

Anticholinergics and Benzodiazepines on Cognitive Impairment among Elderly with Alzheimer's Disease: a One year Follow-Up Study

Rewadee Jenraumjit

Chiang Mai University

Surarong Chinwong

Chiang Mai University

Dujrudee Chinwong

Chiang Mai University

Tipaporn Kanjanarach

Khon Kaen University Faculty of Pharmaceutical Sciences

Thanat Kshetradat

Maharaj Nakorn Chiang Mai Hospital

Tinakon Wongpakaran

Chiang Mai University Faculty of Medicine

Nahathai Wongpakaran (✉ nahathai.wongpakaran@cmu.ac.th)

Chiang Mai University Faculty of Medicine <https://orcid.org/0000-0001-8365-2474>

Research note

Keywords: anticholinergics, acetylcholine esterase inhibitors, prescription, Alzheimer's disease, cognition

Posted Date: December 3rd, 2019

DOI: <https://doi.org/10.21203/rs.2.17956/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Version of Record: A version of this preprint was published on January 2nd, 2020. See the published version at <https://doi.org/10.1186/s13104-019-4874-z>.

Abstract

Objective Age-associated decline in central cholinergic activity makes older adults susceptible to harmful effects of anticholinergics (ACs). Evidence exists of an association between effects of AC medications on cognition. This retrospective cohort study examines how ACs affect cognition among older adults with Alzheimer's disease (AD) who received acetylcholine esterase inhibitors (AChEIs) over the course of 12 months.

Results A total of 133 (80% women, mean age 78.38 years, SD 7.4) were recruited. No difference in sex, age and comorbid diseases was observed between participants who took ACs, Benzodiazepines (BZDs) and AChEIs. The most common prescribed ACs was quetiapine, being used for behavioral and psychological symptoms (BPSD). Multilevel analysis showed that the change of mental state examination scores were significantly predicted in the group using ACs ($t(169), -2.52, p = .020$) but not with the groups using BZD ($t(162), 0.84, p = .440$). Evidence showed that older adults with Alzheimer's disease and exposed to ACs exhibited lower global cognitive scores than those without AC exposure. Using ACs could be a trade-off between controlling BPSD and aggravating cognitive impairment. Highlighting the awareness of the potential anticholinergic effect is important and may be the best policy.

Introduction

Dementia is a common health problem among the elderly. In 2010, five millions of people in the US experience Alzheimer's disease (AD) [1]. In Japan, the prevalence of dementia according to the DSM-IV or DSM-III-R criteria was 3.8% to 11.0% among people aged 65 years old and older [2]. In Thailand, a national survey of 4,048 elderly adults (age 60 and older) reported the prevalence of dementia was 3.3% [3]. Dementia prevalence among Thai elderly adults increased with age [4].

Alzheimer's Disease (AD) is the most common type of dementia. In patients with AD, the most destroyed neuronal cells are cholinergic neurons causing interruption in cholinergic transmission resulting in cognitive impairment [5–7]. Acetylcholine esterase inhibitors (AChEIs) help inhibiting cholinesterase enzyme, resulting in an increase of cholinergic transmission at the synapses. Longitudinal studies have shown that AChEI, particularly higher doses, produced better longitudinal cognitive outcomes [8, 9].

That anticholinergics (ACs) should not be recommended among the elderly is widely known [10–12], and, in particular, patients with dementia [13] because significant detrimental effects of ACs on cognition have been clearly demonstrated [14–16].

Despite the fact that robust evidence exists regarding how ACs can affect both cognition and AChEIs per se due to pharmacodynamics interactions, based on their opposing mechanisms of action [17], most were from cross-sectional and short term follow-up study. A recent 36-month follow-up research showed that high anticholinergic burden negatively affected the treatment response to cholinesterase inhibitors and that an average ACB score >3 was an independent prognostic factor for delirium or mortality among

dementia patients[18]. However, no clear relationships between ACs and the change of cognition were noted in this study.

In addition to ACs, benzodiazepines (BZD), is considered a harmful medication and recommended by the American Geriatric Society to avoid among adults beginning 65 years of age, particularly. It should also be avoided among older adults with dementia, delirium or cognitive impairment due to its worsening cognitive impairment and increased risks of delirium, falls, fractures and accidents [19]. However it can still be found being used among geriatric patients [20].

To focus on using both ACs and/or BZDs among the elderly with dementia, related studies have revealed that a small number of studies investigating the effect of ACs on cognition in longitudinal design suggested a deleterious effect of anticholinergic exposure on long term cognitive function [21]. However, longitudinal studies investigating both ACs and BZDs on cognition with individuals with dementia receiving AChEIs are relatively few. To elucidate these relationships, the aim of this study was to investigate any association between ACs and BZDs on cognition among the elderly with AD receiving these medications and AChEIs in a longitudinal fashion, in addition to exploring the prevalence of using these medications among old aged patients with AD.

Methods

The study was approved by an independent Ethics Committee for Human Research, Faculty of Medicine, Chiang Mai University, Thailand. This was a longitudinal study conducted in 2018 by reviewing outpatient medical records of elderly Thai patients who had experienced AD and were followed up in a university hospital of northern Thailand from 2015 to 2016. The medical records were recruited by the Department of Medical Informatics to identify medical records with ICD–10 diagnoses of codes F00. The inclusion criteria for the present study included 1) the patients who were 60 years old and above, 2) all patients diagnosed by physicians specialized in AD and 3) having a Thai mental status examination score (TMSE) [22, 23] regularly during each visit.

The baseline was determined when the patient received AChEIs and every four months (\pm 3 to 4 weeks), patients were assessed using the TMSE Data including demographic information, i.e., sex, age, underlying diseases etc., and the names of all oral medications prescribed in one year including AChEIs, ACs and BZDs.

Evaluating anticholinergic effects among medications

Anticholinergic effects were evaluated by the Anticholinergic Cognitive Burden (ACB) [24] which describes all possible anticholinergics including those listed with a score of 1; definite anticholinergics including those listed with a score of 2 or 3. An example of a drug in category ACB score 1 was diazepam, score 2 was cyproheptadine and score 3 was amitriptyline.

Statistical analysis

Descriptive data were analyzed in percentages, means and standard deviations (SD). The relationship between prescribing ACs, BZDs and comorbidities, was determined with the Chi-square test. The relationship between prescribing ACs and BZDs and the change of TMSE scores over 12 months was determined using a hierarchical linear model (multilevel analysis). Two-tailed tests were used to determine the statistical significance at p-value less than 0.05. The data were analyzed using IBM SPSS, Version 22.0 (SPSS Inc., Chicago, IL, USA), and longitudinal data analyzed using HLM, Version 8 (Scientific Software International, Inc., Chicago, IL, USA)

Results

One hundred eighty-four medical records were analyzed. A total of 133 (80% women, mean age 78.38 years, SD 7.4) met the criteria for the study. Table 1 shows the demographic data, severity of dementia by TMSE scores and comorbid physical diseases. No statistical difference was found between the groups with or without ACs and the groups with or without BZDs according to age, sex, health privilege, ICD-10 diagnosis and comorbidities. TMSE scores significantly differed at baseline (time 1) between AC and nonAC group, unlike BZD groups. The difference of TMSE scores between groups were observed at time 3 and 4 (at months 8 and 12).

The prevalence of anticholinergic drugs prescription was 31.6%. The common ACs with an anticholinergic burden and doses are shown in Table 2. According to Table 2, the most frequent prescription among the anticholinergics with an ACB score of 3 was quetiapine while the most frequent for the anticholinergics with ACB score of 1 was Aripiprazole. The other ACs prescribed included risperidone, cetirizine, clozapine, codeine, desloratadine, loratadine and olanzapine. For AChEIs, the most commonly prescribed was rivastigmine, while lorazepam was the most common for BDZ (see Table S1 in supplement). Only five (3.8%) of the patients received both ACs and BZD.

The fixed effect from the hierarchical linear modeling showed that the anticholinergic group changed more significantly in the slope of TMSE than the nonanticholinergic group ($b = -2.519$, 95% CI 3.99, 4.639) but not with benzodiazepine ($b = -1.662$, 95% CI -2.232, 5.557). Likewise, advancing age predicted a significantly negative slope of TMSE ($b = -.193$, 95% CI -.327, -.060). However, time was not a predictor of TMSE score (Table 3).

Discussion

To the best of our knowledge, this study was the first to report on the AC prescription among Thai patients with AD including the prevalence of AC prescription, the concomitant use with AChEIs and the association with adverse effects on cognition among elderly Thais with AD.

The authors found a high rate of AC drugs among patients with AD (31.6%) even though this was lower than that in other studies ranging from 46.83% to 65.8 [25, 26]. The reason could be that our participants were collected from tertiary care, a university hospital of northern Thailand. This group of patients had

concomitant medications from other secondary care centers, in which we have not yet had an effective accessible system among hospitals and other health care providers. This gap may have allowed unnecessary and unthoughtful prescription of ACs to take place.

The present study showed adverse effects on cognition among the elderly with AD. TMSE score was lower with statistical significance among patients that were AC concomitant even though they received AChEIs. The study confirmed the negative predictors of TMSE score that could be predicted by advanced age and AC use. These were in line with a 2-year longitudinal study of the elderly in that the use of AC medication with definite anticholinergic effects was associated with a greater decline in MMSE score than not taking anticholinergics, whereas the use of possible anticholinergics at baseline was not associated with further decline [16]. Advancing age was, as expected, another predictor for longitudinal outcome of cognition, as found in related research [9]. Notably, not only did the anticholinergic effect have a direct impact on cognition, a pharmacodynamic drug interaction between AChEIs and AC also nullified the benefit of AChEI at the neuronal level. Therefore, clinicians should be more aware of using ACs among patients receiving AChEIs because it may not only worsen cognition but also become a huge loss regarding economic aspects.

One important point to be noted is that the most common AC drug used was quetiapine, which is mostly related to remedy behavioral and psychological symptoms of dementia (BPSD). This finding was in line with related studies in that quetiapine was the most used drug among patients with dementia and was harmful to cognitive outcome [27, 28]. For what reason, quetiapine has become commonly prescribed for clinicians remains unclear and may not be an easy answer to find using this type of research design. Several atypical antipsychotic drugs can be used among patients with disturbed symptoms of dementia. Aripiprazole and risperidone may be better than quetiapine in terms of anticholinergic effects, but provide more risk of extrapyramidal side effects. In complicated situations of the patient, clinicians should individualize the assessment of safety risks against expected benefits when prescribing atypical antipsychotics. Therefore, it may be difficult to simply suggest not using quetiapine with this situation. Consistent with the recent network meta-analysis, the study revealed a trade-off between the effectiveness and safety of atypical antipsychotics in the treatment of BPSD and assures that a single most effective and safe treatment option does not exist [29].

Regarding BZD, the present study showed that only a small percent of the patients received a combination between both ACs and BZD, which was lower than a related study in a large population (approximately 6%) [30]. A recent cohort study suggested that ACs or BZDs could increase dementia risk at 10-year follow-up. By that an ACB score of 3 was found, but neither BZDs nor ACB score 1 or 2 medications was associated with dementia, particularly in those with good baseline cognitive function [31]. According to a related study, our result demonstrated that BZDs use was not associated with a negative predictor of TMSE score. This finding was also supported by a longitudinal study in that MMSE was not associated with BZD use in the models [32]. Considering a relatively small sample size, we cannot conclude that no long-term effect exists of BZD concerning cognition, on the contrary,

prescribing long term BZDs among the elderly regardless concomitant with AC or no AC should be cautious, as it remains potentially inappropriate due to other harmful effects of BZD [33].

In conclusion, despite the fact that AC medication should be avoided among patients with dementia, it may not be easy to avoid using medication with anticholinergic effects especially atypical antipsychotic to deal with BPSD. AC drugs and age were the strong predictors of negative cognitive outcomes in the long run. Awareness of potential anticholinergic risk of medication seems to be the best policy. In a setting where a geriatric physician or nurse is lacking, the incidence of prescribing such medication is relative high. Therefore, maintaining awareness and monitoring whenever these anticholinergic drugs are used is important regardless of what use they are for.

Limitations

The limitation in the method used made information regarding the patients accessed in other health care centers unavailable. In addition, over-the-counter medications were unreported. Moreover, being prescribed a medication does not mean that the patients have actually taken them. Finally, further prospective studies with larger populations should be warranted to demonstrate proportion and the impact of AC use.

Abbreviations

AC Anticholinergic

ACB Anticholinergic Cognitive Burden

AChEI Acetylcholine Esterase Inhibitor

AD Alzheimer's disease

ARS Anticholinergic Risk Scale

BPSD Behavioral and Psychological Symptoms of Dementia

BZD Benzodiazepine

TMSE Thai Mental Status Examination

Declarations

Declarations Funding

The study was funded by the Faculty of Pharmacy, Chiang Mai University.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request as data sharing is subject to the Ethics Office for approval.

Ethics approval and consent to participate

This project was approved by the IRB of the Faculty of Medicine, Chiang Mai University. All participants were informed about the study and provided informed consent.

Authors' contributions

RJ, SC, DC, TK, TK, and NW designed the conceptualization. RJ, TW made data cleansing. KT, RW, SC, DC, TK, NW, and TW analyzed and interpreted the data and were major contributors in writing the manuscript. All authors read and approved the final manuscript.

Consent for publication

Consent for publication is not applicable.

Competing interests

The authors declare they have no competing interests.

Acknowledgements

No acknowledgements are made.

References

1. Thies W, Bleiler L: *Alzheimer's Association 2011 Alzheimer's disease facts and figures. Alzheimers Dement* 2011, 7:208–244.
2. Kasai M, Nakamura K, Meguro K: *[Alzheimer's disease in Japan and other countries: review of epidemiological studies in the last 10 years]. Brain Nerve* 2010, 62:667–678.
3. Jitapunkul S, Kunanusont C, Phoolcharoen W, Suriyawongpaisal P: *Prevalence estimation of dementia among Thai elderly: a national survey. J Med Assoc Thai* 2001, 84:461–467.
4. Jitapunkul S, Chayovan N, Kespichaywattana J: *National policies on ageing and long-term care provision for older persons in Thailand. In Ageing and Long-Term Care: National Policies in the Asia-*

Pacific. Edited by Phillips DR, Chan ACM. Singapore: Bestprint Printing Co.; 2002: 181–213

5.Evans JG, Williams TF, Beattie BL, Michel J-P, Wilcock GK: *Oxford Textbook of Geriatric Medicine*. Great Clarendon Street, Oxford OX2 6DP: Oxford University Press; 2000.

6.Mufson E, Counts S, Perez S, Ginsberg S: *Cholinergic system during the progression of Alzheimer's disease: therapeutic implications*. *Expert Rev Neurother* 2008, 8:1703–1718.

7.Mesulam M: *The cholinergic lesion of Alzheimer's disease: pivotal factor or side show? Learn Mem* 2004, 11:43–49.

8.Boccardi V, Baroni M, Smirne N, Clodomiro A, Ercolani S, Longo A, Ruggiero C, Bruni AC, Mecocci P: *Short-Term Response is not Predictive of Long-Term Response to Acetylcholinesterase Inhibitors in Old Age Subjects with Alzheimer's Disease: A "Real World" Study*. *J Alzheimers Dis* 2017, 56:239–248.

9.Wattmo C, Wallin AK, Londos E, Minthon L: *Predictors of long-term cognitive outcome in Alzheimer's disease*. *Alzheimers Res Ther* 2011, 3:23.

10.Rudolph J, Salow M, Angelini M, McGlinchey R: *The anticholinergic risk scale and anticholinergic adverse effects in older persons*. *Arch Intern Med* 2008, 168:508–513.

11.Tune L: *Anticholinergic effects of medication in elderly patients*. *J Clin Psychiatry* 2001, 62 Suppl 21:11–14.

12.Mintzer J, Burns A: *Anticholinergic side-effects of drugs in elderly people*. *J R Soc Med* 2000, 93:457–462.

13.Johnell K, Fastbom J: *Concurrent use of anticholinergic drugs and cholinesterase inhibitors: register-based study of over 700,000 elderly patients*. *Drugs Aging* 2008, 25:871–877.

14.Andrade C: *Anticholinergic Drug Exposure and the Risk of Dementia: There Is Modest Evidence for an Association but Not for Causality*. *J Clin Psychiatry* 2019, 80.

15.Carrière I, Fourrier-Reglat A, Dartigues J, Rouaud O, Pasquier F, Ritchie K, Ancelin M: *Drugs with anticholinergic properties, cognitive decline, and dementia in an elderly general population: the 3-city study*. *Arch Intern Med* 2009, 169:1317–1324.

16.Fox C, Livingston G, Maidment ID, Coulton S, Smithard DG, Boustani M, Katona C: *The impact of anticholinergic burden in Alzheimer's dementia-the LASER-AD study*. *Age Ageing* 2011, 40:730–735.

17.Pasqualetti G, Tognini S, Calsolaro V, Polini A, Monzani F: *Potential drug-drug interactions in Alzheimer patients with behavioral symptoms*. *Clin Interv Aging* 2015, 10:1457–1466.

18.Ah YM, Suh Y, Jun K, Hwang S, Lee JY: *Effect of anticholinergic burden on treatment modification, delirium and mortality in newly diagnosed dementia patients starting a cholinesterase inhibitor: A*

population-based study. *Basic Clin Pharmacol Toxicol* 2019, 124:741–748.

19.Picton JD, Marino AB, Nealy KL: *Benzodiazepine use and cognitive decline in the elderly. Am J Health Syst Pharm* 2018, 75:e6-e12.

20.Roux B, Sirois C, Simard M, Gagnon M-E, Laroche M-L: *Potentially inappropriate medications in older adults: a population-based cohort study. Fam Pract* 2019.

21.Andre L, Gallini A, Montastruc F, Montastruc J-L, Piau A, Lapeyre-Mestre M, Gardette V: *Association between anticholinergic (atropinic) drug exposure and cognitive function in longitudinal studies among individuals over 50 years old: a systematic review. Eur J Clin Pharmacol* 2019, 75:1631–1644.

22.Committee TTBF: *Thai Mental State Examination (TMSE) Siriraj Med J* 1993 45 359–374

23.Wangtongkum S, Sucharitkul P, Silprasert N, Intrachak R: *Prevalence of dementia among population age over 45 years in Chiang Mai, Thailand. J Med Assoc Thai* 2008, 91:1685–1690.

24.Boustani M, Campbell N, Munger S, Maidment I, Fox C: *Impact of anticholinergics on the aging brain: a review and practical application. Aging Health* 2008, 4:311–320.

25.Lee EK, Lee YJ: *Prescription patterns of anticholinergic agents and their associated factors in Korean elderly patients with dementia. Int J Clin Pharm* 2013, 35:711–718.

26.Chatterjee S, Bali V, Carnahan RM, Chen H, Johnson ML, Aparasu RR: *Anticholinergic Medication Use and Risk of Fracture in Elderly Adults with Depression. J Am Geriatr Soc* 2016, 64:1492–1497.

27.Valladales-Restrepo LF, Duran-Lengua M, Machado-Alba JE: *Potentially inappropriate prescriptions of anticholinergics drugs in Alzheimer's disease patients. Geriatr Gerontol Int* 2019, 19:913–917.

28.Rockwood K, Walsh R, Martin E, Darvesh S: *Potentially procholineric effects of medications commonly used in older adults. Am J Geriatr Pharmacother* 2011, 9:80–87.

29.Yunusa I, Alsumali A, Garba AE, Regestein QR, Eguale T: *Assessment of Reported Comparative Effectiveness and Safety of Atypical Antipsychotics in the Treatment of Behavioral and Psychological Symptoms of Dementia: A Network Meta-analysis. JAMA network open* 2019, 2:e190828-e190828.

30.Puustinen J, Nurminen J, Vahlberg T, Lyles A, Isoaho R, Räihä I, Kivelä S-L: *CNS medications as predictors of precipitous cognitive decline in the cognitively disabled aged: a longitudinal population-based study. Dement Geriatr Cogn Dis Extra* 2012, 2:57–68.

31.Grossi CM, Richardson K, Fox C, Maidment I, Steel N, Loke YK, Arthur A, Myint PK, Campbell N, Boustani M, et al: *Anticholinergic and benzodiazepine medication use and risk of incident dementia: a UK cohort study. BMC Geriatr* 2019, 19:276.

32.Törmälehto S, Martikainen J, Bell JS, Hallikainen I, Koivisto AM: *Use of psychotropic medications in relation to neuropsychiatric symptoms, cognition and functional performance in Alzheimer's disease over a three-year period: Kuopio ALSOVA study. Int Psychogeriatr* 2017, 29:1723–1733.

33.Panel BtAGSBCUE: *American Geriatrics Society 2019 Updated AGS Beers Criteria® for Potentially Inappropriate Medication Use in Older Adults. J Am Geriatr Soc* 2019, 67:674–694.

Tables

Table 1. Sociodemographic characteristics and clinical data of the sample

| Characteristics | N (%) or Mean(SD) All (n=133) | AC | | BZD | |
|-------------------------|----------------------------------|---------------------------|---------------------------|------------------------|---------------------------|
| | | Yes (n=42) | No (n=91) | Yes (n=9) | No (n= 124) |
| Age (year) | 78.38(7.4), range(60-94) | 77.88(8.04) | 78.60(7.18) | 79.67(7.12) | 78.28 (7.48) |
| Sex, female | 80(60.2) | Range (60-94) 28(66.7) | Range (63-94) 52(57.1) | Range 70-93 6(66.7) | Range (60-94) 74(59.7) |
| Health privilege | | | | | |
| Universal coverage | 1(0.8) | 1(2.4) | 0(0.0) | 0(0.0) | 1 (0.8) |
| Government | 120(90.2) | 39(92.9) | 81(89.0) | 9 (100.0) | 111 (89.5) |
| Social | 1(0.8) | 0(0) | 1(1.1) | 0(0.0) | 1 (0.8) |
| Others | 11(8.3) | 2(4.8) | 9(9.9) | 0(0.0) | 11 (8.9) |
| ICD-10 Diagnosis | | | | | |
| F000 | 22(16.5) | 7 (16.7) | 16 (17.6) | 2 (22.2) | 21 (16.9) |
| F001 | 96(72.2) | 31 (73.9) | 72 (79.1) | 6 (66.7) | 97 (78.2) |
| Others | 15(11.3) | 4 (9.4) | 3 (3.3) | 1 (11.1) | 6 (4.9) |
| Drugs used | | | | | |
| Anticholinergics | 42 (31.6) | - | - | - | - |
| Benzodiazepines | 9(6.8) | - | - | - | - |
| Comorbidity | 116 (87.2) | 41 (97.6) | 75 (82.4) | 8 (88.9) | 108 (87.1) |
| Infection | 2(1.5) | 1 (2.4) | 1 (1.1) | 0 (0.0) | 2 (1.6) |
| Cancer | 2(1.5) | 1 (2.4) | 1 (1.1) | 0 (0.0) | 2 (1.6) |
| Hematology | 5(3.8) | 2 (4.8) | 3 (3.3) | 0 (0.0) | 5 (4.0) |
| Metabolic disease | 68(51.1) | 22 (52.4) | 46 (50.5) | 4 (44.4) | 64 (51.6) |
| Psychiatry | 18(13.5) | 8 (19.0) | 10 (11.0) | 2 (22.2) | 16 (12.9) |
| Neurology | 30(22.6) | 12 (28.6) | 18 (19.8) | 0 (0.0) | 30 (24.2) |
| Eyes and Ears | 3 (2.3) | 1 (2.4) | 2 (2.2) | 0 (0.0) | 3 (2.4) |
| Cardiovascular | 87(65.4) | 28 (66.7) | 59 (64.8) | 5 (55.6) | 82 (66.1) |
| Respiratory | 3(2.3) | 2 (4.8) | 1 (1.1) | 1 (11.1) | 2 (1.6) |
| Gastrointestinal | 4(3.0) | 1 (2.4) | 3 (3.3) | 0 (0.0) | 4 (3.2) |
| Skin | 0(0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Musculoskeletal | 23(17.3) | 14 (33.3) | 9 (9.9) [†] | 2 (22.2) | 21 (16.9) |
| Genitourinary | 16(12.1) | 4 (9.8) | 12 (13.2) | 0 (0.0) | 16 (13.0) |
| TMSE score | | | | | |
| Visit 1 | 18.56(6.71) | 16.38(7.39) | 19.72(6.71)** | 15.80(6.93) | 19.01(6.87) |
| Visit 2 | 18.97(6.59) | 17.21(6.71) | 19.49(6.82) | 17.67(6.16) | 18.78(6.91) |
| Visit 3 | 20.06(5.54) | 18.26(6.21) | 21.45(4.86)** | 18.78(6.91) | 19.88(4.55) |
| Visit 4 | 19.96(6.74) | 16.96(7.08) | 22.46(5.69)** | 14.50(9.22) | 20.80(6.36)* |

AC = Anticholinergic , BZD = Benzodiazepine, SD = standard deviation, ICD-10= International Classification of Disease - 10th edition , F000 = Dementia in Alzheimer’s disease with early onset, F001 = Dementia in Alzheimer’s disease with late onset, TMSE = Thai Mental State Examination

*p<.05, **p<.01

† significant difference between group ($\chi^2(1) = 11.04, p = .002$)

Table 2. Anticholinergic medications with an ACB score, and doses (n =42)

| Medicine | ACB score | N (%) of cases | Dose | | N (%) |
|--------------|-----------|----------------|---------------------|------------------|----------|
| | | | Mean(SD), median | Dose(mg) per day | |
| Quetiapine | 3 | 23(54.8) | 24.54 (14.21), 25.0 | 6.25 | 3(7.1) |
| | | | | 12.50 | 13(31.0) |
| | | | | 25.00 | 17(40.5) |
| | | | | 50.00 | 8(19.0) |
| Aripiprazole | 1 | 7 (16.7) | 3.75(1.46), 5.0 | 1.25 | 2(10) |
| | | | | 2.50 | 7(35) |
| | | | | 5.00 | 11(55) |
| Trazodone | 1 | 3(7.1) | 62.5(13.36), 62.50 | 50.00 | 4(50.0) |
| | | | | 75.00 | 4(50.0) |
| Hydroxyzine | 3 | 2(4.8) | 3.67(.75), 3.5 | 3.00 | 3(50.0) |
| | | | | 4.00 | 1(16.7) |
| | | | | 4.50 | 2(33.3) |
| Others* | - | 7(16.6) | - | - | - |

*including risperidone, cetirizine, clozapine, codeine, desloratadine, loratadine, and olanzapine

Table 3. Predictors for TMSE scores

| Parameter | Estimate | Std. Error | df | t | p-value | 95% Confidence Interval | |
|------------------|----------|------------|--------|-------|---------|-------------------------|-------------|
| | | | | | | Lower Bound | Upper Bound |
| Intercept | 29.93 | 5.80 | 130.06 | 5.16 | 0.000 | 18.45 | 41.41 |
| Time | 0.17 | 0.16 | 273.54 | 1.08 | .282 | -0.14 | .47 |
| Male | -1.34 | 1.02 | 133.36 | -1.32 | .191 | -0.67 | 3.34 |
| Age | -0.194 | .07 | 135.61 | -2.88 | .005 | -0.33 | -0.07 |
| BDZs | -1.66 | 1.97 | 127.16 | 0.84 | .400 | -2.23 | 5.56 |
| Anticholinergics | -2.52 | 1.12 | 129.04 | -2.35 | .020 | 0.400 | 4.64 |

SD = standard deviation, TMSE = Thai Mental State Examination, BZD = Benzodiazepine

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [TableS1.docx](#)