

**PRESCRIBING PATTERN IN DIABETIC OUTPATIENTS
IN A TERTIARY CARE TEACHING HOSPITAL IN NEPAL**

**Dinesh K Upadhyay^{1,2}, Subish Palaian^{1,2}, P. Ravi Shankar²,
Pranaya Mishra^{1,2} and Anil Kumar Sah¹**

¹Department of Hospital and Clinical Pharmacy and ²Department of Pharmacology, Manipal Teaching Hospital / Manipal College of Medical Sciences, Pokhara, Nepal

Summary

Diabetes is a chronic disease associated with significant morbidity and mortality. Diabetics are at a higher risk of polypharmacy and more vulnerable to irrational prescription. Data regarding drug use pattern in diabetes is lacking in South Asian countries.

The present study was conducted with the objectives of collecting the demographic details of diabetes patients, studying the pattern of drug prescribing among diabetic outpatients, calculating the mean prescription cost for the diabetes patients and analyzing the prescriptions according to prescribing indicators.

A cross sectional study was carried out at the Out-patient Pharmacy (OPP), Manipal Teaching Hospital, Pokhara, Nepal from 22nd August to 7th December 2006. All the diabetes patients who visited the OPP during the study period were enrolled after getting verbal consent and interviewed by the researchers based on the study objectives. The details were entered in the structured patient profile form and the filled forms were analyzed.

Altogether 182 patients, 103 males (56.59%) and 79 females (43.41%) were enrolled. Among these 69 (37.91%) were in the age group 51-60 years, 128 (70.33%) had a diabetic history of less than 5 years and 136 (74.72%) had at least one concurrent illness. Two, three and four drugs were prescribed in 39 (21.43%), 35 (19.23%) and 40 (21.98%) patients respectively. Altogether, 685 drugs were prescribed with an average of 3.76 drugs per prescription. Antidiabetics were accounted for 314 (45.84%) of the total drugs. Among the various antidiabetics, Biguanides were accounted for 161 (51.27%) of the total antidiabetic medications. Among the study patients, 28 (15.38%) had an encounter with an injection prescribed and 16 (2.34 %) of the total drugs were fixed dose combinations and 0.88% (n=6) of the drugs were antibiotics. The duration of prescription of medicines ranges from 29-35 days for 41.17% (n=282) of the total drugs and 57-63 days for 44.23% (n=303) drugs. Majority [650 (94.89%)] of the drugs were prescribed in oral dosage form. The average cost per prescription was NPR 1156.15 (USD 16.17). Antidiabetic medications constituted 58.93% of the total cost. Among the antidiabetic medications insulin accounted for 41.07% of the total cost followed by biguanides (32.60%).

Insulin and biguanides were the most commonly prescribed antidiabetics. Similar studies covering large number of patients are needed to confirm our findings.

Keywords: Antidiabetic medication, Diabetes, Nepal, Prescribing patterns.

Corresponding author: Dinesh K Upadhyay M.Pharm, Department of Hospital and Clinical Pharmacy/ Pharmacology Manipal Teaching Hospital/ Manipal College of Medical Sciences Pokhara, Nepal. E-mail: dinesh17dec@rediffmail.com Phone: 061-526420/526416 (Extn 221)

Introduction

Diabetes is a chronic disease affecting nearly 6% of the world population [1]. It is associated with abnormal carbohydrate, protein and lipid metabolism [2]. In Nepal, the incidence of diabetes and impaired fasting glycemia was found to be 14.6% and 9.1% respectively in people aged ≥ 20 years old in urban and 2.5% and 1.3% in rural areas [3]. The management of type-1 diabetes depends on insulin mainly whereas the management of type-2 diabetes is mainly managed using oral hypoglycemic agents (OHAs) [4]. Diabetes, if uncontrolled leads to several acute and chronic complications [5]. The chronic complications of diabetes make it necessary to prescribe drugs for these patients life long. Moreover, a good number of diabetes patients suffer from cardiovascular disease such as hypertension, hyperlipidemia and ischemic heart disease [2]. This further necessitates polypharmacy in these patients.

In Nepal, several problems in drug use patterns have been reported. This includes use of irrational combinations, excessive prescription of multivitamins, use of antibiotics in viral infections etc [6] [7] [8]. Often, the chronically ill patients like the diabetic patients suffer from multiple diseases and hence are prescribed multiple drugs. Moreover, irrational prescribing can lead to an increase in the cost of drug therapy which may lead to non-adherence. A study from the United States of America (USA) reported that about 1.3 million adults with disabilities did not take their medications as prescribed because of cost, and more than half reported health problems as a result [9]. In diabetes, the complications can be prevented only if the patient maintains strict glycemic control [10] [11]. Carrying out a drug utilization study can provide valuable information to the researchers, policy makers and the drug and therapeutics committee members to determine the drug use pattern. There are no studies carried out in South Asia on the prescribing pattern of medications in the diabetic patients. Hence the present study was carried out with the following objectives

1. To study demographic details of diabetes patients.
2. To study the pattern of drug prescribing among diabetic outpatients.
3. To calculate the mean cost of the prescription and
4. To analyze the prescriptions as per the International network for rational use of drugs / World health of organization (INRUD /WHO) indicators

Methodology

Study type: Cross-sectional study.

Study site: Out-patient Pharmacy (OPP), Manipal Teaching Hospital, Pokhara, Nepal.

Study duration: The study was carried out from 22nd August to 7th December 2006.

Inclusion and exclusion criteria: All the diabetes patients who visited the OPP during the study period were enrolled in the study. In case if a diabetic patient has not taken medicines from our OPP, those patients were excluded.

Operational modality: Patients were enrolled in the study after getting a verbal informed consent. Patients were interviewed by the researchers based on the study objectives. The details were entered in the structured patient profile form.

Result analysis: The filled patient profile form was analyzed for various parameters like age distribution and gender of patients, duration of diabetes, concurrent illness, family history of diabetes, number of drugs per prescription, average number of drugs prescribed, therapeutic category of drugs, class of antidiabetics, types of insulin preparations used, dosage form, duration of therapy and the prescribing indicators.

Results

Altogether 182 patients were enrolled in the study.

Demography details: Males were 103 (56.59%) and females were 79 (43.41%). Among these patients, the greatest number were in the age group of 51-60 years [69(37.91%)] followed by 61-70 years [40(21.98%)], 41-50 years [31(17.03%)], 31-40 years [13(7.14%)], 21-30 years [3(1.65%)], less than 10 years [1(0.55%)] and more than 70 years [25(13.74%)]. The mean \pm SD age of the patients was 56.9 ± 12.55 years.

Duration of diabetes (n=182): Among the study population, 128 patients (70.33%) had a diabetic history of less than 5 years followed by 6-10 years in 41 patients (22.53%), 11-15 years in 6 patients (3.30%), 16-20 years in 6 patients (3.30%) and more than 20 years in 1 (0.55%) patient.

Coexisting illness: Among the 182 patients, 136 (74.72%) had at least one coexisting illness during the study period. There were total of 177 illnesses in these 136 patients. The detail regarding the coexisting illness of the study patients is shown in Table 1.

Table 1. Coexisting illness (n=177)

Coexisting illness	Number	Percentage
Hypertension	125	70.62
Gastritis	15	8.47
Asthma	02	1.13
Depression	11	6.21
Angina	09	5.08
Rheumatoid arthritis	05	2.82
Renal Failure	02	1.13
Hepatic failure	02	1.13
Psychiatric illness	03	1.69
Fungal infection	01	0.56
Tuberculosis	01	0.56
Thyroid problem	01	0.56

Family history of diabetes: One (0.55%) had their father and mother suffering from diabetes and 1(0.55%) had brother and sister suffering from the disease. Two (1.1%) patients had their father suffering from diabetes, 3 (1.65%) had mother. Three (1.65%) patients had their son suffering from diabetes and 3 (1.65%) had their daughter. There were total of 6 (3.30%) patients who had their brother suffering from diabetes. The family history of 163 (89.56%) patients was not available.

Number of drugs per prescription (n=182): Among the study patients, one, two, three, four, five and six drugs were prescribed in 12 (6.59%), 39 (21.43%), 35 (19.23%), 40 (21.98%), 26 (14.29%) and 17 (9.34%) patients respectively. More than six drugs were prescribed in 13 (7.14%) patients. The average number of drugs per prescription was 3.76.

Therapeutic category of drugs prescribed: Altogether 685 drugs were prescribed in the study population. Antidiabetics were the commonest class of drugs accounting for 314 (45.84%) of the total drugs. The details regarding the therapeutic category of drugs prescribed are listed in Table 2.

Table 2. Therapeutic category of drugs prescribed (n=685)

Therapeutic classification	No. of drugs	Percentage
Antidiabetics	314	45.84
Cardiovascular drugs	246	35.91
Vitamins, minerals and dietary supplements	20	2.92
Diuretics	16	2.34
Anticoagulants	15	2.19
Antidepressants	12	1.75
Gastrointestinal system drugs	11	1.61
Analgesics and anti-inflammatory	9	1.31
Antihistamines	8	1.17
Antimicrobials	6	0.88
Antiasthmatics	5	0.73
Antiepileptics	4	0.58
Miscellaneous	19	2.77

Class of antidiabetics: Among the various antidiabetics, Biguanides were the common class of drugs accounting for 161 (51.27%) of the total antidiabetics followed by sulfonylureas 111 (35.35%), insulin 25 (7.96%), thiazolidinediones 15 (4.78%), meglitinides and alpha glucosidase inhibitors 1 (0.32%).

Type of insulin prescribed (n= 25): Among the various insulin preparations, Insulin (30/70) was prescribed in 24 (96%) patients and Insulin Human Mixtard in 1 (4%) patient.

Duration of drug therapy: Twenty-three (3.36 %) drugs were prescribed upto 7 days, 23 (3.36%) for 8-14 days, 23 (3.36%) for 15-21 days, 282 (41.17%) for 29-35 days, 5 (0.73%) for 43-49 days, 303 (44.23%) for 57-63 days and 26 (3.80%) for 85-91 days. The mean \pm SD duration of the drugs was 43.69 ± 19.62 days.

Dosage form: Majority of the drugs were prescribed in oral dosage form [650 (94.89%)] followed by parenteral [28(4.09%)], inhalation [4(0.58%)] and topical [3 (0.44%)] preparations.

Average cost of the prescription: The average cost per prescription was found to be NPR 1156.15 (USD 16.17). The details regarding the cost of the prescriptions are listed in Table 3.

Table 3. Cost analysis (n=182)

Cost (NPR)	Number of prescriptions	Percentage
0-600	56	30.77
600-1200	70	38.46
1200-1800	23	12.64
1800-2400	12	6.59
2400-3000	12	6.59
More than 3000	9	4.95

(1 USD = 71.50 NPR)

Cost based on therapeutic category of drugs: Antidiabetics and cardiovascular drugs were the most commonly prescribed. The cost of the drugs based on the therapeutic category is listed in Table 4.

Table 4. Cost of the drugs based on the therapeutic category of drugs prescribed (n=685)

Therapeutic classification	No. of drugs	Percentage of total cost
Antidiabetics	314	45.84
Cardiovascular drugs	210	30.66
Antihypertensives	21	3.07
Vitamins, minerals and dietary supplements	20	2.92
Diuretics	16	2.34
Anticoagulants	15	2.19
Hypolipidemics	15	2.19
Antidepressants	12	1.75
Gastrointestinal system drugs	11	1.61
Analgesics and anti-inflammatory	9	1.31
Antihistamines	8	1.17
Antimicrobials	6	0.88
Antiasthmatics	5	0.73
Antiepileptics	4	0.58
Miscellaneous	19	2.77

Cost distribution among the antidiabetics: Insulin was the antidiabetic drug responsible for the highest percentage of the cost incurred on antidiabetics. The details regarding the cost distribution among the antidiabetic drugs is listed in Table 5.

Table 5. Cost of the drugs based on the class of antidiabetics

Antidiabetic class	Percentage
Insulin	41.07
Biguanides	32.60
Sulfonylureas	21.91
Thiazolidinediones	3.51
Alpha glucosidase inhibitors	0.54
Meglitinides	0.36

Prescribing indicators: The analysis as per the INRUD/WHO indicators are listed in Table 6.

Table 6. Prescribing indicators

Parameter	Number (%)
Number of encounters with an injectable preparation prescribed	28 (15.38)
Number of drugs prescribed from the Hospital drug list	670 (97.80)
Number of fixed dose combinations prescribed	16 (2.34)
Number of drugs prescribed from Essential drug list of Nepal	371 (54.16)
Number of drugs prescribed from the Nepalese National Formulary	428 (62.48)
Number of drugs prescribed from WHO Essential drug list	337 (49.20)
Number of encounters with an antibiotic prescribed	6 (0.88)
Number of drugs prescribed by generic name	325 (47.45)

Discussion

Diabetes is a chronic disease requiring lifelong treatment. Although lifestyle modifications play an important role in diabetes management, drugs become unavoidable in many patients. This study analyzed the prescription pattern in diabetic patients attending out-patient departments in a Nepalese hospital. The average number of drugs per prescription was found to be 3.76. Biguanides were the most commonly prescribed antidiabetics. Majority of the drugs were prescribed in oral dosage form. Antidiabetic medications accounted for more than half of the total prescription cost.

In this study, we found a higher incidence of diabetes among elderly patients with a high incidence in the age group 51-60 years. The mean \pm SD age of patients in this study was 56.9 ± 12.55 years. A study from Netherlands had reported an average age of 67 years [12]. Another study from Spain reported an average age of 60.5 ± 12.8 years [13]. This study reported a lower age of patients as compared to other studies. In general, elderly patients are greater risk of developing type-2 Diabetes Mellitus (DM). The duration of diabetes plays an important role in diabetes management. In patients with a long duration of diabetes tight glycemic control results in a lesser incidence of complications.

In the present study, nearly two third of the patients had a diabetic history of less than 5 years. A study from Spain reported the mean duration of diabetes as 11.8 ± 8.0 years [13]. Patients with a long duration of diabetes are at a higher risk of developing complications.

Among the various complications, cardiovascular complications pose a major threat. In this study, hypertension accounted for 70.62% of the total complications seen in the diabetes patients.

Once the patients are diagnosed to have cardiovascular complications, multiple drugs are required for their management. Polypharmacy is associated with a higher cost, increased risk of side effects, drug interactions and non-compliance [14] [15] [16]. One should be especially aware of the drug interactions between antidiabetics and antihypertensive drugs. Drugs like beta blockers and ACE inhibitors can interact with antidiabetic drugs. Beta blockers are known to mask the symptoms of hypoglycemia if taken with insulin [17]. Similarly, ACE inhibitors are known to have a hypoglycemic effect. In post-marketing studies, hypoglycemia has been reported in patients taking Ramipril and concomitant hypoglycemic agents or insulin [18]. If prescribed simultaneously, the patients should be counseled regarding the possible risk of hypoglycemia.

Depression was responsible for 6.21% of the concurrent complications in our patients. In general diabetes patients are at a higher risk of developing depression. Studies suggest that diabetes doubles the risk of depression [19]. These patients are more vulnerable to miss their medications and the possibility of non-adherence is very high [20]. Moreover, certain antidepressants such as tricyclic antidepressants are known to cause cardiovascular complications and hence the doctor should be careful while prescribing antidepressants to these patients. According to one study, the use of higher-dose of tricyclic antidepressants (TCAs) was associated with an increased risk of sudden cardiac death [21]. In our study, antidepressants accounted for 1.75% of the total drug prescribed.

The average number of drugs per prescription was 3.76. In general, due to multiple diseases, diabetes patients are at greater risk of polypharmacy. Previous studies from our hospital have identified lacunae in drug use pattern in the hospital [6] [7] [22] [23]. Overuse of Vitamins was also observed [24]. In this study, vitamins accounted only for 2.92% of the drugs. This is a positive effect. While prescribing vitamins one must be cautious. Recently, concern has been raised regarding the risk of bleeding due to Vitamin-E [25]. Analgesics and anti-inflammatory drugs accounted for 1.31% of the total drugs. The prescriber should be aware of the interaction between Oral Hypoglycemic Agents (OHAs) and Non Steroidal Anti-Inflammatory Drugs (NSAIDs). Concurrent use of NSAIDs and sulfonylureas may result in an increased risk of hypoglycemia [26].

In this study, antidiabetic drugs accounted for 45.84% of the total drugs prescribed. Among the antidiabetics, biguanides accounted for 51.27% of the total drugs followed by sulfonylureas (35.35%) and insulin (7.96%). A study from Taiwan reported sulfonylureas as the most common drug class followed by biguanides [27]. A similar finding was made by Yuen and coworkers [28]. The choice of antidiabetic depends on the type of patients, their concurrent illness, cost factors, as well as the availability of medicines. In general, Metformin is considered as a safer drug in terms of hypoglycemia and hence to be preferred in our set up.

Moreover, the cost of Metformin is very low thus making it affordable by the patients in economically weak countries like Nepal. In this study, Insulin was prescribed in 7.96% of the patients. A study from Spain reported that 25.3% of the patients were prescribed insulin [13]. However, the Spanish study had a good number (15.6%) of type-1 diabetes patients.

In this study, there were no type-1 diabetes patients. In general, there are several limitations for prescribing insulin in our set up. The major problem being the cost, difficulty in injecting the drugs, risk of hypoglycemia etc. In our hospital however, a medication counseling center is located adjacent to the out-patient pharmacy where patients are counseled by qualified pharmacists [29] regarding the use of insulin syringes and insulin pen among other devices.

The study found that 94.89% of the drugs were prescribed in oral dosage form. This is a good prescribing habit. Oral dosage forms can definitely play an important role in improving patient adherence to treatment. Moreover, these days modified drug delivery systems have been introduced in the market with an objective of increasing patient adherence. In our hospital, once daily Metformin is available.

Cost of drug therapy is a cause for non-adherence. The average prescription cost was NPR. 1156.15 (USD 16.17). We found that antidiabetic drugs accounted for 58.93% of the total prescription cost. Cardiovascular drugs accounted for 22.9% of the total cost burden of drug therapy in diabetic patients. In a study by Wu et al [30], antidiabetic drugs accounted for 45% of the total drug cost and antihypertensives accounted for 39% of the total drug cost. Cost of prescription is important in chronic disease like diabetes. One of the better approaches to decrease the prescription cost is to prescribe cheaper brands. A study from Nepal reported a huge variation in cost among brands of a particular drug [31]. Also in India, a huge variation in cost of antidiabetic medications have been documented [32]. A similar finding has been seen in other developing countries [33]. Thus, there is a huge scope in reducing the prescription cost by prescribing cheaper alternatives. However, while choosing cheaper brands one should keep in mind the quality of the brands. In our hospital, drugs are selected by the Drug and Therapeutics Committee and a drug list is prepared [34]. The prescribers are instructed to prescribe the drugs from this list. This allows the pharmacists to procure cheaper brands. The doctors prescribe the drugs by generic name. In our study, we found 47.45% of the drugs to be prescribed by generic name and 98% from the hospital drug list.

Limitations: Our study had a few limitations. The diabetes patients admitted in the hospital were not included in the study. The diabetic patients who did not buy their medicines from our OPP were also excluded.

Conclusion

The study was successful in studying the prescribing pattern of antidiabetics in a Nepalese teaching Hospital. The study found the incidence of polypharmacy in diabetes patients to be high. The prescription cost can be reduced by choosing cheaper brands and the hospital DTC has a major role in improving the prescribing habits in diabetes patients as well as in procuring economic brands for the hospital. There is also a huge scope for improving prescribing by generic name.

References

1. Mayor S. Diabetes affecting nearly 250 million adults in the world. *Br Med J* 2006; 333:1191.
2. Triplitt CL, Reasner CA, Isley WL. Diabetes Mellitus. In: Dipiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM editors- *Pharmacotherapy: a pathological approach*. 6th ed. New York: McGraw Hill Inc, 2005:1333.
3. Singh DL, Bhattarai MD. High prevalence of diabetes and impaired fasting glycaemia in urban Nepal. *Diabet Med* 2003; 20: 170–171(Letter).
4. Cantrill JA, Wood J. Diabetes Mellitus. In: Walker R, Edwards C editors-*Clinical Pharmacology and Therapeutic*. 3rd ed. New York: Churchill Livingstone 2003: 657-677.
5. Powers AC. Diabetes Mellitus. In: Braunwald E, Fauci AS, Kasper DL, Hauser SL, Longo DL, Jameson JL editors. *Harrison's Principles of Internal Medicines*. 15th ed. New York: McGraw Hill Inc, 2001: 2109-2137.
6. Shankar PR, Partha P, Shenoy NK, Easow JM, Brahmadathan KN. Prescribing pattern of antibiotics and sensitivity patterns of common microorganisms in the Internal Medicine ward of a teaching hospital in Western Nepal: a prospective study. *Ann Clin Microbiol Antimicrob*. 2003; 16:7.
7. Shankar R, Kumar P, Rana M, Dubey A, Shenoy N. A comparative study of drug utilization at different levels of the primary healthcare system in Kaski district, Western Nepal. *N Z Med J*. 2003; 116(1182): U602.
8. Das BP, Sethi A, Rauniar GP, Sharma SK. Antimicrobial utilization pattern in out patient services of ENT department of tertiary care hospital of Eastern Nepal. *Kathmandu Univ Med J* 2005; 3(12):370-375.
9. Kennedy J, Erb C. Prescription noncompliance due to cost among adults with disabilities in the United States. *Am J Public Health*. 2002; 92(7): 1120–24.
10. The Diabetes Control and complications trial research group. The effect of intensive treatment of diabetes on the development and progression of long term complications in insulin dependent diabetes mellitus. *N Engl J Med* 1993; 329: 977-86.
11. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood glucose control with sulfonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes. *Lancet* 1998; 352: 837-53.

12. Van den Brink G, Schwartzberg RR, Hoeve LJ, Porsius AJ, Hoeve LL. The use of hypoglycemic and cardiovascular drugs in 582 patients with diabetes mellitus. Description and quality assessment. *Pharm World Sci* 1993; 15(3):128-31.
13. De Pablos-Velasco PL, Martinez-Martin FJ, Molero R, Rodriguez-Perez F, Puente G, Caballero A. Pattern of prescription of hypoglycemic drugs in Gran Canaria (Canary Islands, Spain) and estimation of the prevalence of diabetes mellitus. *Diabetes & Metabolism* 2005; 31(5):457-462.
14. Ebbesen J, Buajorder I, Erickson J et al. Drug-related deaths in a department of internal medicine. *Arch Intern Med* 2001; 161: 2317–23.
15. Good CB. Polypharmacy in elderly patients with diabetes. *Diabetes Spectrum* 2002; 15: 240-48.
16. Hussar DA. Patients compliance. In: Gennaro AR, Marderosion AHD, Hanson GR, Medwick T, Popovich NG, Schnaare RL, Schwartz JB, White HS editors- Remington: The science and practice of pharmacy 20th ed. Philadelphia 2000:1966-1976.
17. Davis SN-Insulin, oral hypoglycemic agents and the pharmacology of the endocrine pancreas. In: Brunton LL, Lazo JS, Parker KL editors-Goodman & Gilman's: The Pharmacological basis of therapeutics 11th ed. New York McGraw-Hill, 2006:1613-45.
18. Product Information: Altace(R) Capsules, ramipril. Monarch Pharmaceuticals, Bristol, TN, 2004
19. Anderson RJ, Lustman PJ, Clouse RE, et al. Prevalence of depression in adults with diabetes: a systematic review. *Diabetes* 2000; 49(Suppl 1): A64
20. Taj R, Khan S. A study of reasons of non-compliance to psychiatric treatment. Department of Psychiatry, Pakistan Institute of Medical Sciences, Islamabad. Available at <http://www.ayubmed.edu.pk/JAMC/PAST/17-2/Rizwan%20Taj.htm>
21. Ray WA, Meredith S, Thapa PB et al. Cyclic antidepressants and the risk of sudden cardiac death. *Clin Pharmacol Ther* 2004; 75(3):234-241.
22. Alam K, Mishra P, Prabhu M et al. A study on rational drug prescribing and dispensing in outpatients in a tertiary care teaching hospital of Western Nepal. *Kathmandu Univ Med J* 2006; 4: (In press)
23. Sarkar C, Das B, Sripathi H. Antimicrobial drug use in dermatology in a teaching hospital in Western Nepal. *Int J Clin Pract.* 2002; 56(4):258-60.

24. Lamichhane DC, Giri BR, Pathak OK, Panta OB, Shankar PR. Morbidity profile and prescribing patterns among outpatients in a teaching hospital in Western Nepal. *McGill Journal of Medicine (MJM)* 2006; 9(2): 126-133.
25. Liede KE, Haukka JK, Saxen LM, et al. Increased tendency towards gingival bleeding caused by joint effect of alpha-tocopherol supplementation and acetylsalicylic acid. *Ann Med* 1998; 30:542-546.
26. Klasco RK (Ed): DRUG-REAX® System. Thomson Micromedex, Greenwood Village, Colorado (Edition expires [December 2006]).
27. Chiang CW, Chiu HF, Chens CY, Wu HL, Yang CY. Trends in the use of oral antidiabetic drugs by outpatients in Taiwan: 1997-2003. *Journal of Clinical Pharmacy and Therapeutics* 2006; 31:73-82.
28. Yuen YH, Chang S, Chong CKL, Lee SC, Critchley JH, Chan JCN. Drug utilization in a hospital general medical outpatient clinic with particular reference to antihypertensive and antidiabetic drugs. *Journal of Clinical Pharmacy and Therapeutics* 1998; 23(4):287.
29. Mishra P, Subish P, Upadhyay D K, Bista D, Alam K, Bhandari R B. Medication Counseling Center in a teaching hospital: experiences from Western Nepal. *J Nep Med Assoc* 2005; 44 (160): 129-34
30. Wu SYB, Lung BCH, Chang S, Lee SC, Critchley JAJH, Chan JCN. Evaluation of drug usage and expenditure in a hospital diabetes clinic. *Journal of Clinical Pharmacy & Therapeutics* 1998; 23(1):49.
31. Humagain B, Bista B, Maharjan N et al. variation of prices in medicine: a market survey. *Bulletin of Nepal Pharmaceutical Association* 2003; 14: 7-10
32. Perappadan BS. Shocking variation in prices of same medicine. *The Hindu Newspaper*, 31st August 2006, New Delhi, India. (Accessed on 21st December 2006) Available on <http://www.hindu.com/2006/08/31/stories/2006083114080300.htm>
33. Pear R, Freudenheim M. Web Site Shows Variation in Drug Prices. *New York Times*, October 19, 2006, New York. (Accessed on 21st December 2006) Available on <http://query.nytimes.com/gst/fullpage.html?sec=health&res=990CE2D7173DF933A05757C0A9629C8B63&n=Top%2fReference%2fTimes%20Topics%2fSubjects%2fA%2fAged>
34. Mishra P, Alurkar VM, Subish P. Functions of a drug and therapeutics committee in Nepal. *J Pharm Pract Res* 2006; 31: 81