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ORIGINAL ARTICLE

National trends in anti-diabetic treatment in Taiwan, 2000–2009

Chia-Hsuin Chang [a,b], Yi-Der Jiang [a], Ching-Hu Chung [c], Low-Tone Ho [d], Lee-Ming Chuang [a,b,e,*]

[a] *Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan*
[b] *Graduate Institute of Preventive Medicine, National Taiwan University, College of Public Health, Taipei, Taiwan*
[c] *Department of Pharmacology, Tzu Chi University, Hualien, Taiwan*
[d] *Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan*
[e] *Graduate Institute of Clinical Medicine, College of Medicine, National Taiwan University, Taipei, Taiwan*

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Background/Purpose: The impact of the introduction of newer anti-diabetic agents on the treatment pattern in the booming diabetic population remains unclear. We examined the patterns and temporal trends of anti-diabetic drug use in Taiwan, with particular emphasis on combination therapy.

Methods: We searched the Taiwan National Health Insurance Database during 2000–2009 to identify outpatient prescriptions of anti-diabetic drugs, including human insulins and insulin analogues, sulfonylureas, glinides, metformin, thiazolidinediones, alpha-glucosidase inhibitors, and dipeptidyl peptidase-4 inhibitors. Glucose-lowering treatments were classified according to pattern (oral agents only, insulins only, and oral agents and insulins combined) and a number of different classes of anti-diabetic drugs. Insulin therapy and combination therapy with two oral anti-diabetic drugs (OAD) were further classified according to individual drug combination patterns.

Results: Although metformin remained the mainstay of anti-diabetic treatment, patients receiving combination therapy of oral glucose-lowering agents, either with or without insulin, significantly increased, from approximately 40% in 2000 to 60% in 2009, particularly in relation to the newer agents, including glinides, alpha-glucosidase inhibitors, and long-acting insulin analogues. Use of sulfonylureas and thiazolidinediones decreased substantially. For insulin therapy, the most commonly prescribed drugs were premix insulin analogues and basal insulin analogues, accounting for one-third of total insulin prescriptions in 2009.

* Corresponding author. Department of Internal Medicine, National Taiwan University Hospital, 7 Chung-Shan South Road, Taipei, Taiwan.
E-mail address: leeming@ntu.edu.tw (L.-M. Chuang).

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Conclusion: We found an increasing complexity of anti-diabetic therapy during the past decade in Taiwan. Further studies are needed to evaluate whether this treatment pattern will lead to improved clinical outcomes in terms of cost-effectiveness.

Introduction

Type 2 diabetes has continued to be an important public health crisis, despite increased public awareness, intensive monitoring, and aggressive management. It is estimated that more than 366 million people worldwide have diabetes, and this may increase to over 552 million by 2030.[1,2] In the United States, more than 20 million individuals have diabetes, and this number is projected to increase 165% by 2050, accounting for one-third of the population.[3,4] Type 2 diabetes has also become an important challenge in Asia, including Taiwan.[5] In a recently-published study analyzing the National Health Insurance claims database, an universal increase in the prevalence of type 2 diabetes was found for both men and women, with the highest growth among those aged $<$40 and $>$80 from 1999 to 2004.[6] There was a 31% increase in the incidence of type 2 diabetes for men and a 4.3% increase for women in the $<$40 years' old age group, despite the modest decrease in incidence for men and women of age $\geq$40. The tremendous increases in the numbers of patients with diabetes represent a huge economic burden to our society.[7]

There has also been an increasing complexity of medical treatments for diabetes, mostly due to the availability of new drugs and therapeutic classes.[8] Following the decades-long use of metformin and sulfonylureas, four additional classes of oral anti-diabetic drugs (OAD) have come into the market: these comprise alpha-glucosidase inhibitors, thiazolidinediones, the non-sulfonylurea insulin secretagogues glinides, and dipeptidyl peptidease-4 inhibitors. Meanwhile, rapid-acting insulin analogues and long-acting insulin analogues have also become widely used due to their improved pharmacokinetic and pharmacodynamic properties. These anti-diabetic drugs act on different pharmacological mechanisms and have completely different safety profiles, although clinical trials suggest that they have comparable efficacy in terms of their overall glucose lowering effect.[9] Evidence has suggested that some of these newer drugs may either be superior in terms of durability of glycemic control or have potential cardiovascular or cerebrovascular protective effects.[10–13] As a result, physicians have tended to prescribe a combination therapy of anti-diabetic agents for a balanced correction of the underlying metabolic derangements associated with type 2 diabetes and to avoid the adverse reaction associated with high-dose anti-diabetic agent treatment.[14] Although most therapeutic guidelines suggest metformin as the initial treatment for type 2 diabetes, no clear recommendation has been made for the second-line and subsequent treatment strategies of these newer agents.[15] The impact of the introduction of these newer agents to the market on the treatment pattern in the booming diabetic population remains unclear. Although several studies have described changes in anti-diabetic therapy over the past decade, few have focused on the trends in utilization of combination therapy.[16–26] Therefore, we examined the patterns and temporal trends of anti-diabetic drugs use, with particular emphasis on combination therapy.

Methods

A single-payer and compulsory National Health Insurance program was implemented in Taiwan in 1995. The Taiwan National Health Insurance claims database includes data on complete outpatient visits, hospital admissions, prescriptions, disease and vital status for 99% of the Taiwanese population of 23 million people. We established the longitudinal medical history of each beneficiary by linking several computerized administrative and claims datasets, and the National Death Registry and Cancer Registry through the civil identification number unique to each beneficiary, in addition to their date of birth. The protocol of this study was approved by the National Taiwan University Hospital Research Ethics Committee.

We searched the Taiwan National Health Insurance Database for the source population during 2000—2009 to identify any hospitalized event with diabetes as one of the discharge diagnoses (The International Classification of Diseases, 9th Revision, Clinical Modification, ICD-9-CM code 250) and used outpatient claims to find any visit for diabetes (ICD-9-CM code 250 and A code A181). Data from a random sample of one-third of the total number of patients with any diabetes diagnostic codes in the claims database were retrieved. Patients were classified as having diabetes mellitus and included in the analysis if they either had at least one hospital admission with a diagnostic code of diabetes or had three or more outpatient visits with a diabetes diagnostic code in each calendar year.

We identified patients who had ever received outpatient prescriptions of anti-diabetic drugs, including human insulins and insulin analogues, sulfonylureas, glinides, metformin, thiazolidinediones (TZD), alpha-glucosidase inhibitors, and dipeptidyl peptidase-4 (DPP4) inhibitors (anatomical therapeutic chemical classification system codes are provided in a Supplementary Table). Our unit of observation was anti-diabetic prescription, which may include more than one anti-diabetic drug. Glucose-lowering treatments were classified according to pattern (oral agents only, insulins only, oral agents and insulins combined) and number of different classes of anti-diabetic drugs. Insulin therapy and two-OAD combination therapy were further classified according to individual drug combination patterns.

Statistical analysis

We calculated the proportion of prescriptions belonging to a particular anti-diabetic therapy category each year to examine the time trend. The mean number of prescriptions

for the diabetic patients was also calculated with the use of the estimated total number of diabetes patients in Taiwan.

Results

As the prevalence of diabetes mellitus increased in Taiwan, the total number of anti-diabetic prescriptions increased significantly from 4,605,213 in 2000, to 9,548,583 in 2009, with the mean number of prescriptions per person increasing from 6.5 in 2000 to 7.8 in 2009 (Table 1). OAD only therapy made up approximately 90% of the prescriptions in 2000; this decreased slightly to 87.5% in 2009. While 6% of prescriptions were insulin-only therapy, there was a significantly increasing trend for insulin and OAD combination therapy, with the proportion rising from 3.33% in 2000 to 6.49% in 2009. Meanwhile, the proportion of combination therapy with different classes of anti-diabetic agents also increased substantially.

For OAD monotherapy, metformin was the most commonly used medication, with the proportion of prescriptions remaining at 50—60% during the study period (Table 2). In contrast, the proportion of sulfonylurea monotherapy decreased from 40% in 2000 to 30% in 2009. Use of glinides and alpha-glucosidase inhibitors rose significantly, although alpha-glucosidase inhibitors reached a plateau in 2006. Notably, the proportion of TZD monotherapy increased after it became available in Taiwan's market in 2001, reaching 2.28% in 2004, but decreased to less than 1% in 2009 (Table 2).

For two-OAD combination therapy, more than 90% were metformin-based regimens. While metformin-based and sulfonylurea-based therapy decreased significantly, falling from 99% to 90% and 78%, respectively, during the study period, glinides-based and alpha-glucosidase inhibitors-based combination therapy increased substantially (accounting for 14% and 11% of the total number of two-OAD prescriptions in 2009), although alpha-glucosidase inhibitor-based treatment seemed to reach a plateau (Table 3). TZD combination therapy accounted for 10% of the total number of two-OAD prescriptions in 2004 and then decreased to 4% in 2009. For individual two-OAD regimens in 2009, metformin plus sulfonylurea was the most common prescription (70%), followed by metformin plus glinides (10%), metformin plus alpha-glucosidase inhibitors (5%), and sulfonylurea plus alpha-glucosidase inhibitors (4%).

For insulin therapy, the most commonly prescribed drug was premix insulin, rising from 27% of total insulin prescriptions in 2000 to 51% in 2006, and then slightly decreasing to 47% in 2009. Premix insulin analogues became available in 2004 and rapidly increased to 36% in 2009. Similarly, the use of basal insulin analogues rose and accounted for 33% of total insulin prescriptions in 2009, mostly combined with OAD use. In contrast, the use of NPH insulin and a short-acting insulin only regimen decreased substantially during the study period (Table 4).

Discussion

The present study found that anti-diabetic therapy has become increasingly complex during the past decade in Taiwan. Although metformin has remained the mainstay of

Table 1 Pattern of anti-diabetic treatment and number of different classes of anti-diabetic drugs in 2000—2009 in Taiwan.

	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
Number of diabetic patients	707,000	748,000	813,000	868,000	945,000	1,000,000	1,055,000	1,128,000	1,205,000	1,223,000
Total number of prescriptions	4,605,213	5,296,197	5,887,146	6,139,260	7,092,774	7,599,447	8,068,524	8,628,033	9,154,134	9,548,583
Mean number of prescriptions	6.51	7.08	7.24	7.07	7.51	7.60	7.65	7.65	7.60	7.81
Pattern of anti-diabetic treatment (%)										
Oral agents only	89.47	89.80	90.22	90.22	90.51	90.06	89.63	88.90	88.08	87.46
Insulins only	7.20	6.72	6.21	6.21	5.76	6.10	6.21	6.17	6.17	6.05
Oral agents + insulins	3.33	3.48	3.58	3.58	3.74	3.84	4.16	4.92	5.75	6.49
Number of different class of anti-diabetic drugs										
1	62.25	58.90	54.67	50.95	48.33	47.91	46.40	44.57	43.74	42.69
2	36.18	38.04	39.06	39.53	40.09	40.90	41.72	42.43	42.93	42.65
3	1.55	2.92	5.79	8.58	10.32	10.13	10.87	11.86	12.13	13.17
≥4	0.02	0.14	0.48	0.94	1.25	1.05	1.01	1.14	1.20	1.49

Table 2 Proportion of prescriptions of oral anti-diabetic monotherapy in 2000–2009 in Taiwan.

	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
Number of prescriptions	2,534,973	2,763,534	2,853,135	2,762,967	3,019,761	3,177,729	3,242,649	3,313,155	3,439,656	3,498,954
Sulfonylureas, %	39.91	40.59	41.57	42.36	40.78	39.13	38.18	36.04	33.01	30.02
Glinides, %	0.03	1.35	2.74	4.02	4.99	5.16	6.13	6.63	6.89	7.00
Metformin, %	59.87	57.25	53.29	49.68	49.27	50.68	50.72	52.57	55.84	58.47
Thiazolidinediones, %	—	0.41	1.52	2.05	2.28	2.00	1.70	1.32	0.83	0.66
α-glucosidase inhibitors, %	0.19	0.40	0.88	1.89	2.67	3.04	3.27	3.44	3.42	3.34
DPP4-inhibitors, %	—	—	—	—	—	—	—	—	—	0.52

DPP4 = Dipeptidyl peptidase-4.

anti-diabetic treatment, patients receiving combination therapy of OADs with or without insulin significantly increased from approximately 40% in 2000 to 60% in 2009, particularly with the advent of newer agents including glinides, alpha-glucosidase inhibitors, and long-acting insulin analogues. This number was higher than that in the US (53%) and Italy (50%), but lower than that of Canada (69%).[23,25,26]

In regard to OAD treatment patterns, we found that the proportion of metformin use in Taiwan (58.5% of monotherapy and 90.2% of two-OAD combination) was substantially higher than was that in the US, Canada, and Italy (ranging from 46.7% to 66.5%).[23,25,26] In contrast to the relatively unchanged rate of metformin use during the past decade, the use of sulfonylureas, including both monotherapy and combination therapy, significantly decreased by between 20% and 25%. Similar trends of decreasing prescription rates of sulfonylureas were also observed in other countries. Notably, uses of glinides and alpha-glucosidase inhibitors were significantly higher than in Western countries. The proportion of prescriptions involving glinides was as high as 7% of monotherapy and 14% of two-OAD combination therapy, whereas glinides were used in only 2% and 7.6% of prescriptions in the US and Italy, respectively.[23,26] Similarly, alpha-glucosidase inhibitors were involved in 3% of monotherapy and 10% of two-OAD combination therapy in Taiwan and were used in less than 1% of prescriptions in the US and Canada.[23,25] Conversely, TZD was less commonly used (0.6% of monotherapy and 4% of two-OAD combination therapy in Taiwan, compared with a total of 5.7% in Italy, 12.9% in Canada, and 28% in the US).[23,25,26]

There was also a huge difference in insulin utilization between Taiwan and other countries. The overall insulin use (mono- and combination therapy) comprised about 12% of the total prescriptions, which was similar to that in Canada but lower than that in the US (28%) and Italy (22%).[23,25,26] While the proportion of prescriptions of insulin only therapy remained around 6% in Taiwan, the percentage of combination therapy of insulin and oral agents significantly increased from 3.3% in 2000 to 6.5% in 2009. Among all insulin preparations, premixed insulins with insulin analogues and long-acting insulin analogues each made up about one-third of all insulin prescriptions in 2009. There was a decreasing trend in the use of regular insulin and NPH insulin both in Taiwan and in other countries.

As increasingly complex and costly therapies are being applied to an increasing diabetic population, the above prescription patterns have a direct and substantial impact on health care expenditure, for both patients and third-party payers. One earlier study that analyzed data from a national sample of more than half of the retail pharmacies available in the US in 2001–2007 found that increasing use of TZD, newer insulins, sitagliptin, and exenatide were largely responsible for the recent rise in drug expenditures. [23] Furthermore, a recently published study using data from a pharmacy benefit manager with more than 50 million beneficiaries across the US suggested that, among newly diagnosed diabetic patients, higher drug costs over a 6-month period were largely attributed to the initial medication choices, with the greatest expense being involved for those started on new drugs, such as alpha-glucosidase inhibitors, TZD, glinides, and DPP4-inhibitors.[27] Although the study authors suggested that putting all patients on metformin and sulfonylurea as the

Table 3 Proportion of prescriptions of two oral anti-diabetic drugs combination therapy in 2000–2009 in Taiwan.

	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
Number of prescriptions	1,562,478	1,895,280	2,168,805	2,294,409	2,691,204	2,931,429	3,159,714	3,410,397	3,627,672	3,728,157
Metformin + sulfonylurea	98.69	93.07	83.82	77.25	73.41	73.68	73.11	72.49	71.97	70.19
Metformin + glinides	0.09	2.57	4.89	5.95	6.91	6.88	7.64	8.62	10.11	10.16
Metformin + TZDs	—	0.97	4.27	5.56	6.08	5.71	5.28	4.29	3.30	2.70
Metformin + α-glucosidase inhibitors	0.87	1.74	2.12	3.06	3.37	4.00	4.25	4.48	5.10	5.14
Metformin + DPP4-inhibitors	—	—	—	—	—	—	—	—	—	1.96
Sulfonylurea + glinides	0.01	0.07	0.35	1.02	1.42	1.29	1.52	2.07	2.24	2.33
Sulfonylurea + TZDs		0.62	2.35	2.96	3.34	2.72	2.18	1.72	1.09	0.82
Sulfonylurea + α-glucosidase inhibitors	0.35	0.78	1.47	2.72	3.52	3.76	3.96	4.22	4.21	3.92
Sulfonylurea + DPP4-inhibitors	—	—	—	—	—	—	—		—	0.63
Glinides + TZDs		0.07	0.30	0.48	0.53	0.43	0.43	0.37	0.28	0.22
Glinides + α-glucosidase inhibitors	<0.01	0.07	0.25	0.67	0.98	1.10	1.25	1.44	1.50	1.44
Glinides + DPP4-inhibitors	—	—	—	—	—	—	—	—	—	0.23
TZDs + α-glucosidase inhibitors		0.03	0.18	0.32	0.45	0.43	0.38	0.30	0.19	0.14
TZDs + DPP4-inhibitors	—	—	—	—	—	—	—	—	—	0.01
α-glucosidase inhibitors + DPP4-inhibitors	—	—	—	—	—	—	—	—	—	0.11
Metformin + others	99.65	98.35	95.10	91.82	89.77	90.27	90.28	89.88	90.48	90.15
Sulfonylurea + others	99.05	94.54	87.99	83.95	81.69	81.45	80.77	80.50	79.51	77.89
Glinides + others	0.10	2.78	5.79	8.12	9.84	9.70	10.84	12.50	14.13	14.38
TZDs + others		1.69	7.10	9.32	10.40	9.29	8.27	6.68	4.86	3.89
α-glucosidase inhibitors + others	1.22	2.62	4.02	6.77	8.32	9.29	9.84	10.44	11.00	10.75
DPP4-inhibitors + others	—	—	—	—	—	—	—	—	—	2.94

TZD = thiazolidinediones.
DPP4 = Dipeptidyl peptidase-4.

Table 4 Proportion of prescriptions of insulin therapy in 2000—2009 in Taiwan.

	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
Number of prescriptions	484,938	531,429	576,030	590,370	697,548	755,607	837,066	957,342	1,091,166	1,197,669
Premix insulin	27.05	32.61	33.99	37.75	42.56	48.78	51.34	50.33	48.49	46.57
Insulin analogues	—	—	—	—	4.91	16.64	24.61	27.86	32.39	35.92
Alone	—	—	—	—	3.28	10.74	15.43	17.14	19.68	21.13
With OAD	—	—	—	—	1.50	5.43	8.52	10.18	12.17	13.82
With other insulins	—	—	—	—	0.13	0.47	0.66	0.54	0.54	0.97
Human insulins	27.05	32.61	33.99	37.75	37.65	32.14	26.73	22.47	16.10	10.65
Alone	18.43	21.75	22.23	23.95	23.43	20.49	17.10	14.13	10.08	6.70
With OAD	7.72	9.97	11.26	13.31	13.81	11.31	9.30	8.10	5.87	3.77
With other insulins	0.90	0.89	0.50	0.49	0.41	0.34	0.33	0.24	0.15	0.18
Basal insulins	53.58	45.82	43.77	43.91	47.16	41.65	40.57	43.14	46.25	48.42
Long-acting analogues	—	—	—	—	4.39	4.07	8.58	17.66	26.71	32.96
Alone	—	—	—	—	0.46	0.43	0.96	1.88	2.76	3.10
With OAD	—	—	—	—	2.56	2.37	5.43	12.65	20.11	24.65
With other insulins	—	—	—	—	1.37	1.27	2.19	3.13	3.84	5.21
NPH	53.58	45.82	43.77	43.91	42.77	37.58	31.99	25.48	19.54	15.46
Alone	18.35	14.19	12.46	11.21	10.58	9.09	7.56	5.78	4.21	3.13
With OAD	16.28	15.21	16.00	17.48	17.83	15.76	14.00	11.28	8.48	4.76
With other insulins	18.95	16.42	15.31	15.22	14.36	12.73	10.43	8.42	6.85	7.57
Short-acting insulin only	19.37	21.58	22.24	18.34	10.26	9.59	8.08	6.53	5.28	5.02
Short-acting analogues	—	—	—	—	0.35	1.26	1.33	0.89	0.66	0.78
Alone	—	—	—	—	0.26	0.94	0.99	0.66	0.54	0.61
With OAD	—	—	—	—	0.06	0.26	0.32	0.23	0.12	0.16
Regular insulins	19.37	21.58	22.24	18.34	9.91	8.33	6.75	5.64	4.62	4.24
Alone	11.76	12.10	12.92	10.91	5.64	4.79	4.21	3.74	3.14	2.98
With OAD	7.61	9.48	9.32	7.43	4.27	3.54	2.54	1.90	1.48	1.26

OAD = oral anti-diabetic agents.

initial treatment represented an opportunity for payers and policy makers to mitigate drug costs, this policy may not necessarily lead to a better clinical outcome or improved quality of care. Since individual patients differed in terms of age, diabetic duration, blood glucose level and risk of hypoglycemia, body weight, other cardiovascular risk profiles, lifestyle factors, and medication adherence, a personalized approach may be more appropriate than the so-called "one size fits all" approach. Furthermore, concerns have been raised that a health insurance coverage policy solely based on cost containment may actually impair clinically rational and equitable access to pharmacotherapeutic innovation.[19] As increasing evidence suggests that newer anti-diabetic agents may have additional effects other than glucose lowering, and many clinical trials targeted on cardiovascular endpoints are ongoing, we suggest that more research into the comparative effectiveness of clinical and economic outcomes is needed to help in developing clinical practice guidelines and a drug reimbursement policy on anti-diabetic therapy.

There are several limitations to this study. First, due to government regulations, we analyzed data from a random sample of one-third of patients instead of the total number of patients with any diabetes diagnostic codes in the claims database. However, this can still be regarded as a valid sample for nationwide representativeness. Second, we could not exclude the possibility that some diabetic patients may pay out-of-pocket for glucose-lowering medications that were not recorded in this nationwide database. However, this may only comprise a very small proportion because most of the anti-diabetic drugs are costly, especially for long treatment duration. Finally, the cost of DPP-4 inhibitors has been reimbursed by the National Health Insurance since 2009. Although prescription of sitagliptin, a DPP-4 inhibitor released in the US in October 2006, rapidly increased to 10% of treatment visits 1 year later, we could not evaluate the utilization of this drug class due to lack of data after 2009.

In conclusion, in this study we found an increasing complexity of anti-diabetic therapy during the past decade in Taiwan. The number of patients receiving combination therapy of OAD, either with or without insulin, significantly increased, particularly in relation to the inclusion of glinides, alpha-glucosidase inhibitors, and new insulin analogues. Further studies are needed to evaluate whether this treatment pattern will lead to improved clinical outcome in terms of cost-effectiveness.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jfma.2012.09.009.

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