STUDY OF DRUG USE EVALUATION ON ORAL ANTIHYPERGLYCEMIC AGENTS IN TYPE 2 DIABETES MELLITUS AND THEIR POTENTIAL DRUG-DRUG INTERACTIONS

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ABSTRACT
DUE is a system of ongoing, systematic, quality improvement process, which’s designed to review the drug use, & to develop criteria & standards which describe optimal drug use. Hypoglycemia is the common adverse drug reaction of antidiabetic drugs seen in some patients. In this regard drug utilization study was conducted to determine the rational use by describing the drug use pattern. The objective of the study was to evaluate the prescription pattern, assessment of drug interaction, also to evaluate the occurrence of diabetes type-2 with other comorbidities & also to assess the cost minimization. The studies were simple prospective observational study which was carried out for a period of six months in the oxford medical college and research centre, Attibele. 150 patients who satisfy the inclusion and exclusion criteria were included in the study. The information included patient demographic details like age, sex, body mass index, family history, comorbid conditions, number and class of medicines prescribed. Majority 43% of the patients were in the age group 40-60 years. It is seen that 56% were males & 44% were females. Monotherapy was prescribed more frequently during the hospital stay (70.66%). The results of overall usage of different OADD’s revealed that Metformin (40 %) was the most preferred drug of choice for type 2 DM. Comorbid condition was found in 114 patients. The study has shown that the major interaction occurs with anti diabetic and antibiotics which lead to arrhythmia and alteration of blood glucose levels. The present study concluded that biguanides was the most commonly
prescribed class of oral hypoglycaemic drug in the oxford medical college & research center. It is seen that cost of glimepride is found to be more cost compared to metformin, but metformin cause serious major adverse effect lactic acidosis. So it should be given in combination. But at the same time if we use the combination drug the cost will be increased. So it’s better to use glimipride alone. Glimipride can be administered as once daily preparation, effect at low dose, additional anti-platelet activity, minimal adverse effects on cardiovascular system and lower incidence of hypoglyceimia.

**KEYWORDS:** DUE, hypoglycemia, OADDS, metformin, glimipride, biguanides.

**INTRODUCTION**

Diabetes mellitus is also called diabetes. It is a chronic metabolic disorder which is characterized by a high glucose concentration in blood which is also called as hyperglycemia (fasting plasma glucose > 7.0 mmol/l, or plasma glucose > 11.1mmol/l 2 hours after meal).[1]

Hyperglycemia occurs because of uncontrolled hepatic glucose output and lack of efficiency of skeletal muscles in uptake of glucose resulting in reduced glycogen synthesis. When the renal threshold for glucose re absorption is exceeded, the concentration of glucose will be more in the urine (glycosuria) and result in osmotic diuresis (polyuria), which, in turn, results in dehydration, leading to increased thirst resulting in more needity in oral fluid consumption (polydipsia). Insulin deficiency causes wasting through increased breakdown and lack of synthesis of proteins. Diabetic ketoacidosis is a minor emergency. It develops in the absence of insulin because of accelerated converstion of fat to acetyl-CoA, which, occurs in the absence of aerobic carbohydrate metabolism, is resulted in formation of acetoacetate and β-hydroxybutyrate (leading to acidosis) and acetone (a ketone).[1]

Diabetes mellitus can also be defined as a disease resulting due to deficiency or diminished effectiveness of endogenous insulin. It is characterized by hyperglycemia, occurring due to unsatisfactory metabolism and sequelae probably affecting the vasculature. There are three major types of diabetes: Insulin dependent diabetes mellitus (type 1), Non Insulin dependent diabetes mellitus (type 2), and gestational diabetes.

Since the cells can't take in the glucose, which is been build in your blood. High levels of blood glucose can damage the tiny blood vessels in your kidneys, heart, eyes, or nervous system. That's why when diabetes-especially if left untreated-can eventually cause heart disease, stroke, kidney disease, blindness, and nerve damage to nerves in the feet.[2]
An A1C test is a blood test that estimates average blood glucose levels over the previous three months. Periodic A1C testing may be advised to see how well diet, exercise, and medications are effectively acting to control blood sugar and prevent organ damage.

Diabetes is been diagnosed on the basis of one abnormal plasma glucose (random ≥ 11.1 mmol/L or fasting ≥7 mmol/L) along with the presence of diabetic symptoms such as thirst, increased urination, recurrent infections, weight loss, drowsiness and coma.

The World Health Organization (WHO) now recommends that glycated haemoglobin (HbA1c) as diagnostic test for diabetes. Normal HbA1c level of 48 mmol/mol (6.5%) is recommended as the cut-off point to diagnose diabetes. But if the value is less than 48 mmol/mol it does not mean that the patient is not diabetic which is diagnosed previously using glucose tests.\textsuperscript{[2]}

Drug Utilization Reviews (DUR), also referred as Drug Utilization Evaluations (DUE) or Medication Utilization Evaluations (MUE), are referred to authorized, structured, ongoing review of health care provider on prescribing, a pharmacists dispensing, and patients use of medication. DUR is carried out by comprehensive review of patients' prescription and medication chart before, during, and after dispensing. Its carried out to ensure an appropriate medication decision making and positive patient outcomes.\textsuperscript{[3]} According to WHO drug utilization evaluation is an important indicator to assess the clinical and inappropriate drug use over the time. It is being used as supervisory tool in health facilities to measure the effect of an intervention.\textsuperscript{[4]}

\textbf{DURs are classified into three categories}  
1. Prospective - evaluation of a patient's therapy before medication is dispensed.  
2. Concurrent - Its an on-going monitoring of drug therapy during the course of treatment.  
3. Retrospective - review of therapy after the patient has received the medication.\textsuperscript{[3]}

\textbf{Epidemiological Study:} DM is a leading cause of morbidity and mortality the world over. As per World Health Organization in 2014, the prevalence of diabetes globally was estimated to be 9\% among adults aged 18+ years.

In 2012, an estimated 1.5 million deaths were directly occurring as a result of diabetes. More than 80\% of diabetes deaths occur in low and middle-income countries. WHO projects assumes that diabetes can be the 7th leading cause of death in 2030. Healthy diet, regular
physical activity, maintaining normal body mass index and avoidance of tobacco use can prevent or delay the onset of type 2 diabetes.\cite{5}

**Role of Pharmacist**

- Program development, supervision and coordination.
- Education of hospital staff about drug use evaluation.
- Development of data collection methods or software’s.
- Pilot testing, data collection, analysis and report writing.
- Documentation of programme outcome, effectiveness and cost benefits.
- Development of review of audit criteria, guidelines, study protocol and educational material.
- Presentation of drug utilization evaluation results at meetings and conferences.
- Publication of results in peer-reviewed journals.
- Participation on hospital committees concerned with quality assurance.\cite{6}

**MATERIALS AND METHODS**

*Study Site:* The oxford medical college & research centre, Atibelle.

*Study Design:* Its a Simple prospective observational study.

*Study Period:* over a period of 6 months.

*Study Population:* 150 Patients.

**Study Criteria**

**Inclusion criteria:** Both male and female inpatients having type 2 DM and with co morbid conditions.

**Exclusion criteria:** Pediatric age group, pregnant and lactating women’s and out patients.

**Methodology:** Around 150 data’s are scrutinized. Data’s are collected by patient case reports, Glycosylated hemoglobin (HbA1C) test, FBS, RBS & PPBS Levels, demographic details & drugs prescribed. The patients enrolled in the study were grouped based on number of oral ant diabetics like:

- Group 1: Monotherapy
- Group 2: Dual therapy
- Group 3: Triple therapy
- Group 4: More than 3
Potential drug-drug interactions were assessed by Micromedex.

Source of Data: Information’s are collected from case studies, treatment chart, FBS, RBS & PPBS levels and interactions between physicians and patients bystanders.

Plan of Work
- Collection and review of literature related to the project.
- Study protocol was made according to the procedure.
- Collection of patient details such as patients age, sex, any histories of similar disease condition in family, patient life style and habits, economic status, FBS, RBS, PPBS and HbA1c levels

- Selection of 150 patients is carried out based on inclusion and exclusion criteria.
- Evaluation of mode prescription pattern of oral anti diabetic drugs in the hospital.
- Drugs are classified based on mono and dual therapy and found out the most preferable drug of choice.
- Major potential drug-drug interactions were found out by Micromedex.
- Comorbid conditions are found out and it seems to be more.
- Cost minimization analysis is done in 50 patients.
- Submission of report.

Statistical Analysis
To evaluate the pattern of drugs used in this study the data were subjected to percentage value. The patient’s age distribution was calculated on mean ± standard deviation by Graph Pad Instant software. The data analysis was done using Microsoft Excel. Potential drug-drug interaction was screened by using Micromedex Healthcare Series 2.

RESULTS
Table 1: Mean Age

<table>
<thead>
<tr>
<th>AGE</th>
<th>SAMPLE SIZE(N=150)</th>
<th>STANDARD DEVIATION(SD)</th>
<th>MEAN</th>
<th>P VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>MALE</td>
<td>84</td>
<td>12.511</td>
<td>63.82</td>
<td>&gt;0.10</td>
</tr>
<tr>
<td>FEMALE</td>
<td>66</td>
<td>11.803</td>
<td>65.803</td>
<td>&gt;0.10</td>
</tr>
</tbody>
</table>

Table 1 show that means age ± SD of male is 63.82 ± 12.511 and that of females is 65.803±11.803. The P value > 0.10 was considered significant.
Out of 150 patients fig 1 explains that the majority 43% of the patients were in the age group 40-60 years, followed by the age group 61-80 years (39%).

Table 2: Body Mass Index of Patients

<table>
<thead>
<tr>
<th>Body Mass Index</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal weight (18.5-24.9)</td>
<td>68</td>
</tr>
<tr>
<td>Overweight (25-29)</td>
<td>72</td>
</tr>
<tr>
<td>Obese (&gt;30)</td>
<td>10</td>
</tr>
</tbody>
</table>

Table no. 2 explains that around 72 numbers of patients are over weighted according to body mass index calculation.
Life style

In fig 3 it is seen that most of the patients are having sedentary life style (n=90) which is the root cause of type 2 DM.
Figure 5 explains that the 60.66 % (n=59) are non alcoholics and 39.33 % (n=91) are alcoholics in contrast to the journal written by Sivasankari V et. al where 13% (n=12) being alcoholics.

Table 3: Comparison between Smokers and Non Smokers

<table>
<thead>
<tr>
<th>Smoker</th>
<th>Non Smoker</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 90 (60 %)</td>
<td>N = 60 (40 %)</td>
</tr>
</tbody>
</table>

Table no.3 shows that 60% are smokers and 40% are non smokers in fact 30-40% smokers are more likely to develop type 2 DM.

Table 4: Treatment of Type 2 DM with OADD’s

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Number of Patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monotherapy</td>
<td>106</td>
<td>70.66</td>
</tr>
<tr>
<td>Dual Therapy</td>
<td>44</td>
<td>29.33</td>
</tr>
</tbody>
</table>

Table 4 explains that the 106 (70.66 %) patients are coming under monotherapy.

Table 5: Details of Different Drug Uses in Mono and Dual Therapy

<table>
<thead>
<tr>
<th>Type of Therapy</th>
<th>OADD’s Used</th>
<th>Number of patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monotherapy</td>
<td>Metformin</td>
<td>60</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>Glimipiride</td>
<td>33</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>Glipizide</td>
<td>7</td>
<td>4.66</td>
</tr>
<tr>
<td></td>
<td>Voglibosde</td>
<td>2</td>
<td>1.33</td>
</tr>
<tr>
<td></td>
<td>Glipenclamide</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Sitagliptin</td>
<td>1</td>
<td>0.66</td>
</tr>
<tr>
<td>Dual Therapy</td>
<td>Glimapride + Metformin</td>
<td>40</td>
<td>26.66</td>
</tr>
<tr>
<td></td>
<td>Glipenclamide + Metformin</td>
<td>2</td>
<td>1.33</td>
</tr>
<tr>
<td></td>
<td>Glipizide + Metformin</td>
<td>1</td>
<td>0.66</td>
</tr>
<tr>
<td></td>
<td>Voglibose + Metformin</td>
<td>1</td>
<td>0.66</td>
</tr>
</tbody>
</table>

Table 5 shows that the metformin (40 %) is the most preferable and most frequently used drug of choice for treatment of type 2 DM followed by glimipiride (22 %) and glipizide (4.66%).

Table 6: Details of Overall Usage of OADD’s According to Classification

<table>
<thead>
<tr>
<th>Classes of drugs</th>
<th>Number of patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>SULPHONYLUREAS</td>
<td>43</td>
<td>28.66</td>
</tr>
<tr>
<td>Glimepride</td>
<td>33</td>
<td>22</td>
</tr>
<tr>
<td>Glipizide</td>
<td>7</td>
<td>4.66</td>
</tr>
<tr>
<td>Glipenclamide</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>BIGUANIDES</td>
<td>60</td>
<td>40</td>
</tr>
<tr>
<td>Metformin</td>
<td>60</td>
<td>40</td>
</tr>
</tbody>
</table>
Table 6 shows that the mostly prescribed class in type 2 diabetes mellitus is biguanids (40%), followed by sulphonyl urea (28.66%), alpha glycosidase inhibitor (8%) and dipeptidyl peptidase 4 inhibitor (4%).

**Diabetic Patients and Associated Concomitant Diseases**

The % of the concomitant disease has been calculated from 150 cases. It explains that among 150 cases majority were suffering from concomitant diseases, 27 patients is with type 2 uncontrolled type 2 DM with HTN (18%). The comorbid conditions found were gastritis, anemia, osteoarthritis, lower respiratory tract infection, ischemic heart disease, diabetic foot, peripheral neuropathy, urinary tract infection, hypertension, pneumonia, alcoholic liver disease, left ventricular dysfunction, asthma, depression, hyperlipidemia, chonicbronchitis, parkinsonism & COPD.

### Table 8: Potential Drug-Drug Interactions

<table>
<thead>
<tr>
<th>Interactions</th>
<th>Number of patients</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major</td>
<td>32</td>
<td>21.33</td>
</tr>
<tr>
<td>Moderate</td>
<td>54</td>
<td>36</td>
</tr>
<tr>
<td>Minor</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>

Table 8 explains that the 32 major interactions were found out of 150 prescriptions. The major interaction occurs with antibiotics and antidiabetics which alters the blood glucose levels. (7.33%). 54 moderate interactions were seen (36%).

### Table 9: Cost Minimization Analysis for 150 Patients

<table>
<thead>
<tr>
<th>DRUG</th>
<th>Recommended Dose (from discharge medication of 50 patients)</th>
<th>No. of doses</th>
<th>Acquisition price</th>
<th>Total prize for single day</th>
<th>Total prize for recommended days</th>
<th>Cost for treating 150 patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>METFORMIN</td>
<td>500mg OD for 14 days</td>
<td>14</td>
<td>7.90 Rs</td>
<td>7.90 Rs</td>
<td>110.6( 14 days)</td>
<td>16590</td>
</tr>
<tr>
<td>GLIMIPRIDE</td>
<td>2 mg OD for 7 days</td>
<td>7</td>
<td>38 Rs</td>
<td>38 Rs</td>
<td>266( 7 days)</td>
<td>39900</td>
</tr>
</tbody>
</table>

Table 9 shows that the cost of glimipride is more compared to metformin by using cost minimization analysis.
DISCUSSION
Type-2 diabetes is a Indian chronic disease requiring lifelong treatment. Although lifestyle modifications play an important role in diabetes type-2 management drugs become unavoidable in many patients. A prescription based study is considered or pharmaceutical care to be one of the most effective methods to assess and evaluate drug utilization of medication. This study analyzed the drug utilization pattern in type-2 diabetic patients.

Out of 150 patients fig 1 explains that the majority 43% of the patients were in the age group 40-60 years, followed by the age group 61-80 years (39%) and it is in accordance with the study done by Poonam T et al, Alam Shamshir M et al & Sivasankari V et al. The mean age of our study is found to be 50 ± 20.075 with a range of 40-90 years.

Table 1 shows that mean age ± SD of male is 63.82 ± 12.511 and that of females is 65.803 ± 11.803. The P value > 0.10 was considered significant. It’s in contrast with Khushali GA et al where the P value is < 0.05.

From figure 2 it is seen that 56 % were males & 44 % were females and it is accordance with the study Poonam T et al (in this 62.5 % were males and 37.5 % females) and it is in contrast with the study Alam Shamshir M et al (in this 53 % were females and 47 % males).

Table 2 explains that most of the patients are over weighted according to body mass index calculation. It is in accordance with the Vijayan M et al (shows 44.12 % of patient are overweight and 15.44 % were obese).

In fig 3, it is seen that most of the patients are having sedentary life style (n=90) which is the root cause of type 2 DM. This is supported by a journal of Vijayan M et al showing 89 patients are having a sedentary life and only 47 are doing exercise.

Figure 4 shows that 81 individuals (54 %) having a family history of diabetes and it is in accordance with the journal Vijayan M et al where 68.38 % of the patient have positive history of diabetes in the family, and also Sivashankari V et al recorded that 44.6 % patient had a strong family background of diabetes.

Figure 5 explains that the 60.66 % (n=59) are non alcoholics and 39.33% (n=91) are alcoholics in contrast to the journal written by Sivasankari V et al where 13 % (n=12) being alcoholics.
Table 3 shows that 60% are smokers and 40% are non-smokers in fact 30-40% smokers are more likely to develop type-2 DM. It is in accordance with the journal written by Sivashankari V et al were 9.8% (n=9) of patients were smokers.

Table 4 explains that the 106 (70.66%) patients are coming under mono therapy. It is in contrast with the journal written by Baqhar Abdul M., it shows that out of 201 patients 92 (45.8%) is on dual therapy and 71(35.3%) on mono therapy.

Table 5 shows that the metformin (40%) is the most preferable and most frequently used drug of choice for the treatment of type 2 DM followed by glimipride (22%) and glipizide (4.66%). It is in contrast with the journal by Baqhar AM et al where 57.1% is on treatment with glimipride followed by metformin (45.15%). The data obtained with regard to dual therapy demonstrated that the combination of glimipride + metformin was used in maximum number of patients. It is same as the journal published by Baqhar AM et al.

Table 6 shows that the mostly prescribed class is biguanids (40%), followed by sulphonyl urea (28.66%), alpha glycosidase inhibitor (8%) & dipeptidyl peptidase 4 inhibitor (4%), in accordance with the journal Baqhar AM et al (here biguanids were prescribed most (78.6%).

Table 7 explains that among 150 cases majority were suffering from concomitant diseases, 27 patients is with type 2 uncontrolled type 2 DM with HTN (18%). The comorbid conditions found were gastritis, anemia, osteoarthritis, lower respiratory tract infection, ischemic heart disease, diabetic foot, peripheral neuropathy, urinary tract infection, hypertension, pneumonia, alcoholic liver disease, hyperlipidemia, left ventricular dysfunction, chronic bronchitis, asthma, depression, parkinsonism & COPD. It is in accordance with the journal published by Kannan et al (here 33.3% are hypertensive out of 202 patients), Alam Shamshir M et al (here 31% are hypertensive out of 200 patients).

Table 8 explains that the 32 major interactions were found out of 150 prescriptions. The major interactions occur with antibiotics and antidiabetics which alters the blood glucose levels (7.33%). 54 moderate interactions were seen (36%). It is in accordance with Kasi et al (43.28% moderate interactions and 14.42% major interactions).

Here in this study metformin is the main drug of choice. But it cause serious adverse effect called lactic acidosis. Use of only one drug will not control the glucose levels which is highly elevated, so will have to prescribe another drug to gain controlled therapeutic response. So
either use combination drug or select other drug which shows greater therapeutic efficacy with reduced side effects.

**CONCLUSION**

The present study concluded that biguanides was the most commonly prescribed oral hypoglycaemic drug in the oxford medical college & research center followed by sulphonylureas. The management of clinically relevant drug-drug interactions is improved by clinical pharmacist interventions. Advice on withdrawal or substituting the precipitant drug would be more beneficial. It is shows that cost of glimepride is found to be more compared to metformin, but metformin because of serious major adverse affect lactic acidosis. So drugs should be given in combination. But at the same time if we use the combination drug the cost will be increased. So it’s better to use glimipride alone. Glimipride can be administered as once daily preparation, effect at low dose, additional anti-platelet activity, insulin sparing action, predominant tissue specific effect on pancreatic potassium channel with limited interaction with cardiovascular potassium ATP channel, minimal adverse effects on cardiovascular system and lower incidence of hypoglycemia.[7]

This study shows that the patient knowledge about the drugs is low.[8] So as a clinical pharmacist it’s our duty to educate the patients & we should be able to answer those questions asked by them.

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