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Vulnerable Strata to Non-Adherence and Overuse in Treatment for Patients with Cognitive Impairment

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ABSTRACT

Background and purpose: Appropriate medication treatment could enable both cognitively impaired patients and caregivers to hold on their cognitive functioning and quality of life. Thus, medication management and the factors influencing how management for this condition is carried out must be identified. In this study we aimed to evaluate the frequency of medication nonadherence (MNA) or drug overuse for cognitive impairment (DOC) and to extract significant variables, including the demographic and social characteristics, vascular risk factors, and cognitive status, for the diagnosis of MNA and DOC in Korean patients.
Methods: We investigated patients aged over 50 years between March 2019 and June 2019 via the cognitive enHancement of patIents with acQuired cognitive impairment (HIQ) campaign. MNA was defined as a participant who was classified as having cognitive impairment but did not take any cognition-related drugs, whereas DOC was defined as a participant who had normal cognition but was taking cognition-related drugs.
Results: We included 10,767 patients. The MNA group consisted of 337 participants, whereas the DOC group comprised 1,107 participants. The factors that could differentiate the MNA group from the normal-behavior group were age, education, sex, and the total Korean version of Mini-Mental State Examination (K-MMSE) score. The factors that could differentiate the DOC group from the normal medication-behavior group were age, sex, residential distinction, experience of a dementia screening test, and the total K-MMSE score.
Conclusions: The underlying factors contributing to inadequate dementia-medication management must be understood, and intervention or support is needed to enable safe medication management.

Keywords: Cognitive Impairment; Medication Adherence; Patient Compliance; Treatment Adherence and Compliance; Health Care System

INTRODUCTION

Dementia is characterized by a decline in memory, language, problem solving, and other cognitive functions that affect a person's ability to carry out everyday activities. Its most common cause is neurodegenerative disease, among which Alzheimer's disease (AD) accounts for the highest proportion.[1] Although no disease-modifying drugs are currently

available for dementia, patients with AD are advised to continue pharmacological treatment with effective doses of cholinesterase inhibitors (ChEI; donepezil, galantamine, and rivastigmine) or an N-methyl D-aspartate (NMDA) antagonist, such as memantine. Appropriate and steady medication treatment can delay institutionalization and could improve cognitive functioning to promote a better quality of life for both patients and caregivers while simultaneously reducing health-care expenditure.[2] However, adherence to medication is reportedly low among patients with dementia. In an Austrian cohort study, 34.0% and 58.5% of patients stopped taking the initially prescribed antidementia drugs after 6 and 12 months of therapy, respectively[3]. A systematic review of medication nonadherence (MNA) found that the adherence rate for patients with cognitive impairment was only 10.7%–38.0%.[4] MNA may lead to poor therapeutic outcomes, including poor disease control, increased hospitalizations, disability, and early death.[4,5] In contrast, some patients abuse prescription drugs because of anxiety, concerns, and fear of dementia. In South Korea, aside from ChEIs and NMDA antagonists prescribed for the symptomatic treatment of dementia, choline alfoscerate is prescribed for patients with secondary symptoms of cerebrovascular or neurodegenerative disease. Because most patients are reimbursed for the drug by the National Health Insurance Service (NHIS), the prescriptions for choline alfoscerate, L-carnitine, and N-acetylcysteine have continuously increased.[6,7] Drug overuse for cognitive impairment (DOC), which is the excessive use of cognition-related drugs even though no impairment in their activities of daily living are being caused by cognitive decline, not only worsens the government's medical finances but also poses health threats caused by polypharmacy in patients with elderly cognitive impairment. Appropriate medication management is necessary for patients with and caregivers for cognitive impairment. Given that cognitive impairment affects mainly the elderly, it could be more demanding, complicated, and difficult to intervene. Thus, medication management for cognitive impairment and the factors influencing medication management for this condition must be identified. In this study we aimed to evaluate the frequency of MNA or DOC, to extract significant variables, including the demographic and social characteristics, vascular risk factors (VRF), and cognitive status, for the diagnosis of MNA and DOC in Korean patients and to explore the clinical meaning of the results.

METHODS

Participants

We carried out the cognitive enHancement for patIents with acQuired cognitive impairment (HIQ) campaign for preventing dementia among patients aged over 50 years who visited a primary clinic between March 2019 and June 2019. The HIQ campaign was intended to improve the national health and awareness of dementia. This campaign was conducted by one-on-one education on dementia prevention, a dementia screening test, and a patient survey on factors related to cognitive functions. We excluded patients who disapproved of the collection and use of personal information. Ultimately, this study included 10,767 patients in 408 primary clinics.

Measures for the demographic, economic, and health-related characteristics

Ascertained through questionnaires, the information on years of education was classified into less or more than 9 years of education, which matches graduation from middle school. Although the HIQ campaign was conducted throughout the country, the region was

categorized into Seoul or non-Seoul, considering that only 27.4% of the actual respondents lived in Seoul. Social histories, such as smoking, drinking, exercise, hearing difficulty, family history of dementia, and experience with a dementia screening test were also evaluated according to self-reports. Smoking was coded as "smoker" or "past or never." Drinking was categorized into "once or none per week" or "twice or more per week" regardless of the alcohol amount. Exercise was categorized into the exercising group (exercised at least once a week) or the non-exercising group. Hearing difficulty was based on self-reports of being diagnosed with hearing difficulty as a disease. Moreover, the family history of dementia was classified into participants with a family history of dementia among parents or siblings and participants without any family member diagnosed with dementia. Last, the experience with a dementia screening test was classified according to whether or not the participants had ever had a dementia screening test anywhere. VRFs, such as hypertension, diabetes mellitus, dyslipidemia, and cerebrovascular disease, were based on self-reporting. Trained nurses also conducted a Mini-Mental Status Examination (MMSE) on each participant. At the initial validation study of Korean version of Mini-Mental State Examination (K-MMSE), the cutoff point of dementia was defined as 19 or less, whereas that of normal cognition was defined as 24.[8] The K-MMSE provides 1 to 4 points, with 1 point for time orientation and language items and 2 points for attention and calculation items, to participants exhibiting illiteracy. According to the succeeding studies, these cutoff points of the K-MMSE are relatively sensitive and specific for dementia screening (81.1% sensitivity, 81.5% specificity). Furthermore, in the feasibility study of the K-MMSE in people over 60 years old who were admitted to hospitals or nursing homes, a score of more than 24 points is appropriate for diagnosing nondementia according to the Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition, Revised (92.0% sensitivity, 91.5% specificity).[9] To assess the use of cognition-related drugs, we asked the patients if they were taking any drug for cognitive function, including ChEIs, an NMDA antagonist, choline alfoscerate, L-carnitine, or N-acetylcysteine. In this study, MNA was defined as a participant who was classified as having dementia by the MMSE but did not take any cognition-related drugs, whereas DOC was defined as a participant who had a normal MMSE finding but was taking cognition-related drugs. Patients who did not belong to either the MNA or the DOC group were classified into the normal medication-behavior group.

Statistical analysis

To extract significant variables for MNA and DOC diagnoses, we used classification by discriminant analysis with a stepwise method. Except for age and the MMSE score, the demographics, social characteristics, and VRF between MNA/DOC and normal medication-behavior groups were compared by the Mann-Whitney U test. We compared the age and the MMSE score between the 2 groups by a Student's t-test. We analyzed the statistical data using SPSS (version 17.0; SPSS, Inc., Chicago, IL, USA), and $p < 0.05$ was the threshold of significance.

Standard protocol approvals, registrations, and patient consents

Elderly patients (aged over 50 years) who visited a primary clinic were informed of the HIQ campaign, which was eventually carried out for those who were acquiescent. Participants in the campaign provided written informed consents for their personal data to be used for the study analysis.

RESULTS

Participant characteristics

Most of the participants were female (70.1%), and the mean age of the participants was 72.57 years (standard deviation [SD], 8.9; median, 73.0 years; range, 50–100 years). Nearly half of them (47.3%) had less than 9 years of education. Most participants drank alcohol once or none per week (87.0%), but the smoking rate was relatively low (6.4%). More than half the participants did not exercise (57.4%). Few participants had a hearing difficulty (13.6%) or family history of dementia (11.6%). Only 36.9% of the participants had experienced a dementia screening test (**Table 1**). According to the K-MMSE test, most of the participants had normal cognition (n=8,100, 75.2%), and only 485 patients had dementia (4.5%). The mean score on the K-MMSE was 25.38 (SD, 3.14; median, 26.0; range, 2–30), and 15.9% of the participants were taking cognition-related drugs. The MNA group, participants who had dementia but did not take any cognition-related drugs, consisted of 337 participants, whereas the DOC group, defined as those having normal cognition but taking cognition-related drugs, comprised 1,107 participants.

Distinguishing factors of the MNA group

The factors that could differentiate the MNA group from the normal behavior group were age, education, sex, and the total K-MMSE score (**Table 2**). Using these factors, we found that 97.6% of the MNA group could be classified (**Table 3**, **Fig. 1**). The participants in the MNA group were older and less educated, were mostly female, and obtained lower MMSE scores than did those in the other groups (**Table 4**).

Distinguishing factors of the DOC group

The factors that could differentiate the DOC group from the normal behavior group were age, sex, residential distinction, experience with a dementia screening test, and the total K-MMSE score (**Table 5**). Using these factors, we found that 89.4% of DOC patients could

Table 1. Demographic, social, and vascular risk factors of participants (n=10,767)

Category	Values
Age (yr)	72.57 (8.9)
Education (≤9 yr)	5,091 (47.3)
Sex (female)	7,551 (70.1)
Region (non-Seoul)	7,793 (72.4)
Social history	
Smoking (smoker)	691 (6.4)
Drinking (<1 time/wk)	9,372 (87.0)
Exercise (physical inactivity)	6,177 (57.4)
Hearing difficulty	1,461 (13.6)
Family history of dementia	1,250 (11.6)
Experience of dementia screening test	3,969 (36.9)
Vascular risk factors	
Hypertension	6,076 (56.4)
Diabetes mellitus	2,768 (25.7)
Dyslipidemia	3,833 (35.6)
Cerebrovascular disease	643 (6.0)
K-MMSE points	25.38±3.14
≤19	485 (4.5)
20–23	2,182 (20.3)
≥24	8,100 (75.2)
Taking cognition-related drug	1,711 (15.9)

Values are mean±standard deviation and numbers (%) in continuous and categorical variables, respectively.
K-MMSE: Korean version of Mini-Mental State Examination.

Table 2. Factors that can distinguish the MNA group

Factors which can discriminate the MNA group			Canonical discriminant function coefficients
Age			0.013
Education	0=below 9 years	1=more than 9 years	0.001
Sex	0=male	1=female	0.095
K-MMSE score			0.369
Constant			−10.406

Wilkis' Lamda=0.765; χ^2=2,587.146; df=4; *p*-value<0.001.
MNA: medication nonadherence, K-MMSE: Korean version of Mini-Mental State Examination.

Table 3. Classification result by canonical discriminant function coefficients

Original group	Group centroid	Predicted group		Count	Discrimination rate
		Normal	MNA		
Normal	0.105	9,237 (99.1)	86 (0.9)	9,323	97.6%
MNA	−2.915	146 (43.3)	191 (56.7)	337	
		Normal	DOC		
Normal	−0.057	9,323 (100.0)	0 (0.0)	9,323	89.4%
DOC	0.484	1,107 (100.0)	0 (0.0)	1,107	

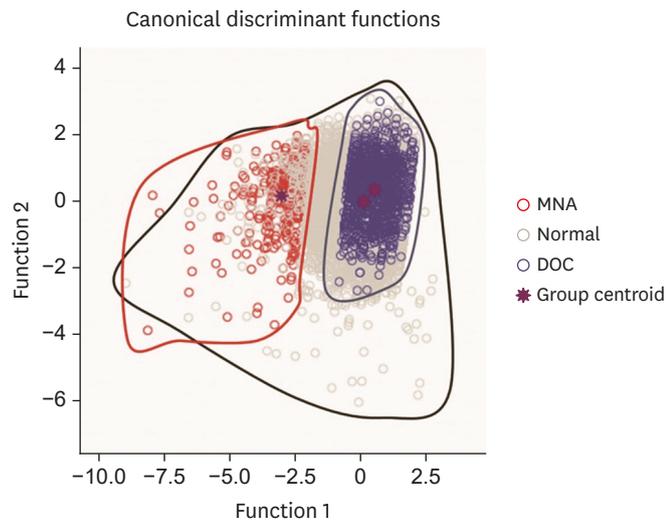MNA: medication nonadherence, DOC: drug overuse for cognitive impairment.

Fig. 1. Canonical discriminant function of MNA or DOC for dementia group.
MNA: medication nonadherence, DOC: drug overuse for cognitive impairment.

be classified (**Table 3, Fig. 1**). The DOC group had more females, more Seoul residents, and more experience with a dementia screening test than did the other groups. They were also older and obtained higher K-MMSE scores than did the others (**Table 4**).

Table 4. Difference of risk factors between MNA or DOC for dementia group and normal medication behavior group

Category	Normal medication behavior group (n=9,323)	MNA group (n=337)	*p*-value[*]	DOC group (n=1,107)	*p*-value[†]
Age (yr)	72.20±9.04	80.71±7.7	<0.001	73.18±7.2	<0.001
Education (≤9 yr)	4,311 (46.2)	281 (83.4)	<0.001		
Sex (female)	6,425 (68.9)	271 (80.4)	<0.001	855 (77.2)	<0.001
Region (non-Seoul)	6,801 (72.9)			765 (69.1)	0.007
Experience of dementia screening test (%)	3,215 (34.5)			657 (59.3)	<0.001
MMSE	25.54±2.85	17.04±2.54	<0.001	26.53±1.69	<0.001

Values are mean±standard deviation and numbers (%) in continuous and categorical variables, respectively.
MNA: medication nonadherence, DOC: drug overuse for cognitive impairment, MMSE: Mini-Mental Status Examination.
[*]*p*-value between normal medication behavior group and MNA group; [†]*p*-value between normal medication behavior group and DOC group.

Table 5. Factors that can distinguish the DOC group

Factors which can discriminate the DOC group			Canonical discriminant function coefficients
Age			0.072
Sex	0=male	1=female	1.058
Residential district	0=Seoul	1=non-Seoul	−0.511
Experience of dementia screening test	0=none	1=yes	−0.002
K-MMSE score			0.357
Constant			−15.769

Wilkis' Lamda=0.973; χ^2=285.928; df=5; *p*-value<0.001.
DOC: drug overuse for cognitive impairment, K-MMSE: Korean version of Mini-Mental State Examination.

DISCUSSION

Factors such as age, education, sex, total K-MMSE score, residential distinction, and experience with a dementia screening test influenced whether medication management for dementia was inadequate for patients over 50 years old who visited primary care clinics participating in the dementia-prevention campaigns.

Inadequate medication management for dementia was observed in 1,444 participants (13.4%), with more participants exhibiting DOC than showing MNA. Most of the inadequate medication management had previously been studied by focusing on medication adherence; however, drug overdoses or unnecessary drug use has seldom been investigated. A few studies reported a high prevalence of unnecessary drug use. In a study of 212 patients with dementia in northern Sweden, 140 patients had drug-related problems (DRPs). Among the 310 DRPs identified by the clinical pharmacists, ineffective drug/inappropriate drug (n=54) and unnecessary drug therapy (n=54) were the most common, followed by dosage too high (n=44). DRPs were classified as adequate doses resulting in adverse drug reactions (n=41), needs additional drug therapy (n=37), transition error (n=26), interactions (n=23), dosage too low (n=14), monitoring need (n=13), and noncompliance (n=4).[10] In another study of 384 frail elderly patients, 44% had at least one unnecessary drug. Gastrointestinal, central nervous system, and therapeutic nutrients/minerals were the most common drug classes prescribed unnecessarily.[11] Compared with these previous studies, our study has a relatively high percentage of participants classified into the MNA and DOC groups, possibly because our definitions, subjects, and national health-care and insurance systems were different from theirs.

A total of 337 participants were classified as the MNA group. This is a ratio of 69.4% of the 485 cognitive-impairment patients, and a higher rate than in other countries' studies, which showed a prevalence of 10.7% to 38%.[4] We thought that these results arose from the negative perception of dementia in our society, or from the simplicity of our diagnostic tools, but it is necessary to study these results. In our study, old age,[12] less education,[13] being female, and lower MMSE score[14-16] were associated with MNA, much as in previous studies. We could not confirm whether the MNA was intentional or accidental. However, considering the risk factors, the MNA is most likely to be an accident caused by decreased cognition or a lack of encouragement to take medicine. It was reported that telehealth monitoring has been effective in patients with old age or polypharmacy.[17] These patients forgot not only the time to take the cognition-related drugs, but even that they had to take the medicine; so, they could not take the drugs on time. Therefore, a supportive system (by either a caregiver or the government) that encourages regular medication use is necessary for elderly patients. Considering that telehealth monitoring encourages patients with dementia to take the

medication while notifying them about the time to take it, less education and low MMSE scores are likely to be factors that cause MNA in the same sense.

Factors that may influence or cause the abuse of cognition-related drugs have also seldom been studied. Although inappropriate medication or unnecessary drug use has been extensively reported, most studies have investigated physician-related factors, considering the nature of "medicine prescription." Meanwhile, only a few studies have focused on patient-related factors that can predict unnecessary drug use; being female and hypertension have been described as related to polypharmacy.[11,18] Among 1,711 participants who were taking cognition-related drugs, 1,107 had normal cognition, a high rate of 64.7%. DOC was more prevalent in our study than in other studies, which reported a prevalence of 20%–50%.[10,11,18] Presumably, most of the cognition-related drugs prescribed to patients without cognitive impairment are choline alfoscerate, L-carnitine, and N-acetylcysteine, because, as described above, they can be prescribed for the secondary symptoms of degenerative brain changes and can be reimbursed by the NHIS in South Korea.[6] Given the lack of research on the medical effect of prescribing cognition-related drugs to patients without cognitive impairment, the prescriptions may depend on the patient's needs or anxiety level. The factors influencing DOC are old age, being female, Seoul residence, experience with a dementia screening test, and a high K-MMSE score; these factors are linked to situations with dementia-related information. In particular, the fact that experience with a dementia screening test is a factor influencing DOC occurrence suggests that national early-dementia screening projects, despite having many advantages, may have side effects.

A limitation of our study includes the self-reporting in some investigations, although the contents were standardized. In addition, cognitive impairment was diagnosed only according to the K-MMSE score. A critical limitation of this study is that we could not clearly distinguish which kinds of cognition-related drugs were being taken by participants. Although examples of the drugs were provided, a patient might not have been fully aware of the drug being taken. In this study, we presumed that most of the cognition-related drugs prescribed to patients without cognitive impairment were choline alfoscerate, L-carnitine, and N-acetylcysteine. However, we cannot confirm such drugs in this study.

There were also limitations in the interpretation of several results. Wilkis' Lamda score is too high (0.973, 0.765) in the results; so these results were simply described. The education level of both groups is also different. Finally, the MMSE score was used for diagnosing cognitive impairment, but using it as another factor behind inadequate medication management for dementia may be a problem. However, the proportion of patients with cognitive impairment is low (4.5%), and the MMSE score, which is a good marker reflecting cognitive function of participants, was used as a covariate.

Despite some limitations, this study is significant because it was a large-scale study conducted nationwide focusing on the quality of medication management for cognitive impairment. To our knowledge, this study is the first to comprehensively investigate the drug-use behavior of patients with cognitive impairment and the demographic, social, vascular, and cognitive factors that could influence such abnormal behavior on a large scale. Intervening for and educating patients with characteristics causing MNA and DOC about normal medication management is the study's main target. Considering that the factors causing or influencing MNA and DOC occurrence are different, we also recommend intervening with or educating patients on each factor relevant for them. Recently, some

policies have been tried to restrict the use of cognition-related drugs; so clinically detailed analyses for MNA and DOC should be more important for these.

In conclusion, timely and appropriate treatment for dementia relieves the patient's clinical course and alleviates the country's socioeconomic burden.[19] MNA was associated with an increased risk of hospitalization or death,[12,20] and inappropriate drug use was linked to substantial morbidity, mortality, and health-resource wastage.[21] The underlying factors causing or contributing to the inadequate medication management for cognitive impairment must be fully understood to allow social-care practitioners and researchers to focus their work on designing interventions that enable safe medication management.[12,20,22] However, further research is required to find out whether medication management can be improved by interventions on factors identified in this study.

ACKNOWLEDGMENT

REFERENCES

1. Choi H, Bae JH, Lim JS, Moon Y, Park KH, Kim SH, et al. Survey of current status and cognition of activities of daily living in dementia patients: the 2018 "Il-sang-ye-chan" campaign. Dement Neurocogn Disord 2019;18:1-9.
   PUBMED | **CROSSREF**
2. Schwartz SM, Day B, Wildenhaus K, Silberman A, Wang C, Silberman J. The impact of an online disease management program on medical costs among health plan members. Am J Health Promot 2010;25:126-133.
   PUBMED | **CROSSREF**
3. Haider B, Schmidt R, Schweiger C, Forstner T, Labek A, Lampl C. Medication adherence in patients with dementia: an Austrian cohort study. Alzheimer Dis Assoc Disord 2014;28:128-133.
   PUBMED | **CROSSREF**
4. Smith D, Lovell J, Weller C, Kennedy B, Winbolt M, Young C, et al. A systematic review of medication non-adherence in persons with dementia or cognitive impairment. PLoS One 2017;12:e0170651.
   PUBMED | **CROSSREF**
5. Thiruchselvam T, Naglie G, Moineddin R, Charles J, Orlando L, Jaglal S, et al. Risk factors for medication nonadherence in older adults with cognitive impairment who live alone. Int J Geriatr Psychiatry 2012;27:1275-1282.
   PUBMED | **CROSSREF**
6. Park J, Bae S, Lee TJ, Son KB. Marketing and pricing strategies of blockbuster drugs in the South Korean market: a 15-year retrospective cohort study for choline alfoscerate. Front Pharmacol 2020;11:232.
   PUBMED | **CROSSREF**
7. Yang Y, Choi H, Lee CN, Kim YB, Kwak YT. A multicenter, randomized, double-blind, placebo-controlled clinical trial for efficacy of acetyl-L-carnitine in patients with dementia associated with cerebrovascular disease. Dement Neurocogn Disord 2018;17:1-10.
   PUBMED | **CROSSREF**
8. Park JH, Kwon YC. Standardization of Korean of the Mini-Mental State Examination (MMSE-K) for use in the elderly. Part II. Diagnostic validity. J Korean Neuropsychiatr Assoc 1989;28:508-513.

9. Suh GH, Kang CJ. Validation of the severe impairment battery for patients with Alzheimer's disease in Korea. Int J Geriatr Psychiatry 2006;21:626-632.
   PUBMED | CROSSREF

10. Pfister B, Jonsson J, Gustafsson M. Drug-related problems and medication reviews among old people with dementia. BMC Pharmacol Toxicol 2017;18:52.
   PUBMED | CROSSREF

11. Hajjar ER, Hanlon JT, Sloane RJ, Lindblad CI, Pieper CF, Ruby CM, et al. Unnecessary drug use in frail older people at hospital discharge. J Am Geriatr Soc 2005;53:1518-1523.
   PUBMED | CROSSREF

12. El-Saifi N, Moyle W, Jones C, Alston-Knox C. Determinants of medication adherence in older people with dementia from the caregivers' perspective. Int Psychogeriatr 2019;31:331-339.
   PUBMED | CROSSREF

13. Okuno J, Yanagi H, Tomura S. Is cognitive impairment a risk factor for poor compliance among Japanese elderly in the community? Eur J Clin Pharmacol 2001;57:589-594.
   PUBMED | CROSSREF

14. Hennein R, Hwang SJ, Au R, Levy D, Muntner P, Fox CS, et al. Barriers to medication adherence and links to cardiovascular disease risk factor control: the Framingham Heart Study. Intern Med J 2018;48:414-421.
   PUBMED | CROSSREF

15. Stoehr GP, Lu SY, Lavery L, Bilt JV, Saxton JA, Chang CC, et al. Factors associated with adherence to medication regimens in older primary care patients: the Steel Valley Seniors Survey. Am J Geriatr Pharmacother 2008;6:255-263.
   PUBMED | CROSSREF

16. Mackin RS, Areán PA. Cognitive and psychiatric predictors of medical treatment adherence among older adults in primary care clinics. Int J Geriatr Psychiatry 2007;22:55-60.
   PUBMED | CROSSREF

17. El-Saifi N, Moyle W, Jones C, Tuffaha H. Medication adherence in older patients with dementia: a systematic literature review. J Pharm Pract 2018;31:322-334.
   PUBMED | CROSSREF

18. Lai HY, Hwang SJ, Chen YC, Chen TJ, Lin MH, Chen LK. Prevalence of the prescribing of potentially inappropriate medications at ambulatory care visits by elderly patients covered by the Taiwanese National Health Insurance program. Clin Ther 2009;31:1859-1870.
   PUBMED | CROSSREF

19. Raina P, Santaguida P, Ismaila A, Patterson C, Cowan D, Levine M, et al. Effectiveness of cholinesterase inhibitors and memantine for treating dementia: evidence review for a clinical practice guideline. Ann Intern Med 2008;148:379-397.
   PUBMED | CROSSREF

20. Aston L, Hilton A, Moutela T, Shaw R, Maidment I. Exploring the evidence base for how people with dementia and their informal carers manage their medication in the community: a mixed studies review. BMC Geriatr 2017;17:242.
   PUBMED | CROSSREF

21. O'Mahony D, Gallagher PF. Inappropriate prescribing in the older population: need for new criteria. Age Ageing 2008;37:138-141.
   PUBMED | CROSSREF

22. Lim RH, Sharmeen T. Medicines management issues in dementia and coping strategies used by people living with dementia and family carers: a systematic review. Int J Geriatr Psychiatry 2018;33:1562-1581.
   PUBMED | CROSSREF