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An Economic Evaluation on the Pharmaceutical Expenditure of Antihypertensive Agents in Taiwan from 1997 to 2002

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ABSTRACT

Antihypertensive medications have represented a tremendous financial burden to the health care plan globally. The utilization pattern of the antihypertensive agents was examined in this study to analyze the underlying reasons responsible for the pharmaceutical expenditure in Taiwan during 1997 to 2002. The claims data were obtained from National Health Insurance Research Database (NHIRD), which include ambulatory service record and prescription data of the entire population. Drug expenditure was decomposed into 5 components: relative drug price, number of patients treated, average physician visit per patient, defined daily dose (DDD) per physician visit and a residual. Total antihypertensive drug spending increased 102% during this period, mainly due to the compounding effect from the increment of patients treated (34%) and DDD per physician visit (33%). The aggregate residual for antihypertensive agents only exerts a 7% effect. Detailed residual analysis revealed that the brand-name product did have 11% increment, while the generic product had a 12% decrement. It also showed that hospital sector had a positive 11% residual, while primary care clinics had an 11% decrement. The most important factors that contribute to the expenditure surge of antihypertensive agents are the number of treated patients and DDD per physician visit. While physicians at the hospital sector adopted more new and innovative medications, their counterparts at the primary care clinics tended to switch some off-patent products to the generics.

Key words: antihypertensive agent, defined daily dose (DDD), drug utilization, pharmaceutical expenditure, pharmacoeconomics

INTRODUCTION

The beneficial effects of antihypertensive medications on mortality and cardiovascular morbidity are well documented in the literatures[1-3]. However, the success also poses a tremendous financial burden to the patients, insurance companies and health care providers. Facing this dilemma in today's medical environment, the economic aspect of the evaluation is gradually gaining its ground to resolve this issue in recent years[4,5].

The National Health Insurance Program started in Taiwan, 1995. Taiwan's healthcare system is mainly publicly managed by the Bureau of National Health Insurance (BNHI). It covered 22 million people (98.7% of the total population) at the end of 2003. The BNHI contracted with 17,022 (93.8%) medical institutions nationwide[6]. Medical institutions are classified into 4 levels by their size: medical center, regional hospital, district hospital and primary care clinic. All hospital settings provide both in-patient hospitalization service and out-patient ambulatory care service. Patients can freely choose to go to primary care clinic or to the out-patient service of any level of hospital for their ambulatory care with tiered registration fee and co-payment. The outpatient prescription drug expenditure is covered by BNHI as part of the benefit package. The national claim data became available since 1997. It is the first time in Taiwan for the public to access such a thorough detailed database. This claim database is licensed to and administrated by the National Health Research Institute (NHRI), a non-profit research organization founded and sponsored by the Department of Health, and been referred as National Health Insurance Research Database (NHIRD). Special request to use data from NHIRD for research has to be reviewed and approved beforehand.

Gerdtham and his coworkers used the term "residual" to explain the changes in treatment patterns[7-9]. Residual is a factor to adjust the differences between the existing price/quantity indices and the true price/quantity. An increased residual usually means a shift towards

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more expensive drug treatment and a decreased residual, on the other hand, means shifting towards less expensive one. Using this residual analysis, Gerdtham *et al*. reported a 67% total residual increase during 1990 to 2000 in Sweden[7]. Darba also reported a 28% total residual increase during 1997 to 2001 in Spain[10]. Both studies indicated that the residual was the most important cost component responsible for the drug expenditure growth in these two countries during 1990 to 2000. We would like to investigate whether this situation also occurred in Taiwan, especially the antihypertensive agents.

Retrospective pharmacoeconomic analysis using claim database is commonly employed to compare health costs associated with competing drugs or intervention[11]. Although this scheme is considered to be inferior to prospective study due to limited patient information in the claim records, it is far less expensive and thus justifies its use to extract preliminary useful information for further study design. In this study, the 1997-2002 ambulatory service records and prescription claim data files from the NHIRD were used to analyze the trend of utilization pattern of antihypertensive agents in Taiwan with the goal of better understanding the underlying reason(s) for the pharmaceutical expenditure surge during this period.

MATERIALS AND METHODS

I. *Data Collection*

All ambulatory antihypertensive medications used in Taiwan during 1997 to 2002 were obtained from the NHIRD, which includes ambulatory service records and prescription claim data. Both files were merged by patients' masked codes with an average matching of 99.6% and a total of 122,397,631 observed data sets for 6,228,094 patients. A total of 1021 antihypertensive products were included for analysis, and which were identified from the NHI pharmaceutical reimbursement database. The data were subsequently grouped by Anatomical Therapeutic Chemical (ATC) classification system using the National Health Insurance Pharmaceutical Coding System previously developed by Yang Kao[12]. According to the ATC system, the antihypertensive agents were classified into the following categories: centrally acting antiadrenergic agents (C02A), peripherally acting antiadrenergic agents (C02C), antihypertensives and diuretics in combination (C02L), agents acting on arteriolar smooth muscle (C02D), combinations of antihypertensives in ATC group C02 (C02N), low-ceiling diuretics, thiazides (C03A), low-ceiling diuretics, excluding thiazides (C03B), high-ceiling diuretics (C03C), potassium-sparing agents (C03D), diuretics and potassium-sparing agents in combination (C03E), beta blocking agents (BB, C07A), beta blocking agents and thiazides (C07B), beta blocking agents and other diuretics (C07C), beta blocking agents, thiazides and other diuretics (C07D), calcium channel blockers with mainly vascular effects (CCB, C08C), calcium channel blockers with direct cardiac effects (C08D), ACE inhibitors (ACEI, C09A), angiotensin II antagonists (AIIA, C09C), and angiotensin II antagonists combinations (C09D).

All data were presented in units per year. Consumer product indices were obtained from the website of Directorate General of Budget, Accounting and Statistics (DGBAS) of Executive Yuan, Taiwan[13].

II. *Method of Analysis*

Gerdtham *et al*. broke down the drug expenditure into 3 components: price of drugs, the quantity of drugs consumed and a residual[8] as shown in equation 1:

Real Annual Drug Expenditure = Relative Drug Index × Annual Drug Quantity Consumed DDD × Residual Eq. (1)

Relative drug index = drug index at 1997/ consumer price index, assuming 1997 price equals to 1.00

Gerdtham further decomposed the quantity component DDD into 3 subcomponents: number of DDD per patient, proportion of the population on medication and the population size[7]. The population size in Taiwan during 1997 to 2002 remained fairly stable around 22 million with less than 3.6% changes and thus can be ignored[14]. We further modify the "DDD per patient" into DDD per physician visit times the number of physician visit per patient and "the proportion of the population on medication" into the number of patients treated with the medication since all these terms were readily available from the claim database. By decomposing "DDD per patient" into "DDD per physician visit" and "the number of physician visit per patient", we will be able to differentiate whether each patient visit physician more frequently (patient factor) or the physician had prescribed more medication (physician factor). If we can find out which factor is the major one, we shall be able to take proper measures to control the growth of that factor. The number of physician visit per patient varies from patient to patient, so we use the number of total annual physician visits divided by the number of total patients treated to obtain "the average physician visit per patient". Since the total population in Taiwan remained fairly constant from 1997 to 2002, "the proportion of the population on medication" used in Gerdtham's study could be converted into "number of patients treated with the medication" by multiplying the total population with the proportion of the population on medication. Therefore, the annual drug quantity consumed can still be decomposed into 3 subcomponents and be expressed as follows:

Annual Drug Quantity (DDD) = No. of annual treated patients × Ave. physician visit/patient/year × DDD/physician visit Eq. (2)

Substitute Equation 2 into Equation 1,

Real Annual Drug Expenditure

= Relative Drug Index × No. of annual treated patients × Ave. physician visit/patient/year × DDD/physician visit × Residual Eq. (3)

Monetary unit used in this study is the local currency, NTD. The exchange rate for NTD to USD is between 28.66 and 34.58 during this period[15]. With more than 20% variation on the exchange rate, NTD was chosen to report the data to avoid the deviation of the raw data since all claims and reimbursements were made in NTD. All data were standardized to 1997 value equal to 1.00.

III. *Statistical Analysis*

All data analysis was performed using SAS package (Windows Release 8.02 version TS Level 02M0) from SAS Institute Inc. (Cary, NC, USA). Chi-square test was used to compare nominal variable and data were considered statistically significant at $p < 0.05$. For linear regression analysis, the least-squares method of best fit curve was done using the analytical tools provided by Microsoft® Office Excel 2003 (Redmond, WA, USA). Analysis of variance (ANOVA) was computed to test the secular correlation of pharmaceutical expenditure.

RESULTS

The average age of the patients taking antihypertensive medication during this period was 56.0 ± 17.2. Age 60 to 70 represented the major patient group with 23.32 ± 0.98% of the total patient population. Female was statistically more than male (53.63 ± 0.22% vs. 45.95 ± 0.17%; $p < 0.01$). The absolute amount of money spent (nominal drug expenditure) for all the antihypertensive medication from 1997 to 2002 increased from 5.89 billion NTD to 11.90 billion NTD (Table 1). A linear regression analysis revealed an annual growth rate of 19.9% ($R^2 = 0.99$, $p < 0.001$). The average nominal annual pharmaceutical cost per patient taking antihypertensive medication increased from 2,531 NTD at 1997 to 3,817 NTD at 2002, a 51% increment. Patient demographics and pharmaceutical cost by pharmacological class of drug are presented in Table 1.

The nominal pharmaceutical expenditure was first normalized with consumer product index and further decomposed into relative drug price, quantity prescribed DDD and a residual according to the equation 1. Among the three components, DDD demonstrated an increment of 91% as shown in Table 2. The number of patients treated with antihypertensive agents annually, average of annual physician visits per patient and DDD per physician visit were presented in Table 3. Although the physician visits per patient had increased only 7% during the six-year period, the number of patients and DDD per physician visit had raised 34% and 33%, respectively. This 34% increment from patient growth is an intrinsic growth and is usually very hard to control. The 33% increase of DDD per physician visit may result from prescribing behavior change and could be corrected through education or other financial incentives. Detailed analysis of the DDD for each sub-pharmacological group

Table 1. Demographics and pharmaceutical cost of antihypertensive agents during 1997 to 2002

	1997	1998	1999	2000	2001	2002	p value
Patient	2,328,204	2,650,132	2,891,479	2,892,826	3,034,745	3,118,601	
Patient Visits	16,073,491	19,194,467	21,206,820	20,296,332	22,024,726	23,063,913	
Mean Age (± SD)	55.36 ± 17.50	55.51 ± 17.67	55.47 ± 17.41	56.22 ± 17.00	56.44 ± 16.91	56.75 ± 16.93	
Gender							<0.001[a]
Female (%)	53.79	53.80	53.79	53.68	53.48	53.26	
Male (%)	45.91	45.74	45.83	45.93	46.05	46.22	
Unknown (%)	0.30	0.46	0.38	0.39	0.48	0.51	
Total drug expenditure (NTD)	5,892,961,870	7,336,156,002	8,855,059,835	9,418,483,671	10,720,666,232	11,904,021,414	
Total expenditure of each category (%)							
Anti-adrenergic agents	311,571,624 (5.29)	392,790,577 (5.35)	450,286,862 (5.09)	454,620,002 (4.83)	507,943,029 (4.74)	533,275,992 (4.48)	0.001[b]
Diuretics	208,095,076 (3.53)	259,401,963 (3.54)	345,964,135 (3.91)	369,500,385 (3.92)	406,087,776 (3.79)	455,917,291 (3.83)	0.132[b]
β-Blocking agents	1,135,364,527 (19.27)	1,366,406,011 (18.63)	1,653,771,792 (18.68)	1,715,953,044 (18.22)	1,871,214,687 (17.45)	1,984,213,988 (16.67)	0.002[b]
Calcium channel blockers	2,522,120,514 (42.80)	3,124,368,581 (42.59)	3,597,835,899 (40.63)	3,741,400,583 (39.72)	4,202,028,177 (39.20)	4,576,013,448 (38.44)	0.001[b]
ACE inhibitors	1,715,810,129 (29.12)	2,109,744,469 (28.76)	2,337,574,910 (26.40)	2,277,668,318 (24.18)	2,358,034,960 (22.00)	2,306,151,809 (19.37)	<0.001[b]
Angiotensin II antagonists	0 (0.00)	83,444,401 (1.14)	469,626,237 (5.30)	859,341,339 (9.10)	1,375,357,603 (12.83)	2,048,448,886 (17.21)	<0.001[b]

[a]Chi-square test was used to compare gender each year. [b]ANOVA F-test was used to compare percentage of total expenditure each year.

Table 2. Indices of nominal drug expenditure, real drug expenditure, relative drug price, DDD and the residual during 1997 to 2002. All measurements and calculations were standardized to 1997 = 1.00

Year	Nominal drug exp.	Real drug exp.[a]	Relative drug price[a]	DDD	Residual
1997	1.00	1.00	1.00	1.00	1.00
1998	1.24	1.22	0.98	1.24	1.00
1999	1.50	1.47	0.98	1.45	1.03
2000	1.62	1.55	0.97	1.52	1.05
2001	1.82	1.76	0.97	1.74	1.04
2002	2.02	1.96	0.97	1.91	1.06

[a]Nominal drug expenditure or drug price divided by consumer price index.

Table 3. Indices of antihypertensive DDD, number of treated patients, average number of physician visit per patient and DDD per physician visit during 1997 to 2002. All measurements and calculations were standardized to 1997 = 1.00

Year	DDD	Treated patient	No. of physician visit/patient	DDD/physician visit
1997	1.00	1.00	1.00	1.00
1998	1.24	1.14	1.05	1.04
1999	1.45	1.24	1.06	1.10
2000	1.52	1.24	1.02	1.20
2001	1.74	1.30	1.05	1.27
2002	1.91	1.34	1.07	1.33

of the antihypertensive agents was presented in Table 4. Detailed analysis of the residual for each sub-pharmacological group of the antihypertensive agents was presented in Table 5. Significant changes were observed in several sub-groups such as combinations of antihypertensives in ATC group C02 (C02N) (68% decrement) and high-ceiling diuretics (C03C) (33% increment). With such dramatic changes in the sub categories, they contributed little to the overall residual due to the relative small DDD changes. Residual analysis, which was performed on the brand name products vs. locally manufactured generic products as well as on the hospital and primary care sectors, demonstrated 11% increment of the brand name products and the hospital sectors (Table 6).

DISCUSSION

Cheng and Hsieh had reported that, during 1996 to 2002, the average annual growth rate on Taiwan's total National Health Insurance drug expenditure was 6.4%[16]. However, the expenditure of antihypertensive drug was increased from 5.89 billion NTD to 11.90 billion NTD from 1997 to 2002 in this study, which indicated that the rate of the antihypertensive drug expenditure in Taiwan grew at almost twice faster than that of the average drug expenditure.

I. *Decomposition of Drug Expenditure Component*

The substantial increase in real drug expenditure (96%), which had adjusted for inflation, is mainly due to the growth of DDD (91%) and the trend of growth is almost identical as shown in Table 2. In contrast to the drug expenditure and DDD, the relative drug price decreased a negligible 3% in this period. The residual was also a minor contributor with only 6% growth in 6 years in our study. The term, "residual", is used to explain the remaining part of real drug expenditure not accountable by relative drug price and quantity[7,8,10]. It is a measure of the impact of changes in drug treatment/utilization pattern on drug expenditure. This is not to say that there were no or very few innovative and new medications introduced into the market at this time. As a matter of fact, quite a few new and significantly improved medications were launched and subsequently widely accepted by physicians during this period such as Angiotensin II antagonist (AIIA) and long-acting calcium channel blocker (CCB).

II. *Decomposition of Quantity Component*

Since the major contributor for the expenditure growth of antihypertensive agents is the DDD, this component is further decomposed into 3 subcomponents as listed in equation 2 and shown in Table 3. The average DDD per physician visit increased from 23.14 to 30.79 in this period. The average number of physician visits per treated patient remains fairly constant for the whole period with the range of 6.9 to 7.4 visits per patient per year. Therefore, the average DDD per treated patient increased from 159.8 at 1997 to 227.7 at 2002, a 42% increment, which was the product from the average DDD per physician visit and number of physician visit per patient (data on file). The number of physician visit per patient using antihypertensive medication in this study from NHI database is much higher than the average number of physician visit per patient per claim year in Japan (taking all medications into account) during 1979 to 1993[17]. The higher frequency of physician visit in Taiwan could be caused by convenient accessibility to health care organizations as

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Table 4. DDD for total and each sub-group antihypertensive drugs during 1997 to 2002

Year	1997	1998	1999	2000	2001	2002
Pharmcological category						
C02A	1,281,385	1,120,161	1,033,503	859,912	815,251	737,447
C02C	8,476,959	11,004,122	13,026,495	13,415,840	15,493,811	16,640,936
C02D	4,392,746	4,027,335	3,749,985	3,041,983	2,780,360	2,436,731
C02L	8,053,730	8,954,631	9,099,353	8,172,606	7,746,674	7,094,360
C02N	7,574	6,601	9,346	5,844	3,661	4,383
C03A	16,233,615	17,704,231	18,539,495	17,783,241	18,681,218	18,416,304
C03B	4,650,203	6,806,295	12,046,063	14,140,979	16,006,696	17,775,024
C03C	18,525,906	22,103,634	24,388,483	24,958,295	27,514,120	29,879,147
C03D	3,220,575	3,654,871	4,148,376	4,527,163	5,249,424	5,702,917
C03E	9,649,576	11,543,994	12,087,818	11,633,341	12,272,230	12,399,447
C07A	90,159,907	107,145,247	121,214,655	122,389,555	134,691,460	139,514,422
C07B	309,370	268,146	87,036	2,359	926	163
C07C	2,054,664	2,518,202	2,248,866	1,974,825	2,132,381	2,148,212
C07D	4,302	2,552	7,328	291	0	0
C08C	98,078,863	127,204,075	151,218,647	161,195,785	190,167,505	215,155,723
C08D	15,367,356	17,535,780	18,785,188	18,583,598	20,546,996	21,140,854
C09A	91,510,909	115,832,460	130,770,657	130,777,000	142,048,356	145,867,836
C09C	0	2,853,253	16,236,910	30,686,995	49,871,875	72,223,464
C09D	0	0	0	0	277,181	2,926,387
TOTAL	371,977,726	460,285,675	538,698,290	564,149,699	646,023,031	707,137,461

C02A: antiadrenergic agents, centrally acting;
C02C: antiadrenergic agents, peripherally acting;
C02D: arteriolar smooth muscle, agents acting on;
C02L: antihypertensives and diuretics in combination;
C02N: combinations of antihypertensives in ATC-gr. C02;
C03A: low-ceiling diuretics, thiazides;
C03B: low-ceiling diuretics, excl. thiazides;
C03C: high-ceiling diuretics;
C03D: potassium-sparing agents;
C03E: diuretics and potassium-sparing agents in combination;
C07A: beta blocking agents;
C07B: beta blocking agents and thiazides;
C07C: beta blocking agents and other diuretics;
C07D: beta blocking agents, thiazides and other diuretics;
C08C: selective calcium channel blockers with mainly vascular effects;
C08D: selective calcium channel blockers with direct cardiac effects;
C09A: ACE inhibitors, plain;
C09C: angiotensin II antagonists, plain;
C09D: angiotensin II antagonists, combinations.

well as lower pharmaceutical amount prescribed of each visit. However, it is still reasonable in this situation since most of the cardiovascular diseases are chronic illnesses that need constant medication treatment. The fact that prescription refill practice is not well established in Taiwan also plays an important role. The other 2 components, number of patients treated and DDD per physician visit, are equally important contributors to the growth of DDD in this period with 34% and 33% increment, respectively. The compounding power of increasing patients and DDD per visit resulted in the substantial growth of the observed DDD during this period.

The number of patients treated grew faster from 1997 to 1999, and slowed down afterwards. This organic growth is more on the demand side and may be due to easier patient accessibility, more elder population, etc. Different means have been proposed to reduce this demand by either denying or limiting reimbursement

Table 5. Indices of residual for total and each sub-group antihypertensive drugs during 1997 to 2002. All calculations were standardized to 1997 = 1.00

Year	1997	1998	1999	2000	2001	2002
Pharmcological category						
C02A	1.00	1.09	1.08	1.10	1.15	1.17
C02C	1.00	1.07	1.10	1.12	1.13	1.13
C02D	1.00	0.99	0.96	0.98	0.97	1.02
C02L	1.00	0.99	0.96	0.95	0.91	0.91
C02N	1.00	0.78	0.53	0.47	0.34	0.32
C03A	1.00	0.98	1.00	1.01	0.98	0.97
C03B	1.00	0.99	0.98	0.95	0.93	0.96
C03C	1.00	1.03	1.10	1.06	1.15	1.33
C03D	1.00	0.99	0.98	0.99	0.94	0.91
C03E	1.00	0.98	0.96	0.96	0.95	0.93
C07A	1.00	1.01	1.08	1.13	1.12	1.15
C07B	1.00	1.01	0.94	0.88	0.91	0.88
C07C	1.00	0.95	0.89	0.85	0.86	0.88
C07D	1.00	0.96	1.01	0.99	-	-
C08C	1.00	0.97	0.96	0.95	0.91	0.89
C08D	1.00	1.00	0.98	0.96	0.91	0.89
C09A	1.00	0.97	0.95	0.93	0.89	0.84
C09C	-	1.00	0.99	0.96	0.94	0.93
C09D	-	-	-	-	1.00	0.99
TOTAL	1.00	1.01	1.03	1.05	1.05	1.06

Pharmacological category is noted as in Table 4.

Table 6. Indices of residual for total, brand, generic antihypertensive drugs, clinics and hospital sector during 1997 to 2002. All calculations were standardized to 1997 = 1.00

Year	Total	Brand	Generic	Clinics	Hospital
1997	1.00	1.00	1.00	1.00	1.00
1998	1.03	1.02	1.00	0.99	1.02
1999	1.05	1.05	1.00	0.96	1.07
2000	1.05	1.08	0.97	0.95	1.10
2001	1.05	1.09	0.92	0.92	1.09
2002	1.06	1.11	0.88	0.89	1.11

of pharmaceutics through co-payment, co-insurance or deductible and providing an incentive for patients to reduce their consumption of drugs[16,18-20]. Drug co-payment scheme was first implemented at August 1998 in Taiwan with a 100 NTD drug co-payment ceiling per physician visit. The co-payment ceiling was further raised to 200 NTD per physician visit at September 2002 to control drug expenditure growth[15]. This intervention may have some influence on slowing down the patient growth after 1999. However, it had little effect on the total expenditure growth of antihypertensive drugs due to the DDD per physician visit growth. This result is similar to that obtained by other researchers from the drug co-payment program[18,19]. It agrees with other researchers' conclusion that it is hard to control the demand side growth.

While residual reflects the direction of drug utilization shift, DDD per physician visit reflects the magnitude of drug utilization. DDD per physician visit increased from 23.14 at 1997 to 30.79 at 2002. It had a slow increment rate from 1997 to 1999, and then grew much faster afterwards. We further analyze the individual DDD per

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physician visit from 4 of the most prescribed sub-groups of the antihypertensive agents-angiotensin converting enzyme inhibitor (ACEI), β-blocker (BB), calcium channel blocker (CCB) and angiotensin II antagonist (AIIA), which accounts for approximately 75-80% of all antihypertensive agents prescribed in this period (data on file), and others. The result of the least-squares best fit curves for total, individual sub-group and others for 1998 to 2002 is shown in Figure 1. The best fit curve for the total DDD per physician visit showed a linear growth with 1.76 increment per year and R^2 = 0.99. DDD per physician visit for ACEI and CCB shared similar linear annual growth pattern with 1.51 and 1.41 increment per year and R^2 = 0.98 and 0.98, respectively. DDD per physician visit for BB remained fairly constant around 14 with a parabolic curve during this period (R^2 = 0.93). AIIA, a new pharmacological class of antihypertensive drugs introduced into Taiwan's market in the first quarter of 1998, accounted for 12% of the total antihypertensive DDD at the 4th quarter of 2002 (data on file). It showed a parabolic growth pattern with a plateau at 27 on 2001, 4 years after its launch. The best fit curve for it is $y = -0.437 x^2 + 3.96 x + 18.3$ with R^2 = 0.999. The rest of 15 other sub-groups (as called others) had a flatter linear growth with 0.66 annual increment and R^2 = 0.99. It is reported by other researchers that BB, ACEI, CCB and diuretics were the most prescribed antihypertensive drugs in the medical institutions in Taiwan at 1998[21,22]. Apparently, AIIA has replaced diuretics as the fourth most prescribed since its introduction. It is also reported that patients initially prescribed with AIIA were more persistent in Italy[23].

Policies intended to affect physicians' prescribing behaviors including clinical guidelines, generic substitution incentive, restrictive formularies, physician prescription feedback system and the use of budget control[16,20,24,25]. Under previous fee-for-service environment in Taiwan, generic substitution did not offer much incentive for the physician or hospital administrator to change the prescribing pattern or purchasing decision since the physician or hospital would get full reimbursement from BNHI. Generic substitution, therefore, did not have much impact in reducing the total drug expenditure. In fact, the monetary market share for antihypertensive generics actually decreased from 26.7% at 1997 to 21.5% at 2002, representing a relative 19.5% market share loss during this period (data on file). This number is even less than that in India (30%)[26]. Clinical guidelines along with a systematic feedback peer review system may be a feasible approach to restrict the growth of DDD per visit to an acceptable range[25]. Global budget control was implemented at the primary care clinics on July 2001 and at the hospital sector on July 2003. The impact on the expenditure of antihypertensive drug remains to be seen in the future when the data become available and warrants further investigation.

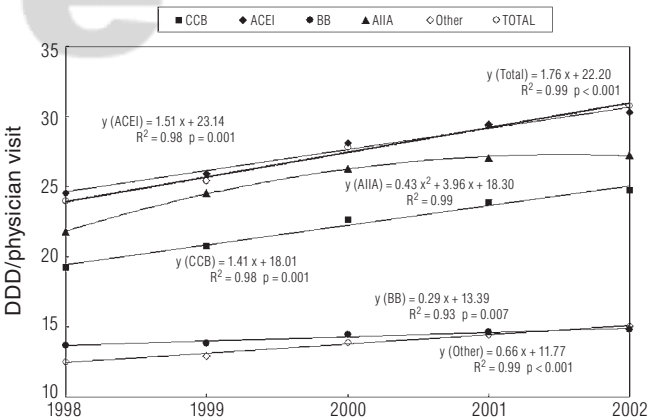

Figure 1. The least-squares best fit curves of DDD per physician visit for total antihypertensive drugs, ACEI, AIIA, BB, CCB and others in Taiwan during 1998 to 2002.

III. *Demographic Residual Analysis*

Detailed analysis of the residual for each sub-pharmacological group of the antihypertensive agents was performed to check whether there is a drug utilization shift within the entire group. The result is presented in Table 5. Though the aggregate residual did not vary much during this period, significant changes were observed in several sub-groups such as C02N (68% decrement) and C03C (33% increment). Thirteen out of 19 groups showed decreased residual and the other 6 groups had increased residual. Among 4 of the most frequently prescribed sub-groups, ACEI, AIIA and CCB showed decreased residual (16%, 7% and 11%, respectively) and only BB had a 15% residual increment. The decrement could not totally be explained by the generic substitution. For example, there is no generic product available for AIIA at this time; however, it still had a 7% residual decrement (Table 5, C09C). This indicated that pricing control policy adopted by Taiwan's BNHI during this period such as pharmaceutical grouping and implementation of reasonable-zone-pricing did have some success in controlling the pharmaceutical expenditure.

Further analysis on the residuals for two sub groups were performed to reveal the relationship between the number of drug pricing change and the magnitude of residual. The 33% C03C residual increment came from the combinational effect of 5 drug pricing increment, 11 pricing cut and 37 unchanged prices during the period. On the other hand, the 16% C09A residual decrement came from the effect of 6 pricing increment, 52 pricing cut and 32 unchanged prices (both data sets on file). This result indicated that residual, as defined as a factor to adjust the difference of the existing price and quantity indices and the true quantity and price, is a very complex factor.

AIIA was introduced into Taiwan's market in the first quarter of 1998. It, therefore, was not included in the 1997 base. By far, AIIA is one of the newest pharma-

cological classes introduced during this period (the other one is the combination of AIIA and diuretics) and also one of the most expensive medication in the entire antihypertensive agents. With its approximately 60% pricing premium over the average price of all antihypertensive agents and more than 10% of the total DDD consumed at 2002 (data on file), the introduction of AIIA did have an impact to the drug utilization shift. It, therefore, partially accounts for the increased aggregate residual while most of the sub-groups showed decreased residual.

Using residual analysis on the brand name products vs. locally manufactured generic products as well as on the hospital and primary care sectors, their effect on utilization pattern can be quantified. With the introduction of AIIA and long-acting CCB into the market, it is not surprising to see the increased residual for the brand name products (11% increment). On the other hand, quite a few off-patent ACEI and CCB brand name products were replaced by the generic counterparts. With more generic products competing with each other and the pricing cut from the BNHI, it is expected to have a 12% decrement on the residual of generic products. This analysis also demonstrated that physicians at primary care clinics had a different drug utilization pattern, reflected by an 11% decrement on the residual value, from their counterparts at hospitals as reflected by an 11% increment on the residual.

IV. *Limitation*

This study was performed based on the most recent available claim data from the NHIRD. In general, health resource allocation is better measured or evaluated by financial amount rather than by volume serviced[11]. Therefore, these claim data focus more on the financial and administrative aspect than on the clinical aspect. Patient profile, for example, only includes age, sex and demographic information for administrative purpose. Relationship between patients such as family members or family history was not released from this database. The retrieval of the data for a particular group of patients is generally obtained through logistic parameters such as geographical or institutional setting[27]. Pharmaceutical expenditure and drug utilization pattern are, however, influenced by multiple variables. Patients' accessibility, patient population profile, physician profile, hospital scale, introduction of new innovative chemical compound or generic products, pharmaceutical marketing effort toward physician or patient, drug approval process, drug pricing and reimbursement policy, pattern of persistence in using medications, number of prescribed medication classes, specific medication at enrollment, etc. are just a few variables that are interwoven together[19]. Information regarding some of the above factors is generally limited or not available at all. Other limitations for database studies includes: data quality, sources of bias, population characteristics, fishing for significance, cohort characteristics and outcomes[27]. What we obtained from the claim database in this case merely represents the final result of the time trend of the pharmaceutical expenditure in the "real world" environment. We could only try to analyze these data through macroscopic point of view. A lot of micro factors then would be grouped into residual or treated patient growth.

CONCLUSIONS

By decomposing the drug expenditure into 5 components, we were able to identify the 2 major factors that contribute to the expenditure surge of antihypertensive drug during 1997 to 2002 in Taiwan, namely number of patients treated with the antihypertensive agents and DDD per physician visit. This result suggests that the demand side (or induced demand) is the major concern that is worth more study or more strict regulation. Despite of many new, innovative and expensive antihypertensive agents launched during 1997 to 2002, the aggregate residual remained very stable with an average annual growth of 1%. This result clearly demonstrates that the drug price is not the major factor for overall rising pharmaceutical expenditure.

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