

Cholinesterase Inhibitors and Behavioral & Psychological Symptoms of Alzheimer's Disease

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Objective: Examine the effect of cholinesterase inhibitors (ChEIs) on behavioral and psychological symptoms of dementia (BPSD) in patients with Alzheimer's disease (AD), and compared the dosages of antipsychotics and SSRIs or SNRIs used to treat BPSD in patients with and without ChEIs.

Material and Method: The cross-sectional study of Alzheimer patients who had been taking ChEIs for at least six months (ChEI+) or had never been on any ChEIs (ChEI-) were enrolled from the Memory Clinic, Ramathibodi hospital between September 1, 2014 and February 28, 2015. All of these patients were evaluated with Mini-Mental Status Exam (MMSE) for cognitive function, Neuropsychiatric Inventory-Questionnaire (NPI-Q) for BPSD, and psychotropic dosage used.

Results: Fifty-one Alzheimer patients were enrolled, 31 patients in the ChEI+ group and 20 patients in the ChEI- group. Mean and SD of MMSEs in ChEI+ and ChEI- were 13.6 ± 1.2 and 11.75 ± 1.4 , respectively (p -value = 0.33). The Mean and SD of NPI scores in ChEI+ and ChEI- were 15.68 ± 14.31 and 19.5 ± 20.1 , respectively (p -value = 0.43). Patients in ChEI+ had tend to had a lower depression severity score (p = 0.10) and lower burden from aggression/agitation (p = 0.08). The differences were not statistically significant. Mean highest dosages per day (olanzapine equivalence) in the ChEI+ and ChEI- were 1.6 mg and 3.1 mg, respectively (p -value = 0.07).

Conclusion: The total off NPI score between the ChEI+ and ChEI- groups were not different, but there were report the trends toward lower depression severity score, aggression/agitation distress score, and antipsychotic dosages use in the ChEI+.

Keywords: Alzheimer's disease, Behavioral and psychological symptoms, Cholinesterase inhibitors, Depression, Aggression, Antipsychotics

J Med Assoc Thai 2016; 99 (4): 433-40

Full text. e-Journal: <http://www.jmatonline.com>

Early signs of Alzheimer's disease (AD) are memory and learning impairments. Other cognitive domains, such as visuospatial, language, and executive functions, are involved later during the course of the disease⁽¹⁾. Behavioral and psychological symptoms of dementia (BPSD) or neuropsychiatric symptoms are common reports in AD⁽²⁾. In Thailand, the incidences of BPSD are found in about 75% and 97.5% of patients with mild cognitive impairment (MCI) and AD, respectively. The evaluation of BPSD was concerning as a critical aspect of dementia diagnosis and management⁽³⁾. The most common BPSD are appetite change (57.5%), apathy (52.5%), and aberrant motor activity (52.5%)⁽⁴⁾. Patients with BPSD are associated with long-term hospitalization, more rapid rate of

cognitive and functional decline, increased medication, decreased quality of life of patients/caregivers⁽⁵⁻⁸⁾, increased caregiver burden⁽⁷⁻¹²⁾, and increased direct costs of care^(7,8). Preventive treatment of these symptoms can help alleviate caregiver burden⁽¹⁰⁾.

Recently, the causes of BPSD were reviewed from the genetic, neurobiological, patient profile (e.g., gender, age, premorbid personality), and other social factors (e.g., environment, caregiver characteristics)^(13,14). Imbalance of different neurotransmitters (acetylcholine, dopamine, noradrenaline, and serotonin) has been proposed as neurobiological mechanism of BPSD⁽¹⁵⁾. Cholinergic system dysfunction seems to play a major role in cognitive deficit and BPSD⁽¹⁶⁾.

Several classes of medications are used to treat BPSD. However, in most cases neither clear clinical guidelines nor FDA-approved indications are available^(14,17). Antipsychotics are frequently used to treat psychosis and aggression although there are concerns regarding cardiovascular adverse effects including death^(18,19). Cholinesterase inhibitors (ChEIs)

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such as donepezil, rivastigmine, and galantamine may improve cognitive function and reduce BPSD by increasing acetylcholine in central nervous system in AD patients⁽²⁰⁻²⁶⁾. However, effects of ChEIs on BPSD are modest and inconsistent⁽²⁷⁻²⁹⁾. The previous meta-analysis showed that their benefit was statistically significant but meaningful clinical benefit is questioned⁽³⁰⁾. To date, there is only one clinical study of ChEIs and BPSD in Thai population⁽²³⁾.

We hypothesized that ChEIs may improve BPSD in AD patients. We collected data in patients taking ChEIs and those who were not taking ChEIs. The primary objective was to compare the severity and distress of BPSD between these two groups. The secondary objective was to compare the highest dosages of antipsychotics, selective serotonin reuptake inhibitors/serotonin norepinephrine reuptake inhibitors (SSRIs/SNRIs), and trazodone needed in the past six months.

Material and Method

We enrolled Alzheimer patients from the Memory Clinic, Ramathibodi Hospital between December 2014 and February 2015. Eligible patients must have AD diagnosed by psychiatrists or geriatricians using National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria and mini mental status examination (MMSE) score below 24. They needed to either had continuously been taking ChEIs for at least six months or had never been on any ChEIs. We excluded patients with possible others types of neurocognitive disorder (delirium, vascular or mixed dementia, or other types of neurodegenerative dementia, etc.), prior history of major psychiatric disorders, history of cerebrovascular disorders, concomitant treatment with cognitive rehabilitation program, caregiver who could not provide behavioral and psychological symptoms of patients, and patients or caregiver who refused to give inform consent.

The protocol was approved by the Ethics Committee on Human Experimentation of Ramathibodi Hospital (IRB no. 08-57-54). Patients and caregivers were explained about research's objectives and methods. Inform consent was given by patient or caregiver (in case that patient was unable to do it).

Study design

The study was a cross-sectional study comparing BPSD measured by Neuropsychiatric

Inventory (NPI-Q) total score, NPI-distress, and NPI-severity between patients who received and did not receive ChEIs. Cholinesterase inhibitor group (ChEI+) consists of the patients who had continuously been taking donepezil, rivastigmine, or galantamine for at least six months. Non-cholinesterase inhibitor group (ChEI-) was a group of patients who had never received any ChEIs.

Demographic data were recorded including sex, age, level of education, years of education, duration of symptoms, underlying diseases, and used of psychotropic medications in the past six months. We used neuropsychiatry inventory questionnaire (NPI-Q)⁽³¹⁾, copyrighted by Jeffrey L Cummings, to evaluate severity and distress of BPSD in 12 domains, delusions, hallucinations, agitation or aggression, depression or dysphoria, anxiety, euphoria, apathy, disinhibition, irritability or lability, aberrant motor behavior, sleep disturbance, and appetite and eating disturbance. The NPI-Q was answered by main caregiver who could provide information about psychological and behavioral symptoms of patients. Severity was graded as 1 = mild (noticeable, but not a significant change), 2 = moderate (significant, but not a dramatic change), and 3 = severe (very mark or prominent, dramatic change). Caregiver distress was graded as 0 = not at all, 1 = minimally, 2 = mildly, 3 = moderately, 4 = severely, and 5 = very severely or extremely. Test-retest reliability of the NPI-Q was acceptable. The NPI-Q was developed and crossed validated with the standard NPI to provide brief assessment of BPSD in routine clinical practice. The prevalence of analogous symptoms reported on the NPI and NPI-Q differed on average by 5%, moderate or severe symptom ratings differed by less than 2%.

The severity of cognitive impairment was graded using MMSE-Thai 2002 version, developed by Institute of Geriatric Medicine, Department of Medical Services, Ministry of Public Health, Thailand⁽³²⁾. Cognitive assessment in MMSE consisted of orientation for time, orientation for place, registration, attention/calculation, recall, naming, repetition, verbal command, written command, writing, and visuoconstruction. Cut-off point in illiterate is 14 from 23 (sensitivity 35.4%, specificity 81.1%, positive predictive value 69.0%, negative predictive value 51.3%). Cut-off for elderly who graduated from primary school was 17 from 30 (sensitivity 56.6%, specificity 93.8%, positive predictive value 88.9%, negative predictive value 71.0%). Cut-off for elderly who graduated higher than primary school was 22 from 30 (sensitivity

92.0%, specificity 92.6%, positive predictive value 91.2%, negative predictive value 93.3%).

Furthermore, highest dosages needed of antipsychotics, SSRIs, SNRIs, and trazodone in the last six months were recorded. We used olanzapine for equivalent baseline of antipsychotics⁽³³⁾ and sertraline for equivalent baseline of SSRIs and SNRIs.

Statistical analysis

The sample size was calculated by PS Power and Sample Size Calculations Version 3.0 (Copyright © 1997-2009 by William D Dupont and Walton D Plummer). We used efficacy or probability of NPI improvement 70% from study of donepezil and 27% improvement of NPI score without donepezil to calculate sample size for the present study⁽²⁰⁾. The sample size required to detect the difference of NPI score were at least 40 cases (case 20 vs. control 20). The data analysis was performed using STATA version 13 (Chicago, IL, USA). The descriptive statistics were presented as mean ± standard deviation (SD) of effect of treatment, median (ranges), or count number and percentage. The Chi-square, Fisher's exact, or t-tests as appropriate were applied for comparative NPI total score and score in each domain between ChEI+ and ChEI- groups. We also used Chi-square, Fisher's exact, and t-tests to analyze NPI total score and interest factors/variables (sex, age, marital status, educational level, MMSE, and use of psychotropic medications). A *p*-value <0.05 is considered as statistically significant.

Results

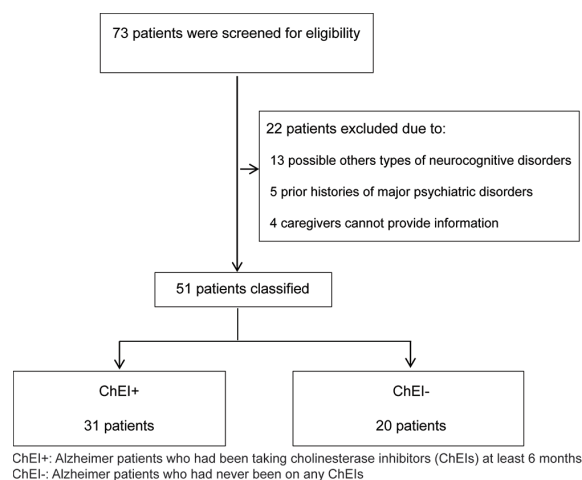
Seventy-three patients were screened and 22 patients were excluded (Fig. 1). Of the 51 AD patients, most of them were women (70.6%), had underlying hypertension (70.6%), and had completed secondary school (37.3%). About half were widowed due to deaths of their spouses (51%). Mean age at enrollment was 80.0 years. Mean MMSE was 12.9. Number of patients with dyslipidemia was significantly higher in ChEI- group (*p*-value = 0.04). Psychotropic drugs were used in 33 patients (64.71%). More specifically, there were uses of memantine in 16 (31.4%), antipsychotics in 19 (37.3%), SSRI/SNRI in 13 (25.5%), trazodone in five (9.8%), benzodiazepine in five (9.8%), and other psychotropic drugs in six (11.76%). Patients in ChEI+ group significantly had higher rate of memantine use (41.9%) compared with ChEI- group (15%) (*p*-value = 0.04). The other of baseline characteristics of sample were showed in Table 1.

Mean (±SD) of NPI total score in ChEI+ and ChEI- group were 15.68±14.31 and, 19.5±20.1 respectively. The difference was not statistically significant (*p* = 0.43). Further analysis also revealed no significant impact on NPI total score from other factors including sex, age, level of education and MMSE score, and the use of psychotropic drugs (*p*-value >0.05).

Analysis of NPI subdomains (see Table 2) showed that the mean of depression/dysphoria severity scores in ChEI+ and ChEI- group were 0.42±0.67 and 0.85±1.18, respectively. The difference did not reach statistical significance (*p*-value = 0.10). Moreover, we analyzed the differences in numbers of patients taking SSRI/SNRI and dosages of antidepressant between the two groups. No significant differences were found although there were slightly more patients taking SSRI/SNRI in the ChEI+ group (29% vs. 20%, *p*-value = 0.47).

The author found that caregivers in ChEI+ group had less burden from aggression/agitation than ChEI- group, although the difference did not reach statistical significance (*p*-value = 0.08). There were no statistically significant differences in numbers of patients taking antipsychotics and dosages of antipsychotics between the two groups. The numbers of patients using antipsychotics was slightly higher and mean dosage was lower in ChEI+ group.

Mean highest dosages per day (olanzapine equivalence) in the ChEI+ and ChEI- group were 1.6 mg and 3.1 mg, respectively. The difference was not statistically significant (*p* = 0.07). There were no



ChEI+: Alzheimer patients who had been taking cholinesterase inhibitors (ChEIs) at least 6 months
ChEI-: Alzheimer patients who had never been on any ChEIs

Fig. 1 Flow diagram of patient enrollment.

Table 1. Baseline of demographic data of patients

Demographic and clinical characteristics	ChEI+ (n = 31)	ChEI- (n = 20)	p-value
Sex, n (%)			
Male	8 (25.8)	7 (35.0)	0.48
Female	23 (74.2)	13 (65.0)	
Age (years), mean \pm SD	79.9 \pm 1.2	80.3 \pm 1.5	0.85
Status, n (%)			
Single	2 (6.5)	1 (5.0)	0.73
Married or live together	12 (38.7)	10 (50.0)	
Death of spouse	17 (54.8)	9 (45.0)	
Education level, n (%)			
None	3 (9.7)	2 (10.0)	0.77
Primary school	7 (22.6)	7 (35.0)	
Secondary school	12 (38.7)	7 (35.0)	
University	9 (29.0)	4 (20.0)	
Length of education (years), median (IQR)	12.0 (0, 20)	8.5 (0, 16)	0.13
Duration of clinical symptoms (years), median (IQR)	4.5 (1, 18)	3.0 (0.5, 12)	0.27
Underlying diseases, n (%)			
Hypertension	19 (61.3)	17 (85.0)	0.07
DM	8 (25.8)	8 (40.0)	0.29
Dyslipidemia	14 (45.2)	15 (75.0)	0.04
Coronary artery disease	4 (12.9)	3 (15.0)	0.83
Thyroid disease	0 (0)	1 (5.0)	0.21
MMSE, mean \pm SD	13.6 \pm 1.2	11.75 \pm 1.40	0.33
Psychotropic medications, n (%)			
Memantine	13 (41.9)	3 (15.0)	0.04*
Antipsychotics	12 (38.7)	7 (35.0)	0.80
SSRI/SNRI	9 (29.0)	4 (20.0)	0.47
Benzodiazepine	2 (6.6)	3 (15.0)	0.37
Trazodone	2 (6.5)	3 (15.0)	0.37
Others	4 (12.9)	2 (10.0)	1.00

ChEI+ = Alzheimer patients who had been taking cholinesterase inhibitors (ChEIs) at least 6 months; ChEI- = Alzheimer patients who had never been on any ChEIs; DM = diabetes mellitus; MMSE = Mini-Mental Status Examination; SSRI/SNRI = selective serotonin reuptake inhibitors/serotonin norepinephrine reuptake inhibitors
p-value <0.05 is considered as statistically significant

significant differences in mean dosages of sertraline equivalence and trazodone between ChEI+ and ChEI- group (see Table 3).

Discussion

The present study aimed to address the association between ChEIs and BPSD in AD patients. Although there was only one of previous study of ChEIs and BPSD in Thai population, but they included only patients who taking galantamine⁽²³⁾. The strength of the present study is clarified that our population was considerably homogeneous by excluded all patients with possible other types of neurological disorders. Therefore, only patients with diagnosed AD were included. The advantages of NPI-Q subdomains were used to identify the effect of ChEIs on specific

symptoms in different aspects, namely severity and distress to caregivers. This can help clinicians to focus on separate symptoms as targets of pharmacological treatment.

The authors found no significant correlation between the use of ChEIs and changes in overall BPSD measured by NPI total score. However, there seemed to be difference in subdomain depression severity score in favor of ChEIs used. This was consistent with other studies that ChEIs may improve depression^(34,35) and can be potential options for depression in AD^(36,37). This effect may be related to hippocampal neurogenesis in hippocampal serotonergic system by long-term used of cholinesterase inhibitor found in animal study^(30,38). Aggressive behaviors are believed to be secondary to cholinergic system disturbance in frontal and

Table 2. NPI severity and NPI distress subdomains between ChEI+ and ChEI- groups

NPI Subdomains	NPI severity score			NPI distress score		
	ChEI+ group (n = 31)	ChEI- group (n = 20)	<i>p</i> -value	ChEI+ group (n = 31)	ChEI- group (n = 20)	<i>p</i> -value
Delusions	0.61±0.92	0.65±0.88	0.89	0.74±1.46	0.75±1.21	0.98
Hallucinations	0.65±0.92	0.60±0.82	0.86	0.81±1.33	0.60±1.14	0.57
Agitation/aggression	0.77±0.99	0.95±1.05	0.55	0.77±1.20	1.55±1.85	0.08
Depression/dysphoria	0.42±0.67	0.85±1.18	0.10	0.52±0.96	0.75±1.37	0.48
Anxiety	0.45±0.72	0.65±0.88	0.38	0.32±0.60	0.75±1.25	0.11
Euphoria	0.23±0.50	0.30±0.73	0.67	0.10±0.30	0.20±0.52	0.38
Apathy	0.84±1.07	1.05±1.10	0.50	0.74±1.15	1.00±1.62	0.51
Disinhibition	0.81±0.98	0.60±0.10	0.45	0.71±1.00	0.65±1.18	0.85
Irritability/lability	0.74±0.89	1.20±1.11	0.11	0.71±1.31	1.10±1.37	0.27
Aberrant motor behavior	0.39±0.80	0.60±0.10	0.40	0.45±1.00	0.85±1.60	0.28
Sleep disturbance	1.29±1.07	1.30±1.17	0.98	1.39±1.70	1.40±1.73	0.98
Appetite-eating disturbance	0.68±1.01	0.70±1.03	0.94	0.55±1.00	0.45±1.00	0.73

NPI = neuro-psychiatric inventory; ChEI+ = Alzheimer patients who had been taking ChEIs at least 6 months; ChEI- = Alzheimer patients who had never been on any ChEIs

p-value <0.05 is considered as statistically significant

Table 3. Comparing of equivalent doses of olanzapine, sertraline, and trazodone between ChEI+ and ChEI- groups

Drugs (mg/day of equivalents dose)	ChEI+ (mean ± SD)	ChEI- (mean ± SD)	<i>p</i> -value
Olanzapine	1.6±0.4	3.1±0.8	0.07
Sertraline	58.3±7.2	56.3±6.3	0.86
Trazodone	75.0±35.4	50.0±43.3	0.55

ChEI+ = Alzheimer patients who had been taking ChEIs at least 6 months; ChEI- = Alzheimer patients who had never been on any ChEIs

p-value <0.05 is considered as statistically significant

temporal cortex⁽³⁹⁾. They are correlated with increased hospitalization⁽⁴⁰⁾ and caregiver burden⁽⁴¹⁾. Previous studies showed that rivastigmine⁽²⁷⁾ and galantamine^(23,27) can significantly improve aggression and agitation. Our study showed that patients in the ChEI+ group seemed to have lower agitation and aggression distress score which was consistent with previous studies. However, the difference did not reach statistical significance (*p*-value >0.05).

We also found that antipsychotic dosages (in olanzapine equivalence) in ChEI+ tended to be lower than ChEI- group although the difference was not statistically significant. In previous studies, symptomatic benefits in BPSD with rivastigmine, resulting in a reduction in concomitant psychoactive medication use^(34,35). There have been growing concerns regarding antipsychotic use in elderly, mainly related to the black box warning of cardiovascular events and sudden death. If the use of ChEIs can result in reduction

of antipsychotic dosage, the risk of cardiovascular deaths from antipsychotics can also be reduced.

However, we had some of limitations in our study. First, our sample size was only sufficient only detect modest benefit of ChEIs. A larger sample is needed in future to detect or compare between other drugs and BPSD in AD through the different outcomes. Second, this was a cross-sectional study. We can only demonstrate the association between ChEIs and BPSD in AD and outcome. It was difficult to draw conclusions in terms of cause and effect from the results. Third, the durations and dosages of each ChEIs were not recorded and analyzed. Last, the concomitant use of other medications, especially memantine, can be a significant confounder regarding NPI scores. Patients in the ChEI+ group were more likely to be on memantine at the same time. There were many possible reasons to why some patients were not taking ChEIs such as financial limitation, concerns for side effects, etc. The same

reasons could explain why there were also not prescribed memantine. It is difficult to conclude if any differences in BPSD subdomain scores were the effects of ChEIs alone, memantine alone or the combination of both.

Conclusion

There was no difference in NPI total score between the ChEI+ and ChEI- group. However, there were trends toward lower depression severity score, lower aggression/agitation distress score and decreased in antipsychotic dosages use in the ChEI+ group. A larger prospective study with concomitant medication stratification will provide a more definitive conclusion regarding effects of ChEIs on BPSD.

What is already known on this topic?

ChEIs such as donepezil, rivastigmine, and galantamine increased acetylcholine in central nervous system that may improve cognitive function and BPSD. Effects of ChEIs on BPSD in AD patients are modest and inconsistent. Their benefit was statistically significant but meaningful clinical benefit is questioned. Galantamine may be an effective treatment for improving psychotic, behavioral, and psychological symptoms in Thai patients with possible AD with or without cerebrovascular disease. Effects of other ChEIs or overall of ChEIs in Thai population are not evaluated.

What this study adds?

This study evaluated effects of all ChEIs on BPSD in Thai AD patients. ChEIs may effect on some symptoms of BPSD. There were trends toward lower depression severity score and lower aggression/agitation distress score. Tendency of decreased in antipsychotic dosages use in patients with ChEIs was found. However, effects on overall BPSD were not significant.

Acknowledgements

The present project was supported by Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Department of Psychiatry, Section of Clinical Epidemiology and Biostatistics, Faculty of Medicine, Ramathibodi Hospital, Mahidol University. The authors would like to thank Dr. Thanavadee Prachason, Dr. Pichai Ittasakul, and Dr. Iyavut Thaipisuttikul, Faculty of Medicine, Ramathibodi Hospital, Mahidol University for language check and preparation some part of manuscript.

Potential conflicts of interest

None.

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ยาด้านเอนไซม์โคลีนเอสเตอเรสกับปัญหาด้านพฤติกรรมและอาการทางจิตในผู้ป่วยโรคอัลไซเมอร์

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วัตถุประสงค์: ศึกษาผลของยาด้านเอนไซม์โคลีนเอสเตอเรส (cholinesterase inhibitors, ChEIs) กับปัญหาพฤติกรรมและจิตใจในผู้ป่วยโรคอัลไซเมอร์ และเปรียบเทียบขนาดยารักษาโรคจิตและยาด้านเศร้าที่ใช้รักษาปัญหานี้ในผู้ป่วยที่ได้รับ ChEIs

วัสดุและวิธีการ: ศึกษาผู้ป่วยโรคอัลไซเมอร์จากคลินิกความจำ โรงพยาบาลตราดที่ 1 ที่ได้รับยาด้านเอนไซม์โคลีนเอสเตอเรสอย่างน้อย 6 เดือน (ChEI+) และกลุ่มที่ไม่เคยได้รับกลุ่มยาด้านเอนไซม์โคลีนเอสเตอเรส (ChEI-) โดยผู้ป่วยทั้งสองกลุ่มจะได้รับการประเมิน cognitive function โดยใช้ mini-mental state examination (MMSE) ประเมินปัญหาพฤติกรรมและจิตใจโดยใช้ Neuropsychiatric Inventory-Questionnaire (NPI-Q) และประเมินขนาดยาจิตเวช

ผลการศึกษา: ผู้ป่วยที่เข้าเกณฑ์การศึกษาทั้งหมดจำนวน 51 ราย ผู้ป่วย 31 ราย ในกลุ่มที่ได้รับยาด้านเอนไซม์โคลีนเอสเตอเรส (ChEI+) และ 20 ราย ในกลุ่มที่ไม่เคยได้รับยา (ChEI-) ไม่พบว่ามีความแตกต่างของคะแนนประเมินโดย MMSE ระหว่างทั้งสองกลุ่ม โดยมีค่าเฉลี่ยและค่าเบี่ยงเบนมาตรฐานเท่ากับ 13.6 ± 1.2 และ 11.75 ± 1.4 ตามลำดับ (p -value = 0.33) ไม่พบความแตกต่างของค่า NPI รวมเฉลี่ย ระหว่างกลุ่มที่ได้รับยาด้านเอนไซม์โคลีนเอสเตอเรส (ChEI+) และไม่ได้รับ (ChEI-) อย่างมีนัยสำคัญทางสถิติ โดยค่า NPI เท่ากับ 15.68 ± 14.31 และ 19.5 ± 20.19 ตามลำดับ (p -value = 0.43) พบว่ากลุ่มที่ได้รับยา ChEI+ มีคะแนนด้านความรุนแรงของอาการซึมเศร้าต่ำกว่า (p -value = 0.10) และอาการก้าวร้าว/สับสน กระสับกระส่ายต่ำกว่า (p -value = 0.08) ขนาดยารักษาโรคจิตต่อวัน (เมื่อเทียบกับ olanzapine) ของกลุ่มที่ได้รับยา ChEI+ และไม่เคยได้รับยา ChEI- ไม่มีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติ โดยมีขนาดเท่ากับ 1.6 mg และ 3.1 mg ตามลำดับ (p -value = 0.07)

สรุป: ไม่พบความแตกต่างของคะแนนรวมประเมินปัญหาพฤติกรรมและจิตใจโดย NPI ระหว่างกลุ่มที่ได้รับยาด้านเอนไซม์โคลีนเอสเตอเรส (ChEI+) และไม่เคยได้รับ (ChEI-) พบแนวโน้มของความรุนแรงของอาการซึมเศร้าและอาการก้าวร้าว อาการสับสน กระสับกระส่าย รวมทั้งขนาดยาในการรักษาอาการทางจิตเวช ในกลุ่มที่ได้รับยาด้านเอนไซม์โคลีนเอสเตอเรส (ChEI+) ที่ต่ำกว่ากลุ่มที่ไม่เคยได้รับ (ChEI-)