The effect of Risperidone, Sertraline as monotherapy and in combination with Cholinesterase inhibitors on cognitive functioning due to Alzheimer’s Disease: A randomized clinical trial

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Abstract

Alzheimer’s disease is a progressive neurodegenerative disorder which is characterized by the progressive decline in memory and other cognitive abilities. Behavioral and personality changes can also be present. Depression is also a neuropsychiatric aspect of Alzheimer’s disease.

Objective: The aim of this study is to compare the effect of risperidone as monotherapy in patients with behavioral problems, sertraline as monotherapy in patients with depression and with the combination of cholinesterase inhibitors on cognitive functioning due to Alzheimer’s Disease.

Methods and Participants: The study comprised 78 participants diagnosed with AD, all over fifty years of age. The participants were split into 4 groups: groups A and B had everyday behavioral problems, while groups C and D had co-morbid depression. Group A was treated with risperidone 1mg daily, group B with risperidone and cholinesterase inhibitors, Group C was treated with sertraline, and group D with sertraline and cholinesterase inhibitors. Baseline assessment of groups A and B was performed using the instrumental activities of daily living (IADL) Scale, Physical Self-Maintenance Scale (PSMS), Mini-Mental State Examination Scale (MMSE), while a follow-up assessment after three and six months was only with MMSE. Groups C and D were assessed with MMSE and the Montgomery-Asberg Depression Rating Scale for baseline assessment and follow-up after 12 months.

Results: It was found that group A (treated with risperidone only) showed a statistically significant improvement in MMSE scores with respect to the baseline assessment after 6 months, An improvement not seen in group B (treated with risperidone and cholinesterase inhibitors). Groups C and D did not show any significant improvement in scores on either assessment scale.

Conclusion: Risperidone used as monotherapy displayed a positive effect on cognitive function due to Alzheimer’s.

Introduction

Alzheimer’s disease is a progressive neurodegenerative disorder which damages the brain and is characterized by the progressive decline in memory and other cognitive abilities [1]. Alzheimer’s Disease (AD) causes sensory and cognitive impairments that in later stages of the disease render the coverage of everyday life demands extremely difficult [2]. This cognitive impairment arises from the presence of dense deposits of beta-amyloid surrounding the nerve cells, as well as by twisted fibers in the nerve cells of the brain, as first described by Dr. Alois Alzheimer in 1906. Cognitive impairment also results from atrophy and accompanying synapse loss [3]. Dementia is characterized by memory deficits (amnesia) as well as impairment of either speech (aphasia), motor function (apraxia), recognition (agnosia), or more complicated functions such as working memory and problem solving, which affect a person’s ability to successfully perform everyday activities [4]. Behavioral and personality changes may also be present, sometimes even before memory impairment begins [5,6]. Even though scientists have concluded that genetic and neurochemical conditions are the most prevalent causes that lead to Alzheimer dementia [7,8], nevertheless the causes of Alzheimer’s Disease are yet to be fully discovered [9]. Sooner or later the neuronal damage affects basic body functions, such as walking and swallowing, resulting in around the clock personal

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care. Alzheimer’s disease is recognized as the most common cause of dementia among seniors ≥65 years [6], with a threefold increase in the incidents for the following decades, as estimated by World Alzheimer’s Report figures [10]. AD is the clinical reason for the cognitive decline in 60%-70% of elderly patients worldwide and in the USA 2.3 million people aged 65 and above are suffering from AD [11].

Many hypotheses for the cause of AD have been studied and published. Neurochemical functions altered in the brain of AD patients give guidelines for specific pharmacotherapeutic pathways. Loss of cholinesterase acetylcholine has made the cholinesterase inhibitors the most common and effective therapy for AD. Their action involves the relief of several behavioral and psychological symptoms of the disorder [12,13]. Psychotic symptoms such as delusions, hallucinations and cognitive disturbances, are evident in AD, making the institutionalization of patients inevitable, since professional medical care is required. For the confrontation of the psychosis in AD, atypical antipsychotics like risperidone are used in clinical practice [14,15].

Depression is also a neuropsychiatric aspect of AD. Guilt, physical stress, anger, cognitive decline and apathy are the most characteristic depressive symptoms which accompany the course of AD in many patients: apathy in 41% and major depression in 24% of the patients [16]. Antidepressants like sertraline, are used for the treatment of the depressive symptoms in AD and they seem to have quite satisfactory effects [17]. Studies for the efficacy of the recommended treatments have been published either presenting monotherapy results or combination therapy results. Some of them have not reached desirable results, whereas some others have given rise to the prospect of potential future treatments.

In our research, we will try to compare the effect on the cognitive function of patients suffering from AD and behavioral problems as well as depression when they were treated with risperidone as monotherapy versus risperidone in combination with cholinesterase inhibitors in combination with cholinesterase inhibitors. Similarly, we will try to compare sertraline as monotherapy versus sertraline with the combination of cholinesterase inhibitors in patients with AD and depression.

Methodology

Subjects

Eighty volunteers were recruited at first from the Alzheimer Disease Center in the City of Chania. Seventy-eight (n=78; Males: n=27, Females: n=51) of them were able to finish the project. Admission criteria: the volunteers should be more than fifty years old, have been diagnosed with Alzheimer’s Disease according to DSM-IV [18,19], baseline-assessment on Mini-Mental State Examination between 15 and 24. The volunteers should also have had Computed Tomography, a CT exam (scan) in the last six months. Only volunteers with a diagnosis of co-morbid depression were included in C and D groups. Exclusion criteria: serious gastrointestinal, nervous, hepatic, endocrine, pulmonary, cardiovascular, or hematologic disease, primary psychiatric or neurological disorder and clinically significant laboratory or electrocardiogram abnormalities.

Volunteers with everyday behavior problems were randomly incorporated in groups A and B. Volunteers of group A (n=17; Males: n=4, Females: n=13) were administered with risperidone, 1 mg daily. Where the dose was considered to be not well tolerated, it was reduced to 0.5 mg daily. Volunteers of group B (n=13; Males: n=7, Females: n=6) were administered with risperidone with the combination of cholinesterase inhibitors. Where the 1 mg daily dose of risperidone was considered to be not well tolerated, it was reduced to 0.5 mg daily. The project on those groups lasted for six months. Volunteers with a diagnosis of depression were randomly incorporated in groups C and D. Volunteers of group C (n=29; Males: n=8, Females: n=21) were administered with sertraline. Volunteers of group D (n=19; Males: n=8, Females: n=21) were administered with sertraline with the combination of cholinesterase inhibitors. The project for those groups lasted for twelve months. For groups A and B we used the Instrumental Activity of Daily Living (IADL) as a baseline-assessment, as well as the Physical Self-Maintenance Scale (PSMS). Subsequently, we used the Mini-Mental Examination Scale for baseline-assessment, first after 3 months and finally after 6 months. For groups C and D we used the Montgomery-Åsberg Depression Rating Scale (MADRS) for baseline-assessment. Subsequently, we used the Mini-Mental Examination Scale for baseline-assessment and we reevaluated it after 12 months.

Instrumental activity of daily living

Instrumental Activity of Daily Living is an instrument adjusted to assess independent living skills. The instrument is useful in identifying how a person is functioning at the present time and in identifying improvement or deterioration over time. The IADL questionnaire contains scales for telephoning, shopping, food preparation, housekeeping, laundering, the use of transport, the use of medicine, as well as financial behavior. There are 8 domains of function measured with the Lawton IADL scale. On the Instrumental Activities of Daily Living, scores ranges from 1 (high function, independent) to 5 (low function, dependent), the overall score ranges from 8 to 31 [20].

Physical self-maintenance scale

The PSMS is a six-item scale that measures the ratings of self-care abilities, in the areas of toileting, feeding, dressing, grooming, locomotion (physical ambulation), and bathing [20,21]. On the Physical Self-Maintenance Scale, scores range from 1 (high function) to 5 (low function). The overall score ranges from 6 to 30, where higher scores indicate greater dependence [20].

Montgomery-Åsberg depression rating scale

The Montgomery and Åsberg Depression Rating Scale is a 10-item clinician-rated scale measuring the severity of depressive symptoms. Items are rated on a 7-point Likert scale (from 0 to 6). The grades 0, 2, 4, and 6 are formulated separately for each item with behavioral examples that may increase the reliability and the total score ranges from 0 to 60. A higher total score indicates more depressive symptoms [21,22].

Mini-mental examination scale

The Mini-Mental Examination Scale (MMSE) is a brief test formed to screen the cognitive functions in patients with dementia. It is a very useful instrument in confirming the diagnosis of dementia and it is widely used in studies with patients suffering from AD, in order to follow the course of cognitive deduction [23,24]. It has been observed that AD patients have similar scores in MMSE to demented patients, but also in Alzheimer’s there are dysfunctions not only in memory but in other cognitive skills as well. The scores of AD patients are longitudinally more disappointing, as the later stages of the disease lead to expanded cognitive impairment [25,26]. The total score ranges from 0 to 30. A higher total score indicates better cognitive function.

Ethics

This research has the approval of the Scientific Committee of the Greek Alzheimer Society and Related Disorders and all participants...
provided informed consent. If the participants were not able to give written consent, then it was given by a first-degree relative.

Statistical analysis

A series of one-way ANOVAs and t-tests were employed accordingly to address study aims. For the risperidone treatment regime a two-way mixed ANOVA with time (baseline, 3 months, 6 months) as the Within-Subjects variable and treatment regime (group A representing risperidone administration and group B representing simultaneous risperidone and cholinesterase inhibitors) were used to address main and interaction effects. Significance was set at p<0.05. The statistical analysis was performed using the software program SPSS 19 (IBM).

Results

Basic demographic information for all four groups addressed in this study is presented in Table 1. One-way ANOVAs revealed no significant differences between groups concerning age F (3,72) =1.925, p=0.133 and baseline scores in MMSE F (3,73) =0.630, p=0.598. Assessment of daily life activity and physical maintenance with IADL and PSMS scales respectively, showed significant differences between the two risperidone treated groups (group A and B; Table1). Levene’s Test was found to be statistical significant F=24.802, p=0.000. However t-test with equal variances not assumed was found to be statistically significant t (27) = -2.480, p=0.024, with group A (mean=11.00) scoring less than group B (mean=16.31) in IADL. The same pattern was seen for PSMS. With equal variance not assumed (Levene’s Test F=8.829, p=0.032) t test [t (27) = -2.399, p= 0.032] it was shown that group A (mean=6.19) was less burdened than group B (mean=7.85). Two-way mixed ANOVA revealed that the main effect of group on MMSE was not significant (p=0.968) but a significant main effect of time on MMSE scores was found (p= 0.006). The two factors had a marginal significant interaction (p=0.047). Simple effect analysis of time within each treatment regime revealed a significant difference only within group A (p< 0.001) but a non-significant difference within group B (p=0.59). Post hoc comparisons (Bonferroni adjusted) in group A showed significant differences only between baseline and 6 months (p< 0.001). Baseline to 3 months (p= 0.231) and 3 months to 6 months (p= 0.06) were not significant. Mean values of MMSE scores by each group over time are shown in Table 2.

For sertraline treated patients (group C and B) no significant differences in MDRS scores were detected between the two groups, t (46) = 1.710, p =0.094 (Table1). Pairwise t-tests between MMSE scores and scores measured after 12 months showed a significant difference for group C [t (28) = -3.078 p= 0.005] but not for group D [t (18) = 0.917 p= 0.371]. Comparisons between the two groups also failed to reach significance for both baseline assessments [t (46) = -0.532 p=0.597] and at end point [12 months; t (46) = 1.323 p= 0.196]. Means and SD are presented in Table 3.

Discussion

Most patients who suffer from Alzheimer’s disease show not only cognitive deficits but also, various behavioral disturbances [27]. These symptoms lead to difficulties in the integration of the patient’s everyday tasks. Furthermore, behavioral disturbances burden the caregivers more, which can increase the incidence of depressive disorders among them [28,29]. In the last few decades, quite a large number of elements related to the neurochemical deficits underlying the neuropsychopathological and clinical symptoms of AD has been revealed. Though the indisputable

Table 1. Basic demographic information for all groups

<table>
<thead>
<tr>
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<th>N</th>
<th>A</th>
<th>B</th>
<th>C</th>
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<tbody>
<tr>
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<td>4</td>
<td>7</td>
<td>8</td>
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<td>12</td>
<td>6</td>
<td>21</td>
<td>11</td>
<td></td>
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<tr>
<td>Age (years)</td>
<td>70.67 (8.56)</td>
<td>75.85 (4.58)</td>
<td>73.48 (8.58)</td>
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<tr>
<td>MMSE baseline</td>
<td>20.88 (4.05)</td>
<td>21.85 (2.91)</td>
<td>20.38 (2.82)</td>
<td>20.84 (3.31)</td>
<td></td>
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<td>IADL</td>
<td>11.00 (3.56)</td>
<td>16.31 (7.02)</td>
<td>16.01 (3.31)</td>
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<tr>
<td>PSMS</td>
<td>6.19 (0.54)</td>
<td>7.85 (2.44)</td>
<td>6.14 (0.54)</td>
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<tr>
<td>MDRS</td>
<td>15.59 (10.49)</td>
<td>[2-52]</td>
<td>10.89 (7.05)</td>
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</table>

Table 2. Risperidone: comparisons of MMSE scores means (SD) by therapy group over time

<table>
<thead>
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<th>Group</th>
<th>Baseline</th>
<th>3 months</th>
<th>6 months</th>
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</thead>
<tbody>
<tr>
<td>A</td>
<td>20.88 (4.05)*</td>
<td>22.25 (3.34)</td>
<td>23.88 (3.07)*</td>
</tr>
<tr>
<td>B</td>
<td>21.85 (2.91)</td>
<td>22.69 (4.42)</td>
<td>22.31 (4.64)</td>
</tr>
</tbody>
</table>

Mean (SD). * Differences at p <0.05 (Bonferroni adjusted)

Table 3. Means and SD values for MMSE scores for Sertraline treated patients

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline</th>
<th>12 months</th>
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</thead>
<tbody>
<tr>
<td>C</td>
<td>20.38</td>
<td>20.84</td>
</tr>
<tr>
<td>D</td>
<td>21.90</td>
<td>20.00</td>
</tr>
</tbody>
</table>

neurochemical changes in dementia and mostly in Alzheimer’s, are yet to be revealed, cholinergic deficits in presynaptic components at the first stages of the disorder and loss of cholinergic neurons in the basal forebrain accompanied with a reduction of Choline Acetyltransferase (ACh) in the hippocampus and the neocortex, in the last stages, have made cholinesterase inhibitors the most popular and unique treatment for AD for many decades [8,30]. Cholinesterase inhibitors help in alleviating the symptoms by restoring the ACh concentration in the cortex, but cause many difficulties in daily life [31]. The "cholinergic hypothesis" for AD was the first finding related to the neurochemical deficits which cause the cognitive and neuropsychiatric conditions in AD [8].

The majority of the currently approved drugs used to treat symptoms of dementia in Alzheimer’s disease are based on enhancing the availability of the neurotransmitter, Acetylcholine. When a patient needs to be administered a drug, cholinesterase inhibitors may be effective in some cases and are consider to be first-line therapy in Alzheimer’s disease. However, they may work better for the prevention of these symptoms than for their treatment once they have emerged [5]. For many years there has been a debate about the efficacy of cholinesterase inhibitors in the management of the symptoms of Alzheimer’s disease. Nowadays, many of ACh inhibitors are available and they have been regarded as a landmark in the treatment of Alzheimer’s disease. However, others argue that despite the modest improvements in scores on assessment scales, there has been no significant clinical benefit [32]. Although cholinesterase inhibitors may slightly improve neuropsychiatric symptoms, they are also associated with adverse effects [33]. Today the use of cholinesterase inhibitors for the treatment of cognitive impairment in dementia is very common,

so many patients will be treated with a combination of Cholinesterase inhibitors and antipsychotic drugs to improve behavioral disturbances. Despite the widespread use of this combination in clinical practice, there is not sufficient data from controlled clinical trials to evaluate the safety and tolerability of such combination therapy [27].

Even today, the treatment of agitation and aggression in dementia is a very controversial area, because antipsychotics are often misused as "chemical straightjackets" to calm down patients, and there is also a risk of cardiovascular episodes and death from these drugs [5]. As there is insufficient data from controlled trials that support the efficacy of antipsychotics and also because of the risk of cardiovascular episodes and increased mortality in elderly patients with dementia, they are not recommended for use to control agitation and behavioral symptoms of Alzheimer's disease. On the other hand, if patients remain untreated, there are also risks such as early institutionalization and the risk of agitated and psychotic behavior in the patient and on their environment. Thus, some patients will nevertheless require antipsychotic treatment with an atypical antipsychotic. In this case, risperidone is often preferred at very low doses [5,34,35]. The efficacy of risperidone has been supported by large randomized controlled trials, which have shown that risperidone reduces the frequency and severity of behavioral and psychological symptoms of dementia in patients with dementia [36]. Of all the atypical antipsychotics, only risperidone and olanzapine currently have the best evidence for efficacy. Doses of 1.0 mg/day of risperidone appear to be at least modestly effective for treating behavioral disturbances and psychotic symptoms in patients with Alzheimer's disease. The administration of such low doses of risperidone reduces the incidence of extrapyramidal symptoms, although sedation remains a concern [8,37].

In a double-blind placebo-controlled study of the efficacy of risperidone in patients with AD and mixed dementia, Brodaty and his colleagues [38] noticed that the mean score in MMSE of the risperidone-treated subjects was similar to the mean score of the total population. The impact of risperidone, compared with the placebo subjects, was evident from the first 2 weeks of the treatment and remained stable until the end of the study. In other double-blind placebo-controlled studies in the USA, Canada, Australia, New Zealand and Europe, the risperidone treated groups showed important improvements in their performance in MMSE and on other behavioral assessment scales [39].

The most popular and effective treatment for AD in the past few decades has been the use of cholinesterase inhibitors. Many studies have compared the efficacy of Cholinesterase inhibitors with atypical antipsychotics for the decrease of agitation in patients with dementia. In research done by Holmes and his colleagues [40], risperidone, which is an atypical antipsychotic, was found to be more effective than the cholinesterase inhibitor, Rivastigmine. In a randomized double-blind, placebo controlled trial, there were groups of people with AD treated with both quetiapine, an antipsychotic, and rivastigmine. The reason for the use of quetiapine was the high risk of stroke in patients with dementia. Treatment with both risperidone and quetiapine is considered to be at least modestly effective for treating behavioral disturbances and psychotic symptoms in patients with Alzheimer's disease. The administration of such low doses of risperidone reduces the incidence of extrapyramidal symptoms, although sedation remains a concern [8,37].

In post-mortem studies of AD patients, reduction in Serotonergic and other neurons, gave evidence for an antidepressant-based treatment for the depressive symptoms in Alzheimer’s dementia [8,44]. It is important to notice that 30% to 50% of the patients with AD display depressive symptoms (guilt, suicidal thoughts, apathy, low self-esteem). Evidence from case studies with depressive symptomatology and cognitive impairment, has led to the belief that depression in AD is a different disorder. However, in AD pharmacotherapy research, a combination of traditional Alzheimer’s treatment and tricyclic antidepressants have a more efficacious impact [45,40].

In addition to the primary effects of AD in cognition, other factors associated with AD can have an impact on cognitive functioning [46]. Depression is a factor highly correlated with AD and seems to affect up to 50% of patients with AD [47]. Due to the severity of the consequences of this on their lives, many depressed patients with Alzheimer’s disease are treated with antidepressants. Sertraline is a selective Serotonin reuptake inhibitor that has been shown to have both antidepressant and anti-anxiety effects. Many clinical trials have demonstrated its efficacy in depression, obsessive-compulsive disorder, panic disorder, social phobia and premenstrual dysphoric disorder [48]. Research on the efficacy of dertraline for the treatment of depression in AD (dAD) has led to conflicting results. While some studies have shown that sertraline was not found to have a beneficial outcome on the treatment of depression in AD [49], some others demonstrate that sertraline is effective for the treatment of major depression in patients with AD [46].

Sertraline is a very common tricyclic antidepressant administered in cases of AD. In a sertraline treatment study with patients presenting with major depressive episodes and cognitive impairment, 38% of the patients fully responded to the treatment and 46% responded partially, as shown by their MMSE scores [46]. In another study 17 out of 26 patients responded to sertraline treatment, after 12 weeks of treatment with a 200mg daily administration and MMSE measurements [50].

In studies with a combination of cholinesterase inhibitors and sertraline, the results are very promising. For instance, Finkel and his colleagues [51], compared the effects of cholinesterase inhibitor Donepezil alone in patients with AD with the effects of donepezil accompanied by sertraline. The results showed that 60% of the patients of the combination treated group responded to the treatment, in comparison with 40% of the patients of the donepezil and placebo treated group. The effect of sertraline treatment on cognitive performance in patients with AD is an under-researched field of study. Prior studies on Sertraline treatment in patients with AD has found no cognitive advantage of Sertraline over placebo and no difference was detected between the treatment groups (Sertraline-treated and placebo-treated) in Mini-Mental State Examination [52,46]. According to Gonzales-Salvador and his colleagues [53], depression in AD has been associated with a severe deterioration of the patient’s quality of life. Moreover, as previous research highlights depression in AD causes disabilities in daily activities [54]. Consequently, in our study we hypothesized that sertraline-treatment would have a positive impact on the cognitive performance of patients, probably as a secondary benefit of reducing depression. Similarly with the previous studies [52, 46], there is also no evidence in our clinical trial that Sertraline has any effect in the cognitive function of patients with AD.

**Conclusion**

Risperidone used as monotherapy displayed a positive effect on Alzheimer cognitive function whereas sertraline as monotherapy or in combination with cholinesterase inhibitors did not show any effect.
Limitations

This research is limited because we were not able to repeat the measurement of the other scales MADRS, IADL, and PSMS after the administration of the medication. We measured only the MMSE after 3 and 6 months. Therefore, our results are limited only to the cognitive function of the patients with AD and we could not evaluate the effect of the medication for depression, physical self-maintenance and independent living skills.

Future research

In future research, we should evaluate all the scales (MMSE, IADL & PSMS) as a baseline-assessment, after 3 months, 6 months and 12 months. Because the effect of sertraline treatment on cognitive performance in patients with AD is an under-researched field of study, we should have more patients with AD treated with sertraline in order to conduct a clinical trial to determine whether sertraline has any impact on cognitive function. In future we should also include scales that measure the burden of the caregivers who play a significant role in a patient’s life and treatment.

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