HHS Public Access

Author manuscript

J Alzheimers Dis. Author manuscript; available in PMC 2018 October 26.

Published in final edited form as:

J Alzheimers Dis. 2017 ; 57(2): 387–393. doi:10.3233/JAD-160758.

Effects of Risperidone and Galantamine treatment on Alzheimer biomarker levels in cerebrospinal fluid

Victor Bloniecki[1], **Dag Aarsland**[1,2,3], **Kaj Blennow**[4,5], **Jeffrey Cummings**[6], **Farshad Falahati**[1], **Bengt Winblad**[7], and **Yvonne Freund-Levi**[1,2,*]

[1]Department of Neurobiology, Caring Sciences and Society (NVS), Division of Clinical Geriatrics, Karolinska Institute, Stockholm, Sweden

[2]Department of Geriatric Medicine, Karolinska University Hospital Huddinge, Stockholm Sweden

[3]Center for Age-Related Medicine, Stavanger University Hospital, Stavanger, Norway

[4]Inst. of Neuroscience and Physiology, Dept. of Psychiatry and Neurochemistry, the Sahlgrenska Academy at University of Gothenburg, Sweden

[5]Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital, Mölndal, Mölndal

[6]Cleveland Clinic Lou Ruvo Center for Brain Health, 888 W. Bonneville Avenue, Las Vegas, NV 89106, USA

[7]Karolinska Institutet, Department of Neurobiology, Caring Sciences and Society (NVS), Center for Alzheimer Research, Division of Neurogeriatrics, Huddinge, Sweden

Abstract

Background—Treatment for neuropsychiatric symptoms (NPS) in dementia is insufficient. Antipsychotics and acetylcholinesterase inhibitors are used generating symptomatic improvements in behaviour and cognition, but few studies have investigated their effect on Alzheimer biomarkers in cerebrospinal fluid (CSF).

Aim—This is a secondary analysis based on an earlier clinical trial comparing the treatment effects on NPS. The aim of this study was to examine whether treatment with risperidone and galantamine affect levels of biomarkers T-Tau, P-Tau, $A\beta_{1–42}$, and Aβ40/42-ratio in CSF. The secondary aim was to test if baseline levels of these biomarkers are associated with the clinical course of NPS.

Methods—83 patients (mean + SD 77.9.6±7.7 years) with dementia and NPS were randomized to galantamine (n=44) or risperidone (n=39) treatment. CSF samples were collected at baseline and after 12 weeks.

Results—Changes in levels of biomarkers between the two treatment groups did not differ significantly. Low baseline levels of $A\beta_{1–42}$ was significantly associated with reduction of irritability at follow up. Low baseline levels of $A\beta_{1–42}$, $A\beta_{42/40}$ and P-Tau were significant correlates of reduction in appetite and eating disorders. CSF $A\beta_{1–42}$ levels in patients treated with

*Corresponding author: Tel: +4673-6481130; Fax: +46858585470, Yvonne.Freund-Levi@ki.se.

No potential financial conflicts were identified for this study.

risperidone were significantly decreased at follow up, showing a 8% (40 pg/mL) reduction as compared with baseline (p=0.03).

Conclusions—Our results suggest that risperidone may affect the CSF profile of AD biomarkers indicating more amyloid pathology. Treatment with galantamine did not affect the CSF biomarkers in any direction. The Alzheimer CSF biomarkers displayed correlations with specific NPS suggesting potential research questions to be pursued.

Keywords

neuropsychiatric symptoms; dementia; NPS; biomarkers; galantamine; risperidone

1. Introduction

Neuropsychiatric symptoms (NPS) are a prominent feature of Alzheimer´s diseases (AD) and other dementias and include symptoms such as apathy, depression, psychosis and agitation [1]. NPS have a major negative impact on the patient's quality of life and constitute the most important determinant of caregiver burden [1, 2]. The pathogenesis of NPS is largely unknown but likely a consequence of complex interaction between biological and environmental factors [3]. Recent research, including neuroimaging, neuropathology and neurochemical studies indicate that specific NPS are associated with the underlying AD pathology in distinct cerebral regions [3–7].

The biomarker correlates of pathological changes in AD can be measured in-vivo using cerebrospinal fluid (CSF) levels of total-tau (T-Tau) reflecting axonal degeneration, phosphorylated-tau (P-Tau) associated with the amount of intracellular tangles or extracellular protein levels during cell-to-cell transmission, and the 42 amino acid isoform of β-amyloid protein ($A\beta_{1–42}$) reflecting cortical amyloid burden [8,9]. Furthermore the ratio of $A\beta_{42}$:$A\beta_{40}$ is used as it normalizes $A\beta_{42}$ levels for total Aβ production and thereby increases diagnostic accuracy [10].

Association of NPS and CSF markers may provide insight with the mechanisms of NPS, but few studies of these relationships exist. We recently showed that agitation was associated with high levels of T-Tau and P-Tau [11]. However, we are not aware of previous studies of the association between CSF markers and the course of NPS.

Atypical antipsychotics and acetylcholinesterase inhibitors (AChEI) are used in the treatment of NPS [12] although the evidence regarding their efficacy is inconsistent. In a recent randomized trial, we found that galantamine, an AChEI, and risperidone, an atypical antipsychotic, treatments were equally effective in treating several NPS domains, although risperidone was more effective than galantamine for irritation and agitation. However, a positive effect on cognition was observed in the galantamine but in the risperidone group [13]. This is the original trial that this secondary trial is based on in which the primary end points were change in rating scales of NPS between baseline and follow-up.

Antipsychotics have potentially severe adverse effects including cerebrovascular events, increased mortality and cognitive impairment [14, 15]. In an earlier autopsy study,

antipsychotics were associated with increased neurofibrillary tangles in the brain, which could possibly explain the increased cognitive decline associated with the treatment [16]. In contrast, there are some indications that AChEIs may reduce the amount of cortical β – amyloid in people with dementia [17]. Currently there is limited information to whether treatment with AChEIs and antipsychotic agents influence AD pathologies in-vivo as measured with relevant CSF biomarkers.

This is an exploratory analysis of the potential effects of commonly used drugs on the profile of CSF AD biomarkers due to the gap in knowledge in this area and the emerging evidence of decreased cognition and increased mortality in elderly people with dementia treated with antipsychotics. Our primary aim of this randomized controlled trial (RCT) was to investigate whether treatment with an AChEI (galantamine) or an antipsychotic agent (risperidone) affects CSF levels of the AD biomarkers T-Tau, P-Tau, $A\beta_{1–42}$ and $A\beta_{42}$:$A\beta_{40}$. We hypothesized that galantamine would reduce and risperidone would increase the AD type CSF pattern, i.e. reduced $A\beta_{1–42}$ and increased total and P-tau. Secondly, we wanted to examine the possible role of these biomarkers for predicting the course of NPS, hypothesizing that more pathological biomarkers at baseline are associated with increased NPS at follow up.

2. Material and methods

2.1 Patients

This is a secondary analysis of a RCT comparing galantamine and risperidone for treatment of NPS in dementia; detailed information regarding study population, assessment and other study specifics can be found elsewhere [13]. Briefly, 100 patients with NPS, defined as a total score of at least 10 points on the Neuropsychiatric Inventory (NPI) [18], and dementia according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) [19] or Mild Cognitive Impairment (MCI) were included. (36% AD, 26 % mixed AD, 17% vascular dementia (VaD), 4% frontal lobe dementia (FTD), 1% Parkinson's dementia (PD), 4% unspecified dementia and 12 % MCI). The study was approved by the regional Ethics Committee of Karolinska Institute, Stockholm Sweden. Registration number: 441/01.

2.2 Assessment

At baseline and at follow-up after 12 weeks, lumbar puncture was performed and CSF collected, medical examinations including psychiatric and neurological evaluation using tests such as Mini Mental State Evaluation (MMSE) [20] were administered. The NPI and Cohen-Mansfield agitation inventory (CMAI) [21] were used for assessment of NPS. At baseline CSF samples were successfully collected in 95 out of the 100 included patients; 12 patients did not complete the trial (See reference 13 for details) and were not eligible for lumbar punctures at follow-up, leaving 83 patients for final analysis in this study.

2.3 Randomization and Intervention

Subjects were allocated to one of the two treatment-groups according to a pre-defined randomisation code. The starting dose of galantamine was 4 mg/day twice daily, and after

one week the dose was increased to 8 mg twice daily and to 12 mg twice daily at start of week 3. Subjects randomised to risperidone received 0.25 mg twice daily at start, which was increased to 0.5 mg twice daily after one week, and to the final dose of 1.5 mg daily at start of week 3. Treatment duration for both drugs was 12 weeks.

2.4 Cerebrospinal fluid analyses

Pre-analytic and analytic procedures have been described in detail elsewhere [11]. In brief, T-tau concentration in CSF was determined using a sandwich ELISA (Innotest hTAU-Ag, Innogenetics, Gent, Belgium) [22]. Tau phosphorylated at threonine 181 (P-tau181) was measured using a sandwich ELISA method (INNOTEST® PHOSPHO-TAU (181P), Innogenetics, Gent, Belgium) [23]. $A\beta_{1–42}$ levels were determined using a sandwich ELISA method (INNOTEST® ß- AMYLOID(1–42), Innogenetics, Gent, Belgium) [24]. CSF levels of Aβ42 and Aβ40 to calculate the Aβ42/40 ratio were measured using the MSD Abeta Triplex assay (MSD, Rockville, MD), using a multiplexed method.

2.5 Statistics

Demographic and clinical variables between the two treatment groups were compared using Student t-test. The CSF markers used in this study were not normally distributed; we had a sufficiently large sample size to support use of parametric statistic as our primary analytic method. Paired T-test was used to compare change between pre- and post-treatment CSF markers in each group. Independent t-test was used for comparing change scores between the two groups. For our secondary objective we created a multiple regression model using change in NPI and CMAI scores between baseline and follow up as the dependent variable and then the baseline biomarkers, dementia diagnosis, age, gender and type of treatment as independent variables. Change was defined as the value at baseline subtracted from the values at follow up. P-level < 0.05 was defined as significant. We performed multiple analyses without adjustment in this exploratory study. Any findings can be regarded as hypothesis-generating and require confirmation.

3. Results

Clinical and demographic characteristics are shown in Table 1. Both treatment groups were matched in clinical and demographic characteristics at baseline. Furthermore, as can be seen in Table 2, the two groups did not differ significantly for the CSF markers at baseline.

3.1 Change in CSF markers during treatment

We first analysed the change in the CSF levels of biomarkers from baseline to follow up within the two treatment groups. We found a significant reduction of CSF $A\beta_{1–42}$ levels at follow up compared with baseline (M=40, SD=108), t(38) = 2,3, p=0,03) in patients treated with risperidone. No other significant CSF biomarker changes were observed, see Table 2. Changes in levels of biomarkers between the two treatment groups did not differ significantly, see Table 2. We then performed the same analyses including only patients with AD and mixed AD. No significant changes in levels of biomarkers were observed within or between the two treatment groups (data not shown).

3.2 Associations between baseline CSF markers and longitudinal change of NPS

For analysis of our secondary aim we created a multiple regression model to examine which variables were significant determinants of change in NPI or CMAI between baseline and follow up. Overall, there were similar improvements of NPI and CMAI in the two treatment groups from baseline to follow-up, NPI decreased by a mean value of 33.2 and 32.8 points in the galantamine and risperidone groups respectively whereas CMAI decreased by 4.9 and 5.9, as previously described [13]. The AD biomarkers did not display any significant associations with change in total NPI and CMAI scores, see Table 3. Further analysis including subscores in CMAI and NPI showed that $A\beta_{1–42}$ was a significant predictor for change in irritability *(Beta = −0.43, p < .05)* displaying a negative correlation i. e. low levels of these biomarkers at baseline were associated with improvement on the NPI-subscale assessing irritability. In this model, age also predicted improvement in irritability *(Beta = 0.28, p < .05).* Additionally $A\beta_{1–42}$, $A\beta_{42/40}$ and P-Tau were shown to be significant correlates of change in NPI subscores assessing appetite and eating disorders, *(Beta = 0.52, p < .05, Beta = −0.46, p < .05 and Beta = 0.53, p < .05 respectively).* Results from the multiple regression model are shown in Table 3. In the models that indicated an effect of biomarkers on NPS none of the included confounders, such as treatment group, were significant predictors of change in NPS.

4. Discussion

The primary aim of this study was to investigate whether treatment with galantamine and risperidone displayed any evidence of disease-modifying effects as measured by AD biomarkers in CSF. Secondly, we wanted to examine the possible role of these biomarkers for the course of NPS, hypothesizing that more pathological biomarkers at baseline are associated with increased NPS at follow up.

We observed significantly lower levels of $A\beta_{1–42}$ at follow-up compared to baseline in the risperidone group, but not in the galantamine group, which to some extent is consistent with our hypothesis. Although there was no difference in between group comparison which could be attributed to small sample size and low power but still this finding suggest a possible negative role of risperidone usage on amyloid pathology. Furthermore, this finding was not evident when including only patients diagnosed with AD and mixed AD. Based on earlier autopsy studies [16] we hypothesized that CSF patterns of dementia biomarkers T-Tau, P-Tau, $A\beta_{1–42}$, and Aβ40/42-ratio would show a worsening of AD-type pathology amongst patients treated with risperidone. Taken together, our findings suggest that risperidone may worsen amyloid pathology in people with dementia and NPS, but did not seem to influence tau pathology as reflected in CSF measures.

Conversely, we hypothesized that treatment with galantamine could reduce AD-type pathology, in particular a relative increase of $A\beta_{1–42}$, given that an earlier autopsy study had indicated treatment with AChEI could reduce β-amyloid [17]. This study does not support our hypothesis that galantamine could reduce AD-type pathology, which is in line with an earlier CSF studies showing no effect of AChEI on Alzheimer biomarkers [25]. Several possible explanations for these negative findings exist. Effects of risperidone and galantamine may be mediated exclusively through transmitter effects producing

symptomatic changes without disease modification. Alternatively, it is possible that a disease modifying effect on AD-type pathology by these drugs may take longer time to develop than the 12 weeks treatment in this study. In addition, the number of patients in each treatment group was relatively low and thus the power to detect statistical difference was relatively low. Patients were at relatively advanced stage of dementia, and it is possible that drug-effect on the AD pathology is stronger in the earlier disease stages. Several studies have indicated that treatment with antipsychotics worsen cognition in AD [26, 27] which would suggest that they accelerate the pathological process causing cognitive impairment in AD. However, this effect may also be due to the anticholinergic or anti-histaminergic effects, or sedation. Recently another atypical antipsychotic drug Olanzapine was shown to exhibit neurotoxic effects by influencing autophagy, demonstrated both in vivo and in vitro [28]. Thus, the potential negative effect of risperidone on AD pathology may be mediated through an effect on autophagy in the neurons.

A possible explanation of the association between risperidone and decreased levels of $A\beta_{1–42}$ could possibly be a natural decrease of the biomarker during progress of the disease. However, earlier studies have shown that $A\beta_{1–42}$ is stable over a time period of at least 6 months when treated with AChEI [25]. Compared to earlier studies the mean levels of AD biomarkers in our study population at baseline displayed a quite severe CSF profile suggesting pronounced AD pathology [29], indicating that further changes due to the disease progression are less likely. Furthermore, a 12 week period may be too short period to observe a natural decrease of $A\beta_{1–42}$ of due to disease progression. We therefore believe that the observed reduction in $A\beta_{1–42}$ in the risperidone group may represent a negative drug effect.

The potential role of T-Tau, P-Tau, $A\beta_{1–42}$, and Aβ40/42-ratio as markers for disease progression is currently undetermined. For our secondary objective, we tested whether CSF markers may predict the course of NPS and found some indications that the course of some specific neuropsychiatric symptoms was associated with baseline CSF markers. We recently reported that Tau-mediated pathology was associated with increased agitation in AD [11]. In this study, low $A\beta_{1–42}$ at baseline was associated with improvement of irritability during treatment. $A\beta_{1–42}$, $A\beta_{42/40}$ and P-Tau were significant correlates of change in appetite and eating disorders. Some studies suggest that these biomarkers, due to their intra-individual stability over time are valuable as surrogate markers in clinical trials and can be used for detection of pathophysiological changes caused by disease-modifying drugs [25, 30, 31]. Contrary, some studies suggest that they have limited value as markers for disease progression and treatment efficacy [32].

4.1 Strengths and Limitations

Several limitations exist in this study and some have already been mentioned. The sample size included is relatively low, yielding low power and the potential for type II errors, and the high number of statistical comparisons without adjustment increases the risk for type I errors. The lack of standardization regarding collection of CSF samples from the study population may have affected the CSF profile of biomarkers. Furthermore, as mentioned in the discussion, it is currently debated whether the classical AD biomarkers are useful for

measuring ongoing changes in the cerebral pathology associated with AD as we have used in this study. The main strength of this study is the unique approach with CSF samples collected before and after treatment which enables examination of the possible effects of commonly used pharmacological treatments on cerebral pathology as measured with CSF biomarkers.

Acknowledgments

We want to express our gratitude to the patients, caregivers and staff at the Outpatient Memory Clinic and inpatient wards at the department of Geriatrics Karolinska University Hospital Huddinge Stockholm Sweden and furthermore Patrizia Vannini, PhD, Massachusets General Hostipatal, for her construcive discussions. This study was an academically initiated study financed by an independent grant from Janssen Pharmaceuticals, Stockholm, Sweden. The company was represented in the trial steering committee with regard to study design and provided the galantamine and risperidone preparations. The company has not been involved in patient and data collection. The support of this work is also gratefully acknowledged by grants from the Petrus and Augusta-Hedlunds Foundation, Demensförbundet and Loo and Hans Osterman Foundation Karolinska Institute as well as Demensförbundet Stockholm.

References

1. Lyketsos CG, Carrillo MC, Ryan JM, Khachaturian AS, Trzepacz P, Amatniek J, Cedarbaum J, Brashear R, Miller DS. Neuropsychiatric symptoms in Alzheimer's disease. Alzheimers Dement. 2011; 7:532–539. [PubMed: 21889116]
2. Cerveira MO, Kochhann R, Godinho C, Forster L, Borba E, de Jesus A, Onyszko D, Franciscatto L, Vieira M, Camozzato AL, Chaves M. Neuropsychiatric symptoms as the main determinant of caregiver burden in Alzheimer's disease. Alzheimers Dement. 2011; 7:S429.
3. Casanova MF, Starkstein SE, Jellinger KA. Clinicopathological correlates of behavioral and psychological symptoms of dementia. Acta Neuropathol. 2011; 122:117–135. [PubMed: 21455688]
4. Vermeiren Y, Van Dam D, Aerts T, Engelborghs S, De Deyn PP. Brain region-specific monoaminergic correlates of neuropsychiatric symptoms in Alzheimer's disease. J Alzheimers Dis. 2014; 41:819–833. [PubMed: 24685637]
5. Cerejeira J, Lagarto L, Mukaetova-Ladinska EB. Behavioral and psychological symptoms of dementia. Front Neurol. 2012; 3:73. [PubMed: 22586419]
6. Hu N, Li X-L, Tan M-S, Yu J-T, Tan L. Behavioral and Psychological Symptoms in Alzheimers Disease. BioMed Research International. 2014; 2014:9.
7. Bensamoun D, Guignard R, Furst AJ, Derreumaux A, Manera V, Darcourt J, Benoit M, Robert PH, David R. Associations between Neuropsychiatric Symptoms and Cerebral Amyloid Deposition in Cognitively Impaired Elderly People. J Alzheimers Dis. 2015; 49:387–398.
8. Blennow K, Hampel H, Weiner M, Zetterberg H. Cerebrospinal fluid and plasma biomarkers in Alzheimer disease. Nat Rev Neurol. 2010; 6:131–144. [PubMed: 20157306]
9. Blennow K, Hampel H, Zetterberg H. Biomarkers in amyloid-beta immunotherapy trials in Alzheimer's disease. Neuropsychopharmacology. 2014; 39:189–201. [PubMed: 23799530]
10. Lewczuk P, Lelental N, Spitzer P, Maler JM, Kornhuber J. Amyloid-beta 42/40 cerebrospinal fluid concentration ratio in the diagnostics of Alzheimer's disease: validation of two novel assays. J Alzheimers Dis. 2015; 43:183–191. [PubMed: 25079805]
11. Bloniecki V, Aarsland D, Cummings J, Blennow K, Freund-Levi Y. Agitation in dementia: relation to core cerebrospinal fluid biomarker levels. Dement Geriatr Cogn Dis Extra. 2014; 4:335–343. [PubMed: 25298777]
12. Wang J, Yu JT, Wang HF, Meng XF, Wang C, Tan CC, Tan L. Pharmacological treatment of neuropsychiatric symptoms in Alzheimer's disease: a systematic review and meta-analysis. J Neurol Neurosurg Psychiatry. 2015; 86:101–109. [PubMed: 24876182]
13. Freund-Levi Y, Jedenius E, Tysen-Backstrom AC, Larksater M, Wahlund LO, Eriksdotter M. Galantamine versus risperidone treatment of neuropsychiatric symptoms in patients with probable

dementia: an open randomized trial. Am J Geriatr Psychiatry. 2014; 22:341–348. [PubMed: 24035407]

14. Ballard C, Hanney ML, Theodoulou M, Douglas S, McShane R, Kossakowski K, Gill R, Juszczak E, Yu LM, Jacoby R, investigators D-A. The dementia antipsychotic withdrawal trial (DART-AD): long-term follow-up of a randomised placebo-controlled trial. Lancet Neurol. 2009; 8:151–157. [PubMed: 19138567]
15. Sink KM, Holden KF, Yaffe K. Pharmacological treatment of neuropsychiatric symptoms of dementia: a review of the evidence. JAMA. 2005; 293:596–608. [PubMed: 15687315]
16. Ballard CG, Perry RH, McKeith IG, Perry EK. Neuroleptics are associated with more severe tangle pathology in dementia with Lewy bodies. Int J Geriatr Psychiatry. 2005; 20:872–875. [PubMed: 16116579]
17. Ballard CG, Chalmers KA, Todd C, McKeith IG, O'Brien JT, Wilcock G, Love S, Perry EK. Cholinesterase inhibitors reduce cortical Abeta in dementia with Lewy bodies. Neurology. 2007; 68:1726–1729. [PubMed: 17502555]
18. Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. Neurology. 1994; 44:2308–2314. [PubMed: 7991117]
19. Diagnostic and Statistical Manual of Mental Disorders IV (DSM IV). American Psychiatric Association; 1995.
20. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975; 12:189–198. [PubMed: 1202204]
21. Cohen-Mansfield J, Billig N. Agitated behaviors in the elderly. I. A conceptual review. J Am Geriatr Soc. 1986; 34:711–721. [PubMed: 3531296]
22. Blennow K, Wallin A, Agren H, Spenger C, Siegfried J, Vanmechelen E. Tau protein in cerebrospinal fluid: a biochemical marker for axonal degeneration in Alzheimer disease? Mol Chem Neuropathol. 1995; 26:231–245. [PubMed: 8748926]
23. Vanmechelen E, Vanderstichele H, Davidsson P, Van Kerschaver E, Van Der Perre B, Sjogren M, Andreasen N, Blennow K. Quantification of tau phosphorylated at threonine 181 in human cerebrospinal fluid: a sandwich ELISA with a synthetic phosphopeptide for standardization. Neurosci Lett. 2000; 285:49–52. [PubMed: 10788705]
24. Andreasen N, Hesse C, Davidsson P, Minthon L, Wallin A, Winblad B, Vanderstichele H, Vanmechelen E, Blennow K. Cerebrospinal fluid beta-amyloid (1-42) in Alzheimer disease: differences between early- and late-onset Alzheimer disease and stability during the course of disease. Arch Neurol. 1999; 56:673–680. [PubMed: 10369305]
25. Blennow K, Zetterberg H, Minthon L, Lannfelt L, Strid S, Annas P, Basun H, Andreasen N. Longitudinal stability of CSF biomarkers in Alzheimer's disease. Neurosci Lett. 2007; 419:18–22. [PubMed: 17482358]
26. Ballard C, Margallo-Lana M, Juszczak E, Douglas S, Swann A, Thomas A, O'Brien J, Everratt A, Sadler S, Maddison C, Lee L, Bannister C, Elvish R, Jacoby R. Quetiapine and rivastigmine and cognitive decline in Alzheimer's disease: randomised double blind placebo controlled trial. BMJ. 2005; 330:874. [PubMed: 15722369]
27. Vigen CL, Mack WJ, Keefe RS, Sano M, Sultzer DL, Stroup TS, Dagerman KS, Hsiao JK, Lebowitz BD, Lyketsos CG, Tariot PN, Zheng L, Schneider LS. Cognitive effects of atypical antipsychotic medications in patients with Alzheimer's disease: outcomes from CATIE-AD. Am J Psychiatry. 2011; 168:831–839. [PubMed: 21572163]
28. Vucicevic L, Misirkic-Marjanovic M, Paunovic V, Kravic-Stevovic T, Martinovic T, Ciric D, Maric N, Petricevic S, Harhaji-Trajkovic L, Bumbasirevic V, Trajkovic V. Autophagy inhibition uncovers the neurotoxic action of the antipsychotic drug olanzapine. Autophagy. 2014; 10:2362–2378. [PubMed: 25551567]
29. Hansson O, Zetterberg H, Buchhave P, Londos E, Blennow K, Minthon L. Association between CSF biomarkers and incipient Alzheimer's disease in patients with mild cognitive impairment: a follow-up study. The Lancet Neurology. 2006; 5:228–234. [PubMed: 16488378]

30. Zetterberg H, Pedersen M, Lind K, Svensson M, Rolstad S, Eckerstrom C, Syversen S, Mattsson UB, Ysander C, Mattsson N, Nordlund A, Vanderstichele H, Vanmechelen E, Jonsson M, Edman A, Blennow K, Wallin A. Intra-individual stability of CSF biomarkers for Alzheimer's disease over two years. J Alzheimers Dis. 2007; 12:255–260. [PubMed: 18057559]

31. Le Bastard N, Aerts L, Sleegers K, Martin JJ, Van Broeckhoven C, De Deyn PP, Engelborghs S. Longitudinal stability of cerebrospinal fluid biomarker levels: fulfilled requirement for pharmacodynamic markers in Alzheimer's disease. J Alzheimers Dis. 2013; 33:807–822. [PubMed: 23034521]

32. Wildsmith KR, Schauer SP, Smith AM, Arnott D, Zhu Y, Haznedar J, Kaur S, Mathews WR, Honigberg LA. Identification of longitudinally dynamic biomarkers in Alzheimer's disease cerebrospinal fluid by targeted proteomics. Mol Neurodegener. 2014; 9:22. [PubMed: 24902845]

Table 1

Baseline comparison of the two treatment groups

	Galantamine n =44		Risperidone n=39		
	Mean	**SD**	**Mean**	**SD**	**p**
Age, yrs	79.1	7.0	76.5	8.3	0.118
MMSE, total	19.5	5.1	20.9	4.5	0.176
NPI, total	50.1	21.4	46.7	27.2	0.523
CMAI, total	47.5	11.4	43.8	12.2	0.155

Data are presented as mean values and standard deviations. MMSE = Mini mental state examination. NPI = Neuropsychiatric inventory. CMAI = Cohen-Mansfield Agitation Inventory.

Table 2

CSF markers before and after treatment. Comparison of difference of biomarkers between baseline and follow up within and between the two treatment groups

	Galantamine			Risperidone			
	Baseline M±SD	**Follow-up M± SD**	**P Between group**	**Baseline M± SD**	**Follow-up M± SD**	**P Within group Galantamine**	**P Within group Risperidone**
Total Tau (pg/ml)	731.8±430.39	728.9±414.89	0.96	755.4±460.1	749.7±568.4	0.930	0,878
Aß1-42 (pg/ml)	468.2±205.2	449.1±155.04	0.39	490.8±175.8	450.8±166.2	0,260	0,026
Phosphorylated-Tau (pg/ml)	103.2±63.38	90.8±39.63	0,147	94.9±56.20	89.1±49.92	0,147	0,210
Aß40/42 ratio (pg/ml)	0.52±0.266	0.51±0.210	0.91	0.54±0.240	0.53±0.203	0.425	0.207

Data are presented as means and standard deviations. Independent T-test was used to analyze effects between treatment groups. Depended T-test was used for analysis of within treatment group effects. Significant results considered at $p<0.05$

J Alzheimers Dis. Author manuscript; available in PMC 2018 October 26.

Table 3

Mutiple regresion model for baseline determinants of change in NPI/CMAI

	T-Tau		P-tau		Aß1-42		Aß40/42 ratio	
	B[x]	p	B[x]	p	B[x]	p	B[x]	p
NPI Total	0.02	0.90	0.04	0.83	0,13	0,51	−0,2	0,3
Delusions	−0,02	0,90	−0,07	0,65	0,12	0,54	−0,22	0,25
Hallucinations	0,20	0,23	−0,09	0,59	0,12	0,55	−0,15	0,44
Agitation	0,17	0,29	−0,07	0,66	0,04	0,82	−0,01	0,95
Depression	0,20	0,22	−0,12	0,47	0,02	0,92	−0,05	0,79
Anxiety	−0,04	0,81	0,14	0,38	0,03	0,89	0,03	0,85
Euphoria	−0,06	0,69	0,23	0,17	0,19	0,32	−0,04	0,84
Apathy	0,01	0,96	−0,17	0,32	−0,05	0,78	−0,12	0,52
Disinhibition	0,05	0,76	0,03	0,85	−0,22	0,25	0,23	0,23
Irritability	0,15	0,32	−0,13	0,40	−0,43	0,02	0,19	0,28
Abberent motor behaviour	−0,09	0,56	0,05	0,76	0,24	0,21	−0,28	0,15
Sleep and nighttime behaviour disorders	−0,19	0,23	0,21	0,21	0,26	0,18	−0,33	0,09
Apetite and eadting disorders	−0,26	0,10	0,32	0,04	0,52	0,01	−0,46	0,01
CMAI Total	0,05	0,75	0,02	0,92	0,12	0,53	0,06	0,77
Agressive phsycial behaviour	−0,00	0,98	−0,05	0,78	0,17	0,38	−0,12	0,52
Non-agressive physical behviour	0,02	0,91	−0,02	0,90	0,13	0,50	−0,06	0,75
Agressive verbal behivour	0,01	0,95	−0,06	0,72	−0,06	0,75	0,03	0,87
Non-agressive verbal behviour	0,08	0,61	0,11	0,51	0,04	0,82	0,23	0,22

Age, gender, dementia diagnosis and treatment type were also included in the model. Significant results considered at $p<0.05$