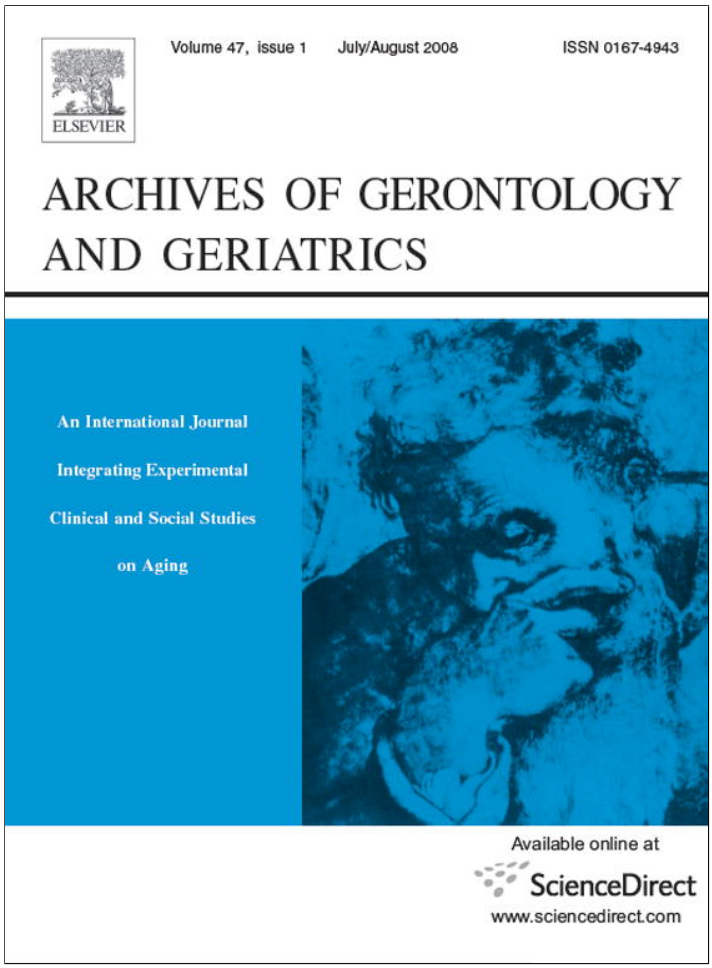

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Analysis of drug–drug interactions (DDIs) in nursing homes in Central Taiwan

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Abstract

With the progressive aging of the population, the long-term nursing care and drug safety for the elderly are gradually gaining attention. In Taiwan, nursing homes are the main institutes helping society or families take care of elderly people suffering from diseases. The aim of this study was to assess the prescribed medications of nursing home residents, the occurrence of DDIs and the association between the number of drugs and DDIs with a view to reinforce drug safety for the elderly. The findings of this study showed that the mean number of medications per resident was 5.74 ± 2.4. Of the 323 samples, 81 (25.1%) had experienced DDIs, 63 (64.95%) were of moderate and 7 (7.2%) of major severity. The findings also showed that the number of potential DDIs increased as the number of medications used per residents increased. The residents with nine or more medications tended to have more DDIs, in comparison to those with one or two medications. The odds ratio (OR) was 11.389, which had reached statistical significance in difference. Therefore, to reduce potential DDIs, the number of medications for the senior people with chronic diseases should be properly controlled.

Keywords: Nursing home; Drug–drug interactions (DDIs); Drug safety

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1. Introduction

In Taiwan, the elderly accounted 9.7% of total population in 2005 (MOI, 2007) and it is projected to reach 21.6% in 2036 (Wu and Chang, 1997). The rapid growth of the elderly population in Taiwan has led to considerable social costs in long-term care. In the past, families had the responsibility of taking care of the elderly or the patients with chronic diseases, but now it is recognized that this responsibility should be shared by the social levels because of the trend toward nuclear families and the increasing participation of women in labor force. In Taiwan, most people choose to live in nursing homes mainly because they suffer from chronic diseases but no family member can take care of them.

Medications are commonly prescribed to nursing home residents with the goals of curing or palliating disease and improving quality of life (Avorn and Gurwitz, 1995). Nursing home residents are prescribed more medications than patients in any other medical setting (Handler et al., 2006) because of the number and severity of chronic comorbid medical conditions. Both the frequency and number of medications given to nursing home residents are higher than those for the community-dwelling geriatric population (Williams et al., 1999; Fick et al., 2003; Roth and Ivey, 2005).

In the elderly, concomitant use of several drugs (polypharmacy) is very common because of chronic health problems and illness. Polypharmacy leads to an increased incidence of adverse drug reactions (ADRs) and DDIs (Gaeta et al., 2002). The incidence of ADRs and DDIs in the elderly has been reported to be two to three times higher than in the younger patients (Nolan and Malley, 1998). The aging of the population and increasing complexity of medication regimens used to treat ambulatory patients and a fragmented health care system with multiple prescribers treating the patients make the occurrence of serious DDIs even more likely (Malone et al., 2005).

In Taiwan, 65–74-year-old senior people have an average of 2.36 chronic diseases, 75-year-old or older ones have 2.75 chronic diseases, respectively (BHP, 2007). Most nursing home residents usually, on a regular basis, go to fixed hospitals for the therapy and medications of their chronic diseases. However, when any resident all of sudden gets sick, the nursing home caregiver often accompanies the resident to a medical institute nearby and receives a medication. Very often the medication could result in DDIs because the doctor does not have any information on the medication that the resident usually takes. Besides, most nursing homes are not staffed with pharmacists and very often their administrators and caregivers lack of drug interaction-related knowledge, so they cannot tell, if the new medication can cause ADRs. This phenomenon needs special attention because it not only influences the resident's health, but also increases medical costs. Therefore, this research aimed to comprehend the frequency and type of drugs prescribed to nursing home residents, the occurrence of potential DDIs, and the association between prescribed drugs and DDIs, in order to remind nursing homes to keep special alert on medication administration and to prevent DDIs.

2. Methods

2.1. Design and data collection

A cross-sectional study was conducted. In September 2006, there were 22 private nursing homes in Taichung County, Taiwan. All the nursing homes owners were solicited through telephone for participating in this study. Nine of them agreed. Then, from the medication administration record of the nursing homes, data of the prescribed medications of the nursing home residents were collected. A total of 323 nursing home residents were included in this study after ruling out 27 residents not taking any oral medicine.

The medications of the selected residents were recorded in Excel, excluding as needed agents, external medicine, over-the-counter (OTC) and herbal medicine. After the medications were recorded, they were classified and encoded according to MIMS Taiwan Medicine Manual 32th ed. (http://www.mimsonline.com/mims.aspx). Then, the DDIs Database Information System (http://dif.doh.gov.tw/) constructed by the Department of Health, Executive Yuan, Taiwan was used for matching the recorded medications. The matching results were classified into three levels (major, moderate and minor) based on their clinical significance.

2.2. Statistical analysis

SPSS 10.0 was used to run statistical analysis, *t*-test was used to identify relationship, and logistic regression was used to predict the relationship between the number of drugs and DDIs.

3. Results

3.1. Demographic features of the sampled residents

The average age of the 323 residents was 75.5 ± 11.8 years (±SD), range 29–96 years, median = 78.0; 54.7% were female.

3.2. Medications currently in use

A total of 1853 drugs were prescribed and the mean number of medications per resident was 5.74 ± 2.4, range 1–15. There were 15 residents in total who were taking 10 or more medications (Table 1). Table 2 describes the distribution of the number of medications prescribed in nursing homes. The most commonly prescribed class of medications was cardiovascular drugs. The range of cardiovascular drugs was broad and included cardiac drugs, anti-anginal drugs, angiotensin-converting enzyme (ACE)-inhibitors, calcium antagonists, angiotensin II antagonists, beta-blockers, diuretics, peripheral vasodilators and cerebral activators, vasoconstrictors, etc.

Table 1
Frequency of nursing home medication

Number of medications used	Number of residents	%
1	13	4.02
2	15	4.64
3	32	9.91
4	35	10.84
5	46	14.24
6	71	21.98
7	48	14.86
8	36	11.15
9	12	3.72
10	5	1.55
11	3	0.93
12	2	0.62
13	1	0.31
14	2	0.62
15	2	0.62
Total	323	100

Table 2
Distribution of the number of medications prescribed per resident ($n = 323$)

No.	Class of medications	Frequency	%
1	Cardiovascular drugs	608	32.81
2	Drugs for gastrointestinal and hepatobiliary system	457	24.66
3	Neuro-muscular drugs	400	21.59
4	Drugs for respiratory system	166	8.96
5	Drugs for endocrine and metabolic system	102	5.50
6	Drugs for allergy and immune system	41	2.21
7	Vitamins and minerals	27	1.46
8	Corticosteroid hormones	25	1.35
9	Drugs for genito-urinary system	10	0.54
10	Antibiotics	10	0.54
11	Other chemotherapeutics	7	0.38
Total		1853	100

3.3. Occurrence of DDIs

Of the sampled nursing home residents, 81 had DDIs (25.1%) and the frequency of DDIs per resident ranged from 1 to 5 (Table 3). Of them, 27 (27.8%) were of potentially minor, 63 (64.95%) of moderate and 7 (7.2%) of major severity (Table 4). In this study, two cases of DDIs with major severity were due to the combination of a digoxin with loop diuretics (e.g., furosemide). And, ACE-inhibitor (e.g., captopril) with potassium-sparing diuretics (e.g., spironolactone, amiloride) also resulted in another two cases. The medications caused higher frequency of moderate-risk DDIs included the combination of aspirin with ACE-inhibitor, beta-blocker and glimepiride, respectively, and their frequency of DDIs were 11, 8 and 7 times, respectively. The rests were the medications caused major-risk DDIs and two or more moderate-risk DDIs (Table 5).

Table 3
Frequency of DDIs on the medications of the sampled residents

Frequency of DDIs	Number of residents	%
0	242	74.92
1	56	17.34
2	16	4.95
3	4	1.24
4	3	0.93
5	2	0.62
Total	323	100

Table 4
The frequency of different levels of DDIs

Level of severity	Frequency	%
1 (major)	7	7.22
2 (moderate)	63	64.95
3 (minor)	27	27.84
Total	97	100

3.4. The influence of prescribed medications on DDIs

This research used independent-sample *t*-test to compare the variables of age, the number of medications, etc. and to check whether mean variance existed. The result showed for the cases with DDIs their number of medications used and the use of

Table 5
DDIs with major severity and with two or more moderate severity

Level of severity	DDI		Frequency
Major	ACE-inhibitors	Amiloride	1
	ACE-inhibitors	Spironolactone	1
	Digoxin	Lasix	2
	Digoxin	Amiodarone	1
	Rifampicin	Isoniazid	1
	Aspirin	Clopidogrel	1
Moderate	Aspirin	ACE-inhibitors	11
	Aspirin	Beta-blocker	8
	Aspirin	Glimepiride	7
	Ticlopidine	Theophylline	5
	Ticlopidine	Phenytoin	5
	Thiazid diuretics	Sulfonylureas	5
	Thiazid diuretics	Furosemid	3
	Madopar	Phenytoin	3
	Quetiapine	Phenytoin	2
	Theophylline	Phenytoin	2
	Corticosteroids	Phenytoin	2
	Digoxin	Metoclopramide	2

Table 6
The variables in the presence or absence of DDIs (mean ± S.E.M.)

Variables	Without DDI	With DDI	$p\leq$
Age (years)	75.93 ± 11.37	74.36 ± 12.93	0.299
Number of medications	5.35 ± 2.15	6.90 ± 2.74	0.001***
Type of medications			
Gastrointestinal and hepatobiliary	1.37 ± 0.94	1.56 ± 1.01	0.129
Cardiovascular	1.74 ± 1.42	2.31 ± 1.71	0.003**
Respiratory	0.45 ± 0.84	0.69 ± 1.01	0.038*
Neuro-muscular	1.13 ± 1.24	1.56 ± 1.44	0.011*
Corticosteroid hormones	0.07 ± 0.26	0.1 ± 0.34	0.427
Antibiotics	0.04 ± 0.21	0.01 ± 0.11	0.310
Other chemotherapeutics	0.02 ± 0.13	0.04 ± 0.33	0.425
Genito-urinary	0.02 ± 0.16	0.05 ± 0.27	0.315
Endocrine-metabolic	0.27 ± 0.62	0.46 ± 0.69	0.022
Vitamins, minerals	0.10 ± 0.32	0.06 ± 0.24	0.448
Allergic and immune	0.14 ± 0.40	0.07 ± 0.31	0.145

* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.001$.

cardiovascular drug, drug for respiratory system and neuro-muscular drug, etc. were higher than those without DDIs. The result reached statistical significance (Table 6). To further identify how the number of medications influenced DDIs, this study used logistic regression to estimate the influence of the number of medications on DDIs. The independent variables were categorized as taking 1–2, 3–4, 5–6, 7–8 and ≥9 medications, respectively. The dependent variables were binary variables (''with'' and ''without'' DDIs). The result of logistic regression analysis indicated that of the 323 valid samples, the correct estimation rate was 76.5%. Nagelkerke $R^2 = 0.105$ showed the use of logistic regression for estimation could effectively explain 10.5% variance. In addition, the Hosmer–Lemeshow goodness-of-fit test statistics was 0.000, $p = 1.000$, suggesting the model's estimates were fit to the data at an acceptable level. The model's analysis result is shown in Table 7. The ≥9 medications had higher DDIs than the 1–2 medications. OR = 11.389 and 95% confidence interval = 2.746–46.222 had reached statistical significance.

Table 7
The influence of the number of consumed drugs on DDIs ($n = 323$)

Variables	Reference group	B (95% CI)	p	Exp (B)
Number of drugs				
3–4	1–2	0.337 (0.345–5.535)	0.631	1.400
5–6	1–2	0.813 (0.630–8.074)	0.212	2.255
7–8	1–2	1.253 (0.965–12.685)	0.057	3.499
≥9	1–2	2.425 (2.746–46.222)	0.001**	11.303
Constant		−2.077	0.001**	0.125

Hosmer and Lemeshow $X^2 = 0.000$; −2 log-likelihood = 339.944; Nagelkerke $R^2 = 0.105$; *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

4. Discussion and conclusions

DDIs are more likely in the elderly because they tend to use multiple medications. Some studies indicate the frequency and number of medications given to nursing home residents are higher than those for the community-dwelling geriatric population (Williams et al., 1999; Fick et al., 2003; Roth and Ivey, 2005). This study showed that in the sampled nursing homes the mean number of prescribed medications per resident were 5.7 ± 2.4 and 4.65% took more than nine medications. In the US, nursing home residents take an average of 8.8 medications per day and 32% take more than 9 medications (Doshi et al., 2005), community-dwelling elderly suggest that the average older person uses between two and six prescribed medications (Stewart and Cooper, 1994). This study only focused on analyzing the DDIs of prescribed medicine. That is, only the data of prescribed oral medicine were used for statistical analysis and the data of others like external medicine and OTC drugs were excluded. Thus, the nursing home residents' number of medications in this study was somewhat lower than reported in other studies.

Many chronic diseases like heart failure, coronary artery disease, cerebrovascular disease and hypertension which often happen to the elderly need cardiovascular drugs for disease control. Like some similar studies, this study found that in the sampled nursing homes, the most commonly prescribed class of medications for their residents were cardiovascular drugs (Golden et al., 1999; Pitkala et al., 2002; Barry et al., 2006). Meanwhile, the analytical result showed most potential DDIs with major severity were due to a combination of digoxin with loop diuretics and that of ACE inhibitor with potassium sparing diuretics. And, a combination of aspirin with ACE inhibitor and that of aspirin with beta-blocker led to in higher frequency of moderate-risk DDIs. Our study also identified that the medications with cardiovascular drugs resulted in more DDIs than those without cardiovascular drugs. Therefore, for the drug safety of elderly people, the physician must take potential DDIs into consideration and be more cautious while more cardiovascular drugs were prescribed.

Because the elderly often suffer from multiple chronic illnesses, polypharmacy is quite common. Consequently, DDIs can occur (Herrlinger and Klotz, 2001). This study found that the occurrence rate of DDIs in the sampled nursing homes was 25.1%. Of it, 27.8% was of potentially minor, 64.95% of moderate and 7.2% of major severity. A recent research found that, of the potential DDIs in the medication of medical patients at hospital discharge, 17.9% were of potentially minor, 69.9% of moderate and 12.2% of major severity (Egger et al., 2003). In contrast, the sampled nursing homes in this study had a lower rate of moderate and major severe DDIs. It is probably because the diseases and medications of the sampled nursing home residents in the two studies are different. However, the results of both studies indicated that for the elderly the medications with potential DDIs, such as ACE-inhibitor with potassium-sparing diuretics, digoxin with lasix, and digoxin with amiodarone, needs special attention. The caregivers of nursing homes need special education on common DDIs to enable them to inform the doctor immediately while drug interactions do happen.

The number of possible DDIs will increase enormously with the number of concurrently administered medication (Herrlinger and Klotz, 2001). We evaluated the effect of the number of medications used with respect to DDI. Residents were categorized as taking

1–2, 3–4, 5–6, 7–8, and 9 or more medications. The number of potential DDIs increased as the number of medications used by the residents increased. Although in some researches positive correlation between the use of ≥9 different scheduled medications and ADRs was found and among these geriatric nursing home residents using ≥9 different scheduled medications were 2.33 times more likely than controls to experience an ADR (Nguyen et al., 2006). Our study only analyzed interactions and found that the occurrence rate of DDIs for nursing home residents using ≥9 different scheduled medications was 11.389 times more than that of nursing home residents using 1–2 medications. It reached statistical significance and is worth special attention.

The DDIs are common in the elderly and those taking multiple medications in nursing homes. As the number of the drugs given concomitantly increases, so doses the probability of a drug interaction. Additional studies are needed to enhance the detection and prevention of DDIs and to reduce their impact on residents' outcomes and quality of life.

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References

Avorn, J., Gurwitz, J.H., 1995. Drug use in the nursing home. Ann. Intern. Med. 123, 195–204.

Barry, P.J., O'Keefe, N., O'Connor, K.A., O'Mahony, D., 2006. Inappropriate prescribing in the elderly: a comparison of the Beers criteria and the improved prescribing in the elderly tool (IPET) in acutely ill elderly hospitalized patients. J. Clin. Pharm. Ther. 31, 617–626.

BHP (Bureau of Health Promotion, Department of Health, Republic of China), 2007. Survey of Health and Living Status of the Middle Aged and Elderly in Taiwan. Survey Report, 2003, Retrieved January 18, 2007 from http://rds.bhp.doh.gov.tw/fileviewer?id=1692.

Doshi, J.A., Shaffer, T., Briesacher, B.A., 2005. National estimates of medication use in nursing homes: findings from the 1997 Medicare current beneficiary survey and the 1996 medical expenditure survey. J. Am. Geriatr. Soc. 53, 438–443.

Egger, S.S., Drewe, J., Schlienger, R.G., 2003. Potential drug–drug interactions in the medication of medical patients at hospital discharge. Eur. J. Clin. Pharmacol. 58, 773–778.

Fick, D.M., Cooper, J.W., Wade, W.E., Waller, J.L., Maclean, J.R., Beers, M.H., 2003. Updating the Beers criteria for potentially inappropriate medication use in older adults: results of a US consensus panel of experts. Arch. Intern. Med. 163, 2716–2724.

Gaeta, T.J., Fiorini, M., Ender, K., Bove, J., Diaz, J., 2002. Potential drug-drug interactions in elderly patients presenting with syncope. J. Emerg. Med. 22, 159–162.

Golden, A.G., Preston, R.A., Barnett, S.D., Llorente, M., Hamdan, K., Silverman, M.A., 1999. Inappropriate medication prescribing in home-bound older adults. J. Am. Geriatr. Soc. 47, 948–953.

Handler, S.M., Wright, R.M., Ruby, C.M., Hanlon, J.T., 2006. Epidemiology of medication-related adverse events in nursing homes. Am. J. Geriatr. Pharmacother. 4, 264–272.

Herrlinger, C., Klotz, U., 2001. Drug metabolism and drug interaction in the elderly. Best Pract. Res. Clin. Gastroenterol. 15, 897–918.

Malone, D.C., Abarca, J., Hansten, P.D., Grizzle, A.J., Armstrong, E.P., Van Bergen, R.C., Duncan-Edgar, B.S., Solomon, S.L., Lipton, R.B., 2005. Identification of serious drug–drug interactions: results of the partnership to prevent drug–drug interactions. Am. J. Geriatr. Pharmacother. 3, 65–76.

MOI (Ministry of the Interior, Republic of China), 2007. Percentage of Population for Ages 65 and Over by Selected Countries. Retrieved January 18, 2007 from http://www.moi.gov.tw/stat/english/index.asp.

Nguyen, J.K., Fours, M.M., Kotabe, S.E., Lo, E., 2006. Polypharmacy as a risk factor for adverse drug reactions in geriatric nursing home residents. Am. J. Geriatr. Pharmacother. 4, 36–41.

Nolan, L., Malley, K.O., 1998. Prescribing for the elderly. Part 1. Sensitivity of the elderly to adverse drug reactions. J. Am. Geriatr. Soc. 36, 142–149.

Pitkala, K.H., Strandberg, T.E., Tilvis, R.S., 2002. Inappropriate drug prescribing in home-dwelling elderly patients. Arch. Intern. Med. 162, 1707–1712.

Roth, M.T., Ivey, J.L., 2005. Self-reported medication use in community-residing older adults: a pilot study. Am. J. Ger. Pharmacother. 3, 196–204.

Stewart, R.B., Cooper, J.W., 1994. Polypharmacy in the aged. Practical solutions. Drugs Aging 4, 449–461.

Williams, B.R., Nichol, M.B., Lowe, B., Yoon, P.S., McCombs, J.S., Margolies, J., 1999. Medication use in residential care facilities for the elderly. Ann. Pharmacother. 33, 149–155.

Wu, S.C., Chang, M.C. (Eds.), 1997. Health Care for the Elderly in Taiwan: A Fact Book, 1993–1994. Health Policy Research Center, College of Public Health, National Taiwan University and Taiwan Provincial Institute of Family Planning, Taichung, Taiwan.