloniki. All patients were diagnosed with Alzheimer's disease after examination from neuropsychologists and a neurologist-psychiatrist and were followed up on every six-month. Each examination consisted of a battery of neuropsychological tests including Mini Mental Status Examination (MMSE), Neuropsychiatric Inventory (NPI), and Functional Rating Scale for Symptoms of Dementia (FRSSD), Geriatrics Depression Scale (GDS-15) and Hamilton Rating Scale for Depression (HRS-D). Depressive symptoms were defined as GDS higher than 5 or HRS-D higher than 15 or the taking of antidepressants [26]. Here we tried to identify the results from potentially masking side effects of the patients. We assigned subjects from both groups, to those who were using only rivastigmine and those who were using both citalopram plus rivastigmine. Both were prescribed additional neuropsychiatric medicine and were followed for the entire test according to the international AD guidelines. The prescribed dose was 20/40 mg citalopram and rivastigmine Patch/Oral 20/40 mg/day. Patients were diagnosed with the standardized guidelines and potential patients were diagnosed by a pathologist (physicians' clinical judgment) and with help from their caregivers and families. Current and past psychiatric disturbance histories were taken after written consent for a compulsory visit to a neurologist for assessment. Finally, neurologic/neuropsychiatric assessment was performed in order to ensure AD diagnosis. This study was conducted between 2011 and 2015.

Statistical analyses

Descriptive statistics at baseline were performed on socio-demographic, clinical, neuropsychological, functional and psycho-behavioral characteristics. Quantitative variables were expressed as a mean ± standard deviation. Continuous variables were assessed using analysis of variance (ANOVA) models. Post hoc comparisons, adjusted using the Tukey correction, were used to make comparisons between group means at baseline.

Generalized Estimating Equation (GEE) methodology was used to check the influence of independent predictors to MMSE, FRSSD, GDS and Hamilton scores over time. GEEs allow the analysis of longitudinal data with repeated measurements by taking into account some correlation structure on the data, while they allow for missing values in the data throughout the course of the study. P-values less than 0.05 were considered statistically significant. Statistical analysis was conducted using SPSS 21.0 (IBM Inc., Armonk, NY) and R v3.0.2 Statistical Software (R Foundation for Statistical Computing, Vienna, Austria; http://www.r-project.org/).

Table 1: Baseline Characteristics of the Sample.

	Total	Rivastigmine no Depression	Rivastigmine and Depression	Rivastigmine + Citalopram, no Depression	Rivastigmine +Citalopram and depression
Number of Patients	1278	751	325	89	113
Women, n (%)	808 (63.2)	438 (58.3)	227 (69.8)	67 (75.3)	76 (67.3)
Age, mean±sd	74.63±7.72	74.73±7.72	74.41±7.32	73.71±7.84	74.05±8.64
Education in years, mean±sd	6.74±4.15	7.04±4.33*	6.16±3.84*	7.083.93	6.11±3.80
MMSE at baseline, mean±sd	16.17±6.89	16.06±7.04	16.73±6.69	14.99±6.48	16.26±6.61
FRSSD at baseline, mean±sd	12.92±7.59	12.70±7.73	12.89±7.12	13.10±7.68	14.35±7.77
GDS at baseline, mean±sd	3.49±3.14	2.04±1.76*	6.26±3.40*	2.021.72*	6.38±3.12*
Hamilton at baseline, mean±sd	9.93±6.39	6.81±3.94*	14.90±6.57*	5.77±4.07*	14.83±5.22*

*p<0.05 values are based on ANOVA model with post hoc comparisons, adjusted using the Tukey correction.

Study oversight

The study has been overseen at the 3rd Department of Aristotle University of Thessaloniki, Greece without funding. Full ethical approval was received from The Greek AD Association, Greece. The author vouches for the accuracy and completeness of the data and for the fidelity of the study to the protocol.

Results

Patients characteristics

Analysis 1278 patients who were diagnosed with Alzheimer's disease. Overall, there were 470 men and 808 women, with a mean age of 74.63 (SD = 7.72), and a mean education of 6.74 years (SD = 4.15). The proportion of patients diagnosed with depressive symptoms was 41.24 percent. All these subjects were evaluated for four years. Table 1 below presents in detail the socio- demographic characteristics of the patients.

At baseline, 751 of these were not diagnosed as depressed and were treated with rivastigmine, 325 were classified as depressed and were treated with rivastigmine only, 89 were not diagnosed as depressed and were treated with rivastigmine and citalopram and 113 were diagnosed with depression and were treated with rivastigmine and citalopram. As summarized in Table 1, there were no statistically significant baseline differences between the four groups in terms of socio-demographic characteristics. As expected, there were differences in the GDS and HRS-D scores between patients with depression and patients without depression. Table 2 shows the number of patients for each group at each time point during the study.

After four years of follow up, there were no significant differences in MMSE between the four groups (p>0.05) (Figure 1). The FRSSD score of patients treated with rivastigmine and diagnosed with depression was significantly higher than patients treated with rivastigmine and no depression (Beta=1.127, 95%CI: (0.128, 2.127), p=0.027) (Figure 2). The GDS score did not differ between patients

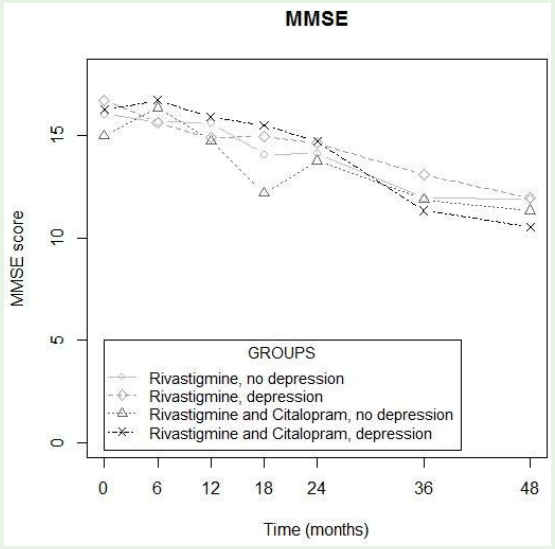

Figure 1: Mean MMSE score over the four years of the study for the four groups.

Table 2: Number of patients at each of the groups at each time point during the study period.

	Exelon, no Depression	Exelon and Depression	Exelon+Citalopram, no Depression	Exelon+Citalopram and Depression
Baseline	751	325	89	113
6 months	247	141	28	53
12 months	228	110	32	41
18 months	126	59	17	26
24 months	120	67	17	28
36 months	84	49	14	21
48 months	48	31	6	17

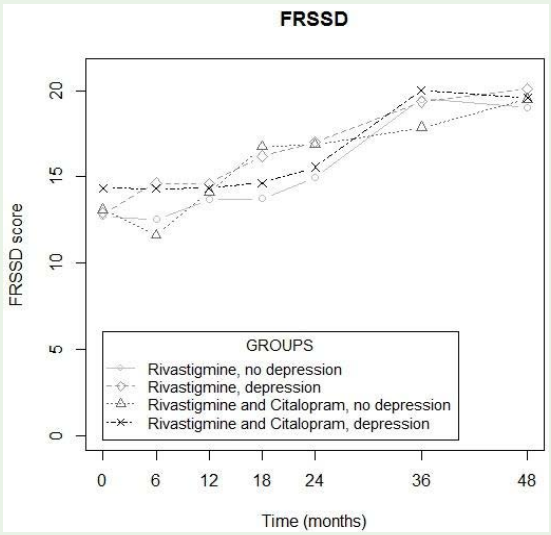

Figure 2: Mean FRSSD score over the four years of the study for the four groups.

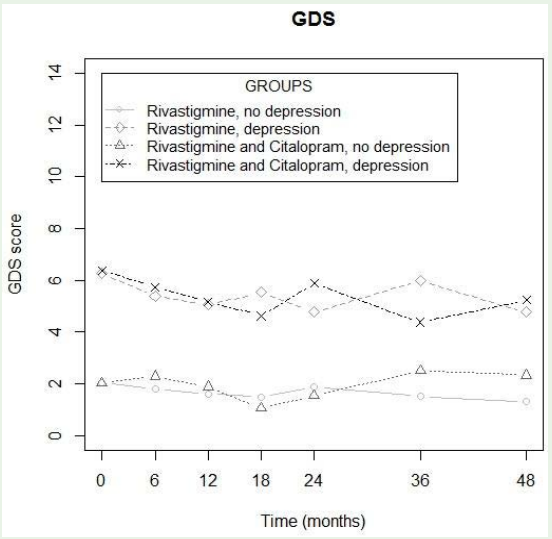

Figure 3: Mean GDS score over the four years of the study for the four groups.

Table 3: Results of the MMSE, FRSSD scores for the gender, Age group and years of education group for each study group for the total four-year period.

GROUP	Rivastignime, no Depression		Rivastignime and Depression		Rivastignime +Citalopram, no Depression		Rivastignime +Citalopram and depression	
	Beta (SE)	p	Beta (SE)	p	Beta (SE)	p	Beta (SE)	p
MMSE								
Gender								
Female	-0.69 (0.59)	0.238	0.82 (1.01)	0.416	1.79 (2.21)	0.418	0.98 (1.40)	0.483
Male (ref)								
Age Group								
>80	- 0.34 (1.38)	0.806	-1.68 (2.43)	0.489	1.67 (2.96)	0.572	1.18 (2.98)	0.691
71-80	0.45 (1.35)	0.736	-1.40 (2.32)	0.546	3.82 (2.81)	0.175	2.11 (2.89)	0.466
61-70	-0.78 (1.45)	0.593	-1.00 (2.52)	0.690	4.82 (2.86)	0.092	-3.33 (3.27)	0.308
<=60 (ref)								
Years of education								
13+	2.67 (0.84)	<0.001	4.53 (1.43)	0.002	6.36 (2.14)	0.003	1.62 (4.31)	0.706
10-12	3.81 (0.96)	0.001	1.87 (1.94)	0.336	3.21 (2.02)	0.112	-1.32 (2.48)	0.593
0-9 (ref)								
FRSSD								
Gender								
Female	-0.4 (0.61)	0.949	-2.18 (0.90)	0.016	-3.85 (2.36)	0.103	-0.81 (1.50)	0.593
Male (ref)								
Age Group								
>80	2.15 (1.21)	0.075	1.02 (1.93)	0.599	2.84 (2.10)	0.176	2.51 (2.67)	0.347
71-80	0.83 (1.16)	0.476	0.84 (1.74)	0.631	-1.64 (1.92)	0.392	-0.72 (2.44)	0.766
61-70	0.97 (1.28)	0.446	0.08 (1.95)	0.965	-3.73 (2.21)	0.091	3.03 (3.25)	0.351
<=60 (ref)								
Years of education								
13+	-2.06 (0.83)	0.013	-2.32 (1.64)	0.159	-4.05 (2.06)	0.049	0.84 (4.43)	0.849
10-12	-2.04 (0.95)	0.032	-0.03 (1.66)	0.987	-1.44 (2.85)	0.614	-0.63 (2.82)	0.823
0-9 (ref)								

Table 4: Results of the GDS and HRS-Dscores for the gender, Age group and years of education group for each study group for the total four-year period.

GROUP	Rivastignime, no Depression		Rivastignime and Depression		Rivastignime +Citalopram, no Depression		Rivastignime +Citalopram and depression	
	Beta (SE)	p	Beta (SE)	p	Beta (SE)	p	Beta (SE)	p
GDS								
Gender								
Female	0.21 (0.11)	0.049	0.53 (0.32)	0.099	0.19 (0.33)	0.561	0.51 (0.45)	0.264
Male (ref)								
Age Group								
>80	0.19 (0.26)	0.457	0.11 (0.78)	0.887	-0.29 (0.53)	0.576	0.26 (0.88)	0.761
71-80	0.04 (0.25)	0.875	-0.31 (0.73)	0.664	-0.35 (0.44)	0.422	-0.66 (0.70)	0.345
61-70	0.04 (0.27)	0.877	-0.60 (0.78)	0.441	-0.32 (0.49)	0.514	-1.13 (0.77)	0.141
<=60 (ref)								
Years of education								
13+	-0.29 (0.15)	0.048	-0.63 (0.49)	0.196	-0.04 (0.43)	0.926	0.18 (0.91)	0.843
10-12	-0.45 (0.17)	0.008	0.06 (0.50)	0.901	-0.19 (0.42)	0.634	0.11 (0.49)	0.817
0-9 (ref)								
HRS_D								
Gender								
Female	0.51 (0.44)	0.254	2.19 (0.84)	0.009	1.32 (1.06)	0.211	1.29 (1.09)	0.240
Male (ref)								
Age Group								
>80	-0.06 (1.04)	0.950	3.06 (1.85)	0.097	0.46 (1.54)	0.762	3.92 (1.75)	0.026
71-80	-0.17 (1.03)	0.865	2.03 (1.68)	0.227	0.14 (1.17)	0.903	3.02 (1.29)	0.020
61-70	-0.09 (1.08)	0.935	1.56 (1.78)	0.379	0.41 (1.38)	0.767	3.11 (1.46)	0.033
<=60 (ref)								
Years of education								
13+	-1.34 (0.84)	0.111	0.34 (1.48)	0.817	-1.65 (1.44)	0.251	-1.35 (1.26)	0.284
10-12	-2.36 (0.66)	<0.001	-1.54 (1.28)	0.227	-0.82 (1.35)	0.541	0.83 (0.94)	0.378
0-9 (ref)								

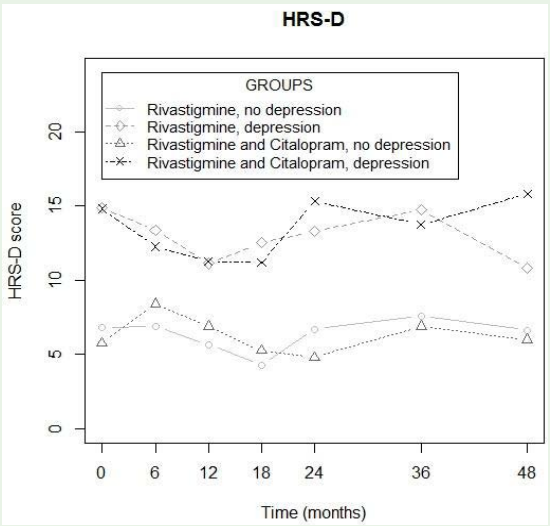

Figure 4: Mean HRS_D score over the four years of the study for the four groups.

with depression who were treated only with rivastigmine and patients with depression who were treated with rivastigmine and citalopram (p>0.05). There was also no difference in the GDS score between patients with depression and treated with rivastigmine or rivastigmine and citalopram (p>0.05) (Figure 3). Similarly, the HRS-D score did not differ between patients with depression who were treated only with rivastigmine and patients with depression who were treated with rivastigmine and citalopram (p>0.05). There was also no difference in the HRS-D score between patients with depression treated with rivastigmine or rivastigmine and citalopram (p>0.05) (Figure 4).

Tables 3 and 4 shows the results of the GEE model for each group separately for gender, age groups and years of education for each of the MMSE, FRSSD, GDS and HRS-D scores. Patients without depression, treated with rivastigmine only, who have more than 9 years of education, have significantly better scores for MMSE, FRSSD, GDS and HRS-D measurements. Furthermore, older patients with depression, treated with rivastigmine and citalopram, have significantly higher HRS-D measurements.

Discussion

Diagnosis of depression in AD is challenging given the overlapping features between 'desperation and AD'. The answer to how possibly is diagnose depression in AD patients and which therapy significantly reduces depression still remains under debate. Therefore, can depression considered as one of the symptoms of AD or treating AD is way to depression considered as one of the symptoms of Ad; or treating AD is a way to depression as well? One of the secondary symptoms of AD is "depression" including anxiety, hallucination, aphasia, agitation, insomnia and delusion, all of which are the hallmarks of AD and are non-cognitive behavioural situations; all of which commonly affect patients and their caregiver's quality of life.

Our study was conducted with a follow-up of 48 months with diagnosed AD subjects and we applied both citalopram and rivastigmine therapy – to those who were already demonstrating clinically significant and some not so significant results for anti-depressive drugs- some studies follow in the below paragraphs and are analysed as proof. Combined trial studies with Rivastigmine plus Citalorpam are hard to find, but here we have investigated co-relationship between them with respect to Alzheimer patients. Our study compares both therapies with AD and could be a valid contribution to this debate. In other studies, those therapies have been applied separately to AD patients and to our knowledge there are not any studies that consider a combination of citalopram and rivastigmine to AD patients without depression. Moreover, this combined study is also the first study within the Greek population.

Current AD therapy is based on the administration of the drugs donepezil, galantamine, rivastigmine and memantine. Still, current drugs are not so simple with respect to the treatment and administration strategies. In advanced stages of AD, physicians who find a higher tolerability rate continue to provide treatment with higher doses as well as, ease of use, easy-to-follow schedule, less administration time spent by the caregivers who result in greater adherence to the treatment. As a result, they may be anticipating options for treatment of future AD [27,28].

Improvement was shown on a number of depression and behavioural disturbances [29]. A review on cholinesterase inhibitors therapies and neuropsychiatric manifestations of AD, evidently favours a benefit of the ChE-Is in reducing Neuropsychiatric symptoms, including mood alterations, psychosis, hallucinations, agitation, and apathy [30]. In addition, antidepressants like citalopram can prevent AD from progressing quickly and have been used for the past two decades but there are warnings that higher doses trigger dangerous irregular heartbeats. Our findings open a new avenue in the hunt for drugs to prevent the devastating brain disease of AD. Still, separate scientific studies have been too few to conclusively prove anything [31].

This research is focused on finding the effectiveness of citalopram and rivastigmine with depression and Alzheimer patients. The results of our long-term clinical study demonstrate that there are no significant differences between citalopram and rivastigmine in improving symptoms of depression in patients with mild to moderate AD. The use of citalopram and rivastigmine in the same population who were diagnosed with AD did not reveal any significant association with respect to age, education, with or the tests of MMSE, NPI, GRDS and HRS-D. In our population we measured the mean change in MMSE between the four groups ($p>0.05$) (Figure 1). The FRSSD score of patients treated with rivastigmine and diagnosed with depression was significantly higher than patients treated with rivastigmine and no depression (Beta=1.127, 95%CI: (0.128, 2.127), $p=0.027$) (Figure 2). The benefits of both medicines were not significantly correlated with the results of FRSSD, GDS and HRS-D measurements. Additionally, our results showed that patients without depression, who were treated with rivastigmine only, and had more than 9 years of education, had significantly better scores at MMSE, FRSSD, GDS and HRS-D measurements. But older patients with depression, treated with rivastigmine and citalopram, showed significantly higher HRS-D score. However, the long-term effects of rivastigmine and citalopram drugs remain largely unknown.

Furthermore, Apler A. [32] summarised in his review that one study showed a significant difference between citalopram and a placebo (RR¼1.59, 95% CI 1.10 to 2.31). Likewise, meta-analysis of response rates in five studies (n¼1010) noticed a positive effect from citalopram (RR¼1.42, 95% CI 1.17 to 1.73). Similarly, meta-analysis of change from baseline scores in five studies (n¼1541) calculated a standardised mean difference (Hedges' g) of _0.27 (95% CI _0.38 to _0.16), showing a reduction in MDD to be significant for citalopram relative to a placebo. in addition, in an open study citalopram was shown to be safe, tolerable, and efficient for treatment with emotional disturbances within 123 elderly patients with symptoms of depression and anxiety- all of whom were (76%) demented, had completed 12 months of a treatment process and their symptoms were significantly reduced for factors such as, depressed mood, irritability, anxiety, restlessness and fear-panic. The severity of the illness from baseline to month 9 was rated as significantly improved. The side effects were infrequent and mostly mild [33].

In 1992, two inter-Nordic multi-center controlled studies, studied the effect of citalopram on elderly patients with depression and emotional disturbances. In this study 98 patients were diagnosed with Alzheimer type dementia and vascular dementia with emotional disturbances. After four weeks of treatment with citalopram (10-30 mg/daily) the results showed significant improvement in depressed mood, restlessness, confusion, irritability, anxiety and no effects were pointed out with respect to intellectual capacity or motor performance for patients. Additionally, another study was conducted, in which citalopram and placebo was compared as a treatment for depression during a six trial. Demented as well as non-demented patients were included. The HRS-D, the Montgomery-Adberg Depression Rating Scale and The Clinical Global Impressions all recorded an effect for citalopram superior to that of the placebo. In both studies, depressive symptoms as well as agitation, anxiety, restlessness and irritability were improved. Citalopram is therefore considered not only an anti-depressive drug but also an emotional stabilizer. It is also well tolerated by elderly often corporally ill patients with few side effects remaining [34].

A retrospective study was conducted to evaluate the effects on cognition in patients with AD treated with antidepressants over 9 months. Data on antidepressants was used for patients with AD, who were receiving cholinesterase inhibitors. The data for cognition was analysed to compare users and non-users of antidepressants from the 210 patient's sample. Commonly prescribed antidepressants for the patients showed sertraline (mean dose: 82

mg/day) and citalopram (mean dose: 35 mg/day). Furthermore, a study from the USA did not find differences for the baseline mean MMSE rate and a cognitive decline between 9 months of study periods, for those who were receiving antidepressant treatment and not taking antidepressant. However, this data may have been too small a size to generalize that there are no differences in baseline MMSE and cognitive decline between both these groups, suggesting antidepressants did not contribute significantly to cognitive decline over a utilization period of at least 9 months [35].

Besides the above-mentioned studies, one additional study with citalopram has shown effectiveness for cognitive functioning impairment with AD and in difficulties with activities of daily living through improvement in mood and non-mood symptoms. Furthermore, because increased agitation adds to the burden of the caregivers of those with AD, treatment with antidepressants has the potential to benefit those who care for patients with AD. Citalopram drugs and AD will serve as an efficient setting for addressing these secondary hypotheses and for exploring the interrelationships between these outcomes. The results demonstrate that rivastigmine and citalopram are able to improve symptoms of depression, memory and cognitive loss in AD patients. Populations treated with Citalpram and Rivstigmine showed an improvement in depression and global functions as measured by the MMSE, HRS-D and NPI. Significant improvements in MMSE were maintained until 48 months of treatment, where subsequently, a gradual and progressive decline of performances was observed, indicating continued disease progression symptoms.

A Dutch study in 2012, observed with 8.9 years duration in 3358 patients, noted that use of rivastigmine or glantamine resulted in serious cardiac events which increased before ChEI initiation. Furthermore, they suggested that the increased risk of cardiac exposure may be pathways for a possible pharmacology mechanism [36]. The benefits of cholinesterase inhibitors for the treatment of mild-to-moderate Alzheimer's disease has been shown in the Clinical trials [37]. And as a result, cholinesterase inhibitors are a mainstay in the treatment of mild to moderate AD [38]. A review study summarized that both donepezil and rivastigmine can delay cognitive impairment and deterioration in global health for at least 6 months in patients with mild to moderate AD [39]. In the UK, ChEIs are considered to play an important role in the treatment of dementia with Lewy bodies and Parkinsons, but at this point there would seem to be only a limited case for recommending ChEIs in mild cognitive impairment, Down syndrome, progressive supranuclear palsy, pure vascular dementia, frontotemporal lobar degeneration, Huntingtons disease, multiple sclerosis, epilepsy, delirium, traumatic brain injury, sleep-related disorders or certain psychiatric disorders like, schizophrenia and bipolar disorder. The observed clinical practice with respect to non-Alzheimers disease indicates that use of ChEIs may vary according to jurisdiction, specifically with regards to whether national guidelines effectively limit off-licence drug use [40].

In one pilot study of single-blind randomized controlled clinical trial- the efficacy of an integrated treatment with rivastigmine patch and Cognitive Stimulation (CS) in AD patients showed a significant improving result in cognition, depressive and neuropsychiatric symptoms, functional status, and mortality risk in comparison with a group of AD patients receiving only rivastigmine patch at 6-month duration for 90 patients. All of which were measured on the basis of MMSE, Clinical Dementia Rating (CDR), HRS-D, GDS, NPI, Neuropsychiatric Inventory and a standardized Comprehensive Geriatric Assessment, including also Activities Of Daily Living (ADL), Instrumental Activities Of Daily Living (IADL), and the Mini Nutritional Assessment (MNA). Accordingly, there were significant differences between both Group-A and B, but in our study we could not find the relationship with the above mentioned aspects with patients. According to a Spanish finding- a retrospective analysis was done in rivastigmine oral after a 26-week in multicentre, randomized, double-blind, placebo-controlled study. Data included 104 rivastigmine-treated patients and 106 patients receiving placebo. Significantly fewer declines were observed on the previously defined memory and language subscales, and the newly defined working memory subscale in rivastigmine-treated patients (all $P < 0.05$ versus placebo). Calculation of effect sizes demonstrated numerically greater efficacy of rivastigmine versus placebo on each of the subscales, and a broad range of SIB items; greatest effect sizes were observed on SIB items assessing the current month (effect size = 0.30) and digit span series (effect size = 0.33). This data suggests that the observed efficacy of rivastigmine in moderately severe to severe AD is likely a cumulative effect across a range of tasks. Rivastigmine demonstrates broad cognitive efficacy in this patient population [41,42].

A current study screened in Thailand with total of 116 AD patients, in multicentre, hospital-based, prospective observational - data was collected at the baseline, weeks 4-8 and after week 16. One-third of all patients had been using antipsychotic or antidepressant medication. Common co morbidities were hypertension and dyslipidemia. The Thai Mental State Examination score significantly increased from 18.6 to 20.3 (weeks 4-8) and 20.4 (week 16+) ($P < 0.001$). Physicians' and caregivers pointed out the side effects of itching, which was the most common adverse symptom. Moreover, Rivastigmine was safe and well tolerated [43].

Analysis of effectiveness and tolerability of patch rivastigmine in the treatment of AD in daily practice in a German prospective multi-centred observational study was conducted over 4 months of treatment. Outcomes showed changes in the clock-drawing test, MMSE, Caregiver Burden Scale, Clinical Global Impression, physicians' assessments of tolerability, and the incidence of adverse events. In 257 centres 1113 patients were enrolled. After 4 months, 67.4% of patients were on the target dose of 9.5 mg/day and 21.8% remained on 4.6 mg/day. MMSE significantly improved in patients with and without pre-treatment (ΔMMSE, 0.9 ± 3.4 and 0.8 ± 3.4, respectively, both $P < 0.001$); the CGI score improved in 60.9% and 61.3% of patients, respectively. With rivastigmine treatment the percentage of patients taking psychotropic co-medication decreased, and other oral acetylcholinesterase inhibitors and transdermal rivastigmine may improve cognition [44].

In previous studies citalopram, has been recognised as the first choice for selective serotonin reuptake inhibitors (SSRI); and globally in places like Europe (the UK) and the USA, it is one of the antidepressant drugs that clinicians use for routine depression care [45]. In terms of efficacy, tolerability and acceptability-some statistically significant differences were found between citalopram and other antidepressants for the acute phase treatment of major depression. Each study was conducted as Randomised controlled trials allocating patients with major depression to citalopram versus many other antidepressants.

At present, new diagnostic criteria have been developing, and can be sufficient on drug development with susceptible AD patients, before clinical onset [46]. Thus, it is urgent to develop novel and effective medications for AD that go beyond AChEIs and NMDA (N-methyl-D-aspartate) antagonists to delay deterioration or improve [47] the functional outcomes in AD patients. Modern research has focused on discovering effective disease-modifying therapies, which specifically target the pathophysiologic cascade, hoping to delay the onset of the disease and slow its progression.

Finally, Gene therapy is under investigation and assessment for future research in the hope that it helps to slow down and prevent AD as well as the production of beta-amyloid aggregation. Both Donazapil and Rivastigmine are more effective and safe than Tacrine, which is less used due to its hepatotoxicity. Antioxidant therapy, Vitamin E and Selegeline can prevent or halt pathological processes; and they disrupt or prevent the free radical beta- amyloid recirculating cascade. Estrogen replacement therapy in post-menopausal woman and nonsteroidal anti-inflammatory drugs may play a role in slowing or preventing AD. In previous studies for the drugs of AD, no one addressed the question of effectiveness of citalopram and rivastigmine together and their ability to reduce depression; however, this remains in a disastrous condition so we have to change it in the coming days for clinical practice. Furthermore, seeing the results of AD drugs takes around 10 years and as of yet, there have been no changes to the treatment protocols; although newly adapted drugs are able to relieve the symptoms but poorly affect the progression of the disease.

Our study suggests that larger populations are needed to confirm these results in the treatment of Alzheimer's with depression patients, so the use of both drugs can be justified. In addition, this study attempts to establish that there are no significant effects from combined therapy. Furthermore, we stated that the antidepressant citalopram in AD patients should be started separately.

Conclusion

Our results indicate that rivastigmine and citalopram have no effect in the treatment of AD patients. On the contrary, the combined treatment with rivastigmine and citalopram has been shown to be unable to manage depression as successfully as each medication alone. In addition, cognitive status continues to decline and psychotic symptoms to increase at the same pace in all groups. More research is needed to determine the exact link between these medications and AChEI or BuChEI. However, AD patient with depression do not benefit from this combination to show compelling evidence of efficacy in a predominantly Greek population. Future studies should apply standardised depression scale in Alzheimer's disease diagnostic criteria.

Limitations

First of all there is a limitation with respect to sample size. Secondly it is from one clinical centre only.

Acknowledgements

We would like to gratefully acknowledge those patients for their consent in this study and for the collaboration of the Greek Alzheimer association center and "G. Papanikolaou" Hospital, Greece in completing the research.

Funding

No financial support for the research, authorship and publication.

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Citation: Tsolaki M, Pathak KP, Verikouki E, Messini CZ, Gaire T and Devranis P. Depression in Alzheimer's disease: Citalopram and Rivastigmine can better?. SM J Neurol Neurosci. 2017; 3(1): 1007.